Modelling Clinical Decision Processes to Optimise Maintenance Chemotherapy in Children with Acute Lymphoblastic Leukaemia

Tushar Dilip Mungle

Modelling Clinical Decision Processes to Optimise Maintenance Chemotherapy in Children with Acute Lymphoblastic Leukaemia

Thesis submitted to

Indian Institute of Technology Kharagpur
for award of the degree of

Doctor of Philosophy

by
Tushar Dilip Mungle

Under the guidance of

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School of Medical Science & Technology
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To all the children fighting
against acute lymphoblastic leukaemia

भगवान् को मानते हो?
पर कभी सोचा है, कि भगवान् किसको मानता है?

-गणेश गायतोंडे

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CERTIFICATE

This is to certify that the thesis entitled ***Modelling Clinical Decision Processes to Optimise Maintenance Chemotherapy in Children with Acute Lymphoblastic Leukaemia*** submitted by *Tushar Dilip Mungle* to Indian Institute of Technology Kharagpur, is a record of bona fide research work under my supervision, and I consider it worthy of consideration for the award of the degree of Doctor of Philosophy of the Institute.

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Declaration

I certify that

(a) The work contained in this thesis is original and has been done by me under the guidance of my supervisors.

(b) The work has not been submitted to any other Institute for any degree or diploma.

(c) I have followed the guidelines provided by the Institute in preparing the thesis.

(d) I have conformed to the norms and guidelines given in the Ethical Code of Conduct of the Institute.

(e) Whenever I have used materials (data, theoretical analysis, figures, and text) from other sources, I have given due credit to them by citing them in the text of the thesis and giving their details in the references.

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Tushar Dilip Mungle
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Lastly, I would like to acknowledge the continued support from my family through out my stay at IIT Kharagpur.

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Abbreviations

6-MP 6-Mercaptopurine.

ADAM Automated Dose Advice Method.

ALC Absolute Lymphocyte Count.

ALL Acute Lymphoblastic Leukaemia.

ANC Absolute Neutrophil Count.

CBC Complete Blood Count.

CDSS Clinical Decision Support System.

CI5-X Cancer Incidence in Five Continents Volume.

CTU Clinical Trials Unit.

DI Dose Increase.

E-MTX Erythrocytes Methotrexate.

E-TGN Erythrocytes Thioguanine.

EFS Event Free Survival.

HDI Human Development Index.

HIC High Income Countries.

HMS Hospital Management System.

HR High Risk.

IOA Index of Agreement.

IQR Inter Quartile Range.

IR Intermediate Risk.

IT MTX Intrathecal Methotrexate.

LIC Low Income Countries.

MCV Mean Corpuscular Volume.

MIC Middle Income Countries.

MRD Minimal Residual Disease.

MT Maintenance Therapy.

MTD Maximum Tolerated Dose.

MTX Methotrexate.

NC New Cohort.

NCI National Cancer Institute.

OC Original Cohort.

OS Overall Survival.

PLC Platelet Count.

pTTR Proportion Time in Treatment Range.

RMSE Root Mean Square Error.

SR Standard Risk.

TMCK Tata Medical Center, Kolkata.

TTCRC Tata Translational Cancer Research Centre.

WBC White Blood Cells.

wmANC Weighted Mean Absolute Neutrophil Count.

wmAnMtb Weighted Mean Anti-metabolites Dose Intensity.

Contents

Abstract

We developed analytic methods to build a clinical decision support system (CDSS) to optimize the maintenance phase of therapy for children with acute lymphoblastic leukaemia (ALL). We conducted a retrospective cohort study of children with ALL who completed 96 weeks of maintenance therapy (MT), at Tata Medical Centre Kolkata, on the ICiCLe-ALL-14/INPOG-ALL-15-01 protocol. With this data, we developed summary measures to understand the effectiveness of MT, and developed an automated dose advice method, to assist physicians during MT dosing.

The MT phase spans two years, and requires strict adaptive dosing of the antimetabolites 6-mercaptopurine (6-MP) and methotrexate (MTX). Optimal dosing of these drugs, involves finding the maximum tolerated dose for myelosuppression, while avoiding toxicity. Suboptimal dosing, doubles the risk of relapse. Informatics based CDSS may bring consistency to MT practice.

We looked at data from 56 children with ALL, who completed MT from February 2016 to September 2018. Using semi-automated methods, we built a data repository. We analysed 2,704 dosing decisions.

Dose escalation to treat to maximum tolerated dose is desirable to sustain myelosuppression, however toxicity, i.e. severe neutropenia, needs to be minimized. Most children 45/56 (80%) had at-least one dose escalation during MT. The median time to first dose increase was in week 30. Most cases of severe neutropenia, with absolute neutrophil count (ANC) $\leq$ 500, occurred in cycle 1. Using conditional probability, we evaluated 2,010 physicians' dosing decisions. Dose interruption, reduction, and increase decisions were made 62%, 13.5%, and 67% of times. These results show an opportunity to improve dosing practice.

We then developed analytic methods to visualise the effectiveness of MT. The 96 weeks of longitudinal information for each child was summarised with the following measures: weighted mean anti-metabolite dose intensity (wmAnMtb), weighted mean ANC (wmANC), and proportion in target treatment range (pTTR). Anti-metabolite dose was defined as the mathematical product of 6-MP and MTX doses. Effect of prescribed anti-metabolites on myelosuppression was visualised by plotting wmAnMtb vs wmANC. Also, amount of time spent in the therapeutic range was plotted with wmAnMtb vs pTTR. We presented these scatter-plots to prescribers as part of a continuing education on protocol adherence, in May 2017. In a new cohort of 37 children, who commenced MT after June 2017, we re-analysed dosing practice. Intensified dosing was observed with 49% (18/37) of children having a wmAnMtb>1, as compared to 23% (13/56) in the original cohort (p=0.02).

With an expert physician, we investigated 421 decisions, to develop an automated dose advice method (ADAM). Iteration one, produced a root mean square error (RMSE) of $> 10\%$ for the prescribed dose by the expert physician, against ADAM's predicted output. Errors in ADAM and the physician's dosing were rectified. Iteration two produced a RMSE $< 3\%$. The Index of Agreement between ADAM and the expert physician's decisions was 0.99.

We propose a CDSS with ADAM as the decision support vehicle. The CDSS could incorporate the analytic methods we developed to assist physicians in monitoring MT progression for the individual child, as well as the cohort.

Chapter 1

Background and Motivation

This thesis is about applying medical informatics, to optimise the maintenance phase of chemotherapy for paediatric acute lymphoblastic leukaemia, in resource limited settings. The focus of this work has been on developing the analytic methods to build a clinical decision support system, for the maintenance phase of paediatric ALL treatment. In this chapter, I discuss the background, and motivation behind this work, and the objectives carried out.

1.1 Acute Lymphoblastic Leukaemia

Cancer is characterized by continuous growth and spread of malignant cells in surrounding tissues [1]. Bone marrow producing lymphoid stem cells become lymphoblasts, and eventually develop into lymphocytes. Lymphocytes are of three types: B-lymphocytes, T-lymphocytes, and natural killer cells [2]. Acute Lymphoblastic Leukaemia (ALL) is a cancer characterized by excessive proliferation of immature lymphoid cells in the bone marrow [3].

Leukaemia dominates all cancer across the globe in children aged 0-14

years, with an incidence rate of 46.4 per million persons-years [4]. Paediatric ALL accounts for more than 75% of paediatric leukaemia [5] [6].

Over the past two decades, progressive advances in the field of molecular and cellular biology, have assisted medical practitioners in prognosis and treatment of paediatric ALL. The 5-year survival for paediatric ALL has increased up to 90% in some parts of the world [7] [8]. In Europe, Oceania and North America, 5-year overall survival rates of paediatric ALL, have reached 80-90% since the mid-1990s. The overall survival rates however, in countries of Central and South America, and Asia, vary from 60-80% [9]. The report by Bonaventure et al. shows high income countries (HIC) achieving better 5-year survival than middle and low-income countries (MIC and LIC) in recent years [9]. In India, with an exception of one reported study, the 5-year survival rates are between 40-67% [10] [11].

The success of paediatric ALL treatment has been due to the development of standardized protocols based on clinical trial collaborations among multiple centres [12]. The collaborative multicentre national trial for newly diagnosed children with acute lymphoblastic leukaemia - ICiCLe-ALL-14 - has brought multiple centres in India together, to introduce standardized risk stratified treatment for Indian children [13]. With the introduction of risk-stratified therapy through the ICiCLe initiative, outcomes have improved by an estimated 10%, which still does not match the best outcomes achieved globally.

1.1.1 Maintenance Therapy in Acute Lymphoblastic Leukaemia

Treatment for ALL consists first of an intensive inpatient phase consisting of induction and post induction treatment across six months, followed by 2 years of maintenance treatment as an outpatient. Maintenance therapy (MT) is a critical component of ALL treatment, and involves the antimetabolite drugs 6-mercaptopurine (6-MP) and methotrexate (MTX), which are dosed bi-weekly based on blood counts [14] [15]. The goal of maintenance therapy is to expose the child to the highest tolerated dose of antimetabolites over the course of the two year period, with the aspiration of ensuring long term remission. Optimal dosing of 6-MP and MTX involves finding the maximum tolerated dose for myelosuppression for a child, while avoiding severe toxicity [16]. Suboptimal dosing of the antimetabolite drugs during MT, doubles the risk of relapse for the child [17] [18].

In the ICiCLe-ALL-14 protocol, the 2 year phase of MT is divided into *8 cycles*; each cycle consists of *12 weeks*. Antimetabolites are started at a $60mg/m^2/day$ dose for 6-MP and $20mg/m^2/week$ dose for MTX. Complete Blood Count (CBC) parameters, specifically white blood cells (WBC), absolute neutrophil count (ANC) and platelet count (PLC) are followed every two weeks [15]. Doses of 6-MP and MTX are adjusted based on ANC and PLC values. This is called ***adaptive dose adjustments*** [19]. The range of accepted ANC, PLC, and WBC are stated in the ICiCLe-ALL-14 protocol.

In each cycle, along with 6-MP and MTX, intrathecal methotrexate (IT MTX) is administered directly into the intrathecal space, the region surrounding the spinal cord. IT MTX is given once every three months in the protocol followed at Tata Medical Center, Kolkata. In addition

to this, supportive antibiotics specifically trimethoprim/sulfamethoxazole (TMP/SMX) are prescribed. Figure 1.1 demonstrates an outline of a maintenance therapy protocol.

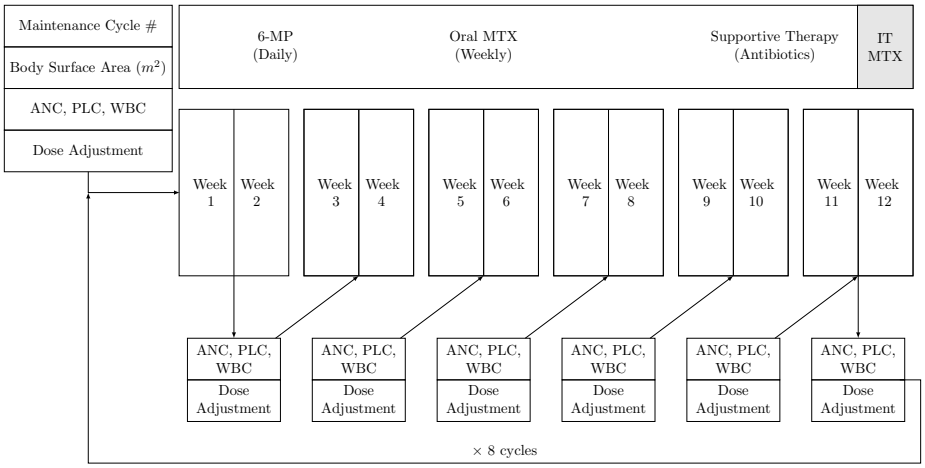


Figure 1.1: Maintenance therapy over 96 weeks

1.1.2 Challenges in Maintenance Therapy

The maintenance phase of ALL therapy requires strict adaptive dosing of the antimetabolite drugs 6-MP and MTX, to ensure myelosuppression. Myelosuppression is determined by bi-weekly checks of the complete blood count, with specific attention to the WBC, ANC, and PLC.

Adaptive dose adjustment is challenging for physicians dosing 6-MP and MTX during MT [15] [20]. The drugs are adjusted every two weeks to reach the maximum tolerated dose for myelosuppression [21] [22]. Doses may have to be reduced or stopped, in response to toxicity measured by drops in ANC and PLC. Similarly, doses may have to be increased to keep the ANC and PLC within a narrow range. Dose adjustment is a critical activity during maintenance therapy [23]. The

ICiCLe-ALL-14 protocol dictates that the treatment has to be stopped for severe neutropenia (ANC $\leq 500 \times 10^6/L$) and severe thrombocytopenia PLC ($\leq 50,000 \times 10^6/L$) conditions. Doses are reduced to half for moderate neutropenia ($(501 < ANC \leq 750) \times 10^6/L$) or thrombocytopenia ($(50,000 < PLC \leq 75,000) \times 10^6/L$). The dose of 6-MP nad MTX is increase if stable ANC (between 750 to 1,500 $\times 10^6/L$) or PLC ($> 75,000 \times 10^6/L$) counts are observed over a period of 6 weeks.

1.2 Motivation

Outcomes for childhood ALL in India lag behind those in the developed world. In India, the majority of reported 5-year ALL survival outcomes are below 70%, as compared to high income countries with more than 90% survival [11].

The outcome disparity may be specifically narrowed down to the following potential contributors: (1) suboptimal risk stratification due to limited availability of quality-assured specialised laboratory studies required for risk stratification; (2) variable quality of generic cytotoxic drugs, resulting in inferior outcomes; (3) distinct biological features of ALL in India, influencing response to therapy; and (4) suboptimal supervision of chemotherapy treatment, specifically the 2-year maintenance phase [11, 15, 20].

One area to improve outcomes in paediatric ALL is to focus on optimizing adaptive dosing during the 2-year maintenance phase of chemotherapy. Evidence from international ALL study groups indicate that suboptimal intensity of drug treatment during the maintenance phase, is associated with higher risk of relapse [17] [18]. Optimization of maintenance therapy

requires strict adherence to a set of dosing rules by prescribers, intensive supervision through 96 weeks of treatment by the team, and treatment adherence on the part of families [20] [23].

In the ICiCLe-ALL-14 protocol, the goal of maintenance therapy is to expose the child to the highest tolerated dose of antimetabolites over the course of the two year period, with the aspiration of ensuring long term remission. Doses may have to be reduced, or stopped in response to toxicity, measured by drops in ANC and PLC. Similarly, doses may have to be increased, to keep the ANC and PLC within a narrow range.

Adaptive dose adjustment is challenging [15] [20]. Optimal dosing of 6-MP and MTX involves finding the maximum tolerated dose for myelosuppression for a child, while avoiding severe toxicity [16]. This is not an easy thing to do, even for experienced physicians. Adaptive dosing also requires longitudinal monitoring of blood count trends and review of serial dose changes, not easily done in a busy clinic.

Bringing consistency to the practice of drug dosing during MT, may come from medical informatics interventions, such as clinical decision support systems (CDSSs), that incorporate rule based or machine learning approaches, to find the optimum tolerated dose for the antimetabolites, at any given time. Also, a clinical decision support system will help track deviations in practice and allow review of the reasons for deviation, as well as refinement of dosing rules if required.

1.3 Rationale

Development of a computerised dosing algorithm to ensure consistent and optimal adaptive dosing of antimetabolites would standardise the man-

agement of MT. Integration with relevant endpoint measures of adaptive dosing practice would enable review of prescribing practice (possibly in real-time) and provide an opportunity for refinement in dosing rules where indicated.

1.4 Objectives

We defined the following objectives for our work:

- **Objective 1** - To develop a single data repository for maintenance therapy from paper and electronic based records
- **Objective 2** - To understand current dosing practice by conducting a retrospective cohort study in children who completed MT at Tata Medical Centre, Kolkata.
- **Objective 3** - To develop analytical methods to measure the effectiveness of MT
- **Objective 4** - To develop an automated dose advice method (ADAM) to aid 6-MP and MTX dosing during maintenance therapy

1.5 Organization of Thesis

The thesis is organized into nine chapters: 1) Chapter 1 is Background and Motivation; 2) Chapter 2 is a Literature Review; 3) Chapter 3 gives a background to the study setting; 4) Chapter 4 describes the data gathering process; 5) Chapter 5 looks at analysis of dose escalation events along with toxicity events, and conditional probability analysis of dosing decisions; 6)

Chapter 6 presents a visual summary method for the analysis of maintenance therapy across the cohort; 7) Chapter 7 presents analysis of dosing practice following introduction of analytic methods discussed in Chapter 6; 8) Chapter 8 presents the automated dose advice method; 9) Chapter 9 is Conclusion and Future Work.

We present an overview of the thesis as a work-flow diagram, in Figure 1.2, depicting how each chapter builds the need for a medical informatics solution - a clinical decision support system with its modules for ALL treatment. The green colour text represents the outcome or conclusion from the respective chapter.

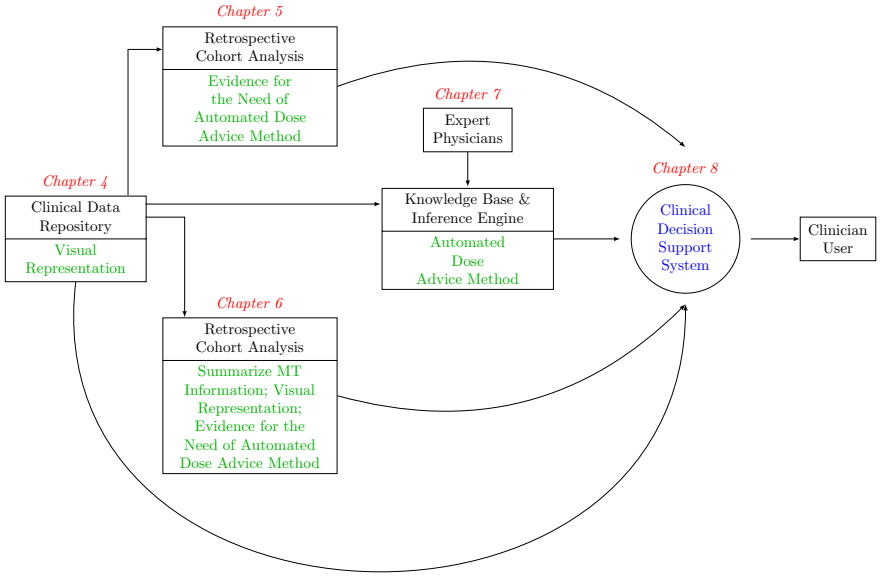


Figure 1.2: Overview of thesis

Chapter 2

Literature Review

2.1 Introduction

In this chapter, I present a review of the published literature on the burden of ALL globally and in India, prognostic factors, the basics of ALL treatment, and maintenance therapy. Next, the challenges of ALL treatment in low resource settings like India are discussed. Further, I discuss the use of clinical decision support systems in paediatrics, and specifically for chemotherapy.

2.2 Acute Lymphoblastic Leukaemia

2.2.1 Burden of ALL Globally and in India

The most updated population based estimates available on the epidemiology of leukaemia is given by Filho et al. in 2018 [7]. Filho et al. used the Cancer Incidence in Five Continents Volume (CI5-X) as a data source for cancer incidence from 2003-2007. This data source has 290 registries from 68 countries. There is a bi-modal distribution of incidence of ALL with the first peak in children age 0-4, and the second in adults over

75. Data for ALL is more readily available from high human development index (HDI) countries. ALL is the single most common type of leukaemia. Data from middle and low HDI nations including India were more likely to not have the distribution of the specific types of leukaemia.

Katz et al. used the same data source, CI5-X, to report ALL estimates in 21 selected countries [24]. They did not have data from India; however, they projected an incidence of 6,990-7,730 new cases of ALL in 2020, for children aged 0-19 years in China a country with a similar population size. The authors also estimated the average potential years of life lost (AYLL) due to ALL for China, to be 68.6 years for children aged 1-19 years.

In India, the documentation of incidence of leukaemia and specifically ALL is limited. In 2011, Marwaha et al. estimated 10,000 cases of paediatric ALL each year in India [25]. They thought this in itself to be an underestimate, due to the lack of national registries and barriers to access to care.

In a recent study by Asthana et al, the incidence of leukaemia not specifically ALL, was reported from 24 population based cancer registries for 2012-14 as part of the National Cancer Registry Program (NCPR) [26]. The number of leukaemia cases in children, per year in Kolkata, reported during 2012-14 was only 22. Kolkata was the only location from the Eastern zone represented. The reported numbers here is an underestimate of actual ALL incidence. As of September 13^{th} 2020, the population of India is 1382.7 million [27]. In India, around 41% or $\sim$463 million population has age $<$ 18 years [28]. The incidence of acute leukemia for population age $<$ 18 years is 33 per million [4].

Given the above facts, the estimated annual incidence of pediatric (0-18 years) acute leukemia in India would be $\sim$15,300. The estimated an-

nual incidence of pediatric acute lymphoblastic leukemia in India would be ∼12,250 (based on the understanding that acute lymphoblastic leukemia constitutes 80% of acute leukemia diagnosed in children 0 - 18 years).

A review of the published literature on paediatric cases of ALL in India from 2000-2015, by Arora et al., report on only 3,761 cases, though one would expect as the authors point out data from 90,000 children with leukaemia across a decade given the size of the country [29]. This review included one population based study, and eight hospital based studies. The authors point out the great need for collaborative multi-centre studies and clinical trials nationally, regionally, and internationally, to capture the full understanding of ALL incidence, treatment, and prognosis, in the Indian context.

The overall survival for children with ALL in India is around 60% [29]. Arora points out three broad reasons contributing to poor outcomes: 1) treatment abandonment, 2) relapse, and 3) toxicity related deaths [29]. An improvement in ALL treatment outcomes is visible only in specific specialised centre [11], which could be boosted with the available resources in hand.

The incidence of ALL in India is not reported to its fullest. Various agencies for surveillance across the country need to take initiatives, to understand the burden of disease. Rates for incidence, mortality, and survival, are essential to progress further in terms of treatment methods, outcomes, and health care policies. The disparities in treatment success between high income countries, and low and middle income countries, can be attributed to inadequate diagnostic methods, lack of access to treatment, and the lack of organized multi-centre treatment groups systematically conducting clinical studies [4, 7, 29].

2.2.2 Prognostic Factors

Clinical, biological and genetic features of leukaemic cells and early response to treatment are the major prognostic factors considered in initiating and deciding treatment intensity. The initial risk group is identified with the help of clinical features, including age, and WBC count at the time of diagnosis. Children age 1-10 years with initial WBC $< 50,000/mm^3$ and absence of bulky disease, are considered to have a favourable risk profile and may be classified as standard risk. This initial risk classification is based upon the National Cancer Institute (NCI) classification system [30].

ALL is then further delineated into T cell ALL, or precursor B-cell ALL by immunophenotyping. B-cell ALL has a more favourable prognosis. Treatment is based on the type of ALL. Further, cytogenetic features are evaluated to establish the intensity of the treatment [30] [31]. Cytogenetic features such as high hyper-hyperdiploidy and ETV6-RUNX1, are associated with favourable outcomes, where as BCR-ABL1, hypodiploidy, and MLL rearrangement with poor outcomes.

Final risk stratification is based on early treatment response, at the end of the induction phase of ALL treatment. Minimal Residual Disease (MRD)[†] is determined following induction. This is evaluated by means of molecular techniques, such as flow cytometry to determine the final risk group. MRD expresses the number of leukaemic cells per 10^4 to 10^6 normal cells in bone marrow. Depending upon the MRD expression children are categorized into 3 risk groups: (1) Standard Risk (SR), (2) Intermediate Risk (IR), and (3) High Risk (HR). The risk group establishes the intensity

[†]MRD are leukaemic/cancer cells from bone marrow, present during/after treatment or remission (no symptoms or signs of disease). It is considered as a cause of relapse in leukaemia. DNA, RNA or proteins base sensitive molecular biology tests are present today, to measure levels of leukemic cells. *Source: https://en.wikipedia.org/wiki/Minimal_residual_disease*

of treatment.

2.2.3 Treatment

ALL treatment involves multi-drug treatment using a combination of anticancer drugs in defined phases, across 2.5 - 3 years. The development of an intensive eight drug, eight week, induction, followed by consolidation therapy, by Riehm et al., was a fundamental contributor to modern day therapy [32]. The regime became the basis for the Berlin-Frankfurt-Münster protocol, and protocols followed thereafter. Modern treatment protocols for children diagnosed with ALL include two phases of therapy: (1) Intensive phase and (2) Continuation phase. Intensive phase is divided into the induction and the post-induction phase.

1. ***Intensive Phase***

   (a) *Induction phase*: It lasts 4-6 weeks. Various drugs such as vincristine, Asparaginase, intrathecal methotrexate, prednisolone along with optional use of an anthracycline, are dosed based on initial risk stratification. The aim is to achieve complete remission. The majority of children achieve remission during this phase of treatment, but relapse is inevitable if no further treatment is given.

   (b) *Post-induction phase*: Post-induction phase (5 - 7 months) is further subdivided into consolidation, interim maintenance, and intensification phases.

      i. *Consolidation phase*: Intensive combination of chemotherapy is delivered to consolidate remission and prevent occurrence of overt central nervous system leukaemia.

ii. *Interim maintenance*: The main aim of this phase is to destroy any leukaemic cells left in child's bone marrow or blood.

iii. *Intensification*: This phase is helpful in preventing leukaemic cells from re-occurring. Delayed intensification may be administered thereafter which could include pulsed dexamethasone, vincristine, intrathecal methotrexate, Asparaginase, Cycophosphamide, Cyratrabine, 6-Mercaptopurine, and Doxarubicin or Mitoxantrone [33].

2. ***Continuation phase***: It is the last phase of paediatric ALL treatment and lasts for approximate 2 to 2.5 years [14] [15]. It is also called the maintenance phase or maintenance therapy. The therapy includes a daily dose of oral 6-mercaptopurine or thioguanine, and weekly oral methotrexate. Maintenance therapy is discussed in the next section.

The goal of paediatric ALL treatment is cure. Carrying out risk-based/risk-directed/patient-tailored therapy, and balancing toxicity to treatment, need to be managed through the entire course of treatment. Periodic assessment of treatment response are carried out with bone marrow studies, to determine leukaemia clearance.

Figure 2.1 Standard treatment protocol for children diagnosed with ALL.

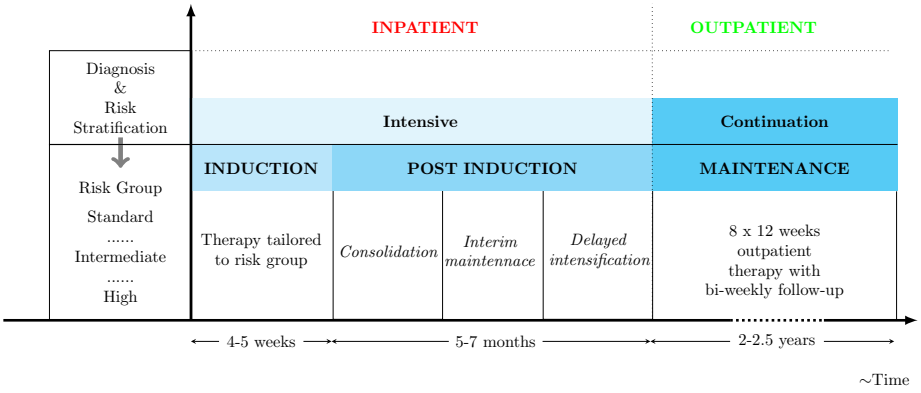


Figure 2.1: Treatment protocol for paediatric ALL

2.3 Maintenance Therapy

Maintenance therapy (MT) starts with prescribing the anti-metabolites 6-MP and MTX, keeping WBC, ANC and PLC, suppressed within a set range for myelosuppression. Dose adjustments are made biweekly.

Myelosuppression is defined as reduction in bone marrow activity, resulting in fewer white blood cells, red blood cells, and platelets [34]. Children need sustained myelosuppression during maintenance chemotherapy, and dosing to achieve this is the point of MT. Sustained myelosuppression during MT is key to survival [22].

Table 2.1 presents five protocols by major institutional and collaborative groups along with the group from India. The table shows CBC variables WBC, ANC and PLC - with desired target range and anti-metabolite drugs administered during maintenance therapy by the five study groups [15].

Table 2.1: Values for chemotherapy drugs - 6-MP and MTX - administration and CBC parameters used during MT according to various study groups

Group	**Geographic Location**	**WBC** ($\times 10^9/L$)	**ANC** ($\times 10^9/L$)	**PLC** ($\times 10^9/L$)	**6-MP** (mg/day)	**MTX** (mg/week)
BFM	Germany	2-3	> 0.2	> 50	50	20
DCOG	Netherlands	2-4	None	None	50	20/30[†]
JACLS	Japan	2-3	> 0.2	> 50	50	25/150[‡]
NOPHO	Nordic Countries	1.5-3.5	None	None	75	20
SJCRH	United States of America	1.5-3.5	0.3-1.0	> 50	75	40
InPOG-ALL-15-01[$]	India	None	0.75-1.5	> 50	60	20

BFM, Berlin-Frankfurt-Münster; DCOG, Dutch Childhood Oncology Group; JACLS, Japan Association of Childhood Leukemia Study; NOPHO, Nordic Society of Paediatric Haematology and Oncology; SJCRH, St Jude Children's Research Hospital; InPOG-ALL-15-01, Indian Paediatric Oncology group - Acute lymphoblastic Leukaemia
WBC, White Blood Count; ANC, Absolute Neutrophil Count; PLC, Platelet Count
[†] Higher dose ($30mg/m^2$ per week) given intravenously for high-risk cases.
[‡] Higher dose ($150mg/m^2$ every 2 weeks) given intravenously to high-risk cases
[$] Unpublished study

Doses for both the drugs are regulated upwards by following dose adjustment rules to achieve myelosuppression, by maintaining the ANC or WBC in the narrow range, as shown in column 3 and 4 of Table 2.1. The procedure of prescribing chemotherapy drugs based on CBC parameters is known as *adaptive dosing*. The emphasis is to prescribe the maximum tolerated dose for an individual to keep the bone marrow sufficiently suppressed.

The dosing of each drug is based on a child's WBC, ANC and PLC. In fact, ANC has been shown to be the single most important haematological target for dose adjustments during maintenance chemotherapy [19]. Schmiegelow et al. have shown that using only ANC for adaptive dosing helps, in the prevention of disease recurrence after treatment completion.

2.3.1 Toxicity

The downside to intensifying maintenance therapy through adaptive dosing, to achieve optimal myelosuppression, is the risk of toxicity. The principal toxicity is the risk of severe neutropenia (ANC $\leq 500 \times 10^6$ /L), and the attendant risk of infection. In most cases, neutropenia is not

severe and recovers promptly ($\leq$ 2 weeks) with treatment interruption. But neutropenia following dose escalation may be prolonged in children with constitutional deficiency of enzymes, required for the metabolism and detoxification of antimetabolites. The risk of severe thrombocytopenia (PLC $\leq 50,000 \times 10^6$ /L) is observed to be low with adaptive dosing practice. In a proportion of children, increasing doses of antimetabolites, may result in complications other than low blood counts. These complications include liver injury resulting in raised serum bilirubin; hepatic veno-occlusive disease, associated with injury of the endothelial lining of liver sinusoids resulting in disproportionately lower platelet count as result of peripheral platelet consumption; and acute pancreatitis.

Over 7 years at the Tata Meical Center Kolkata (Sep 2013 to Sep 2020), 8 of 460 (1·7%) patients have been diagnosed with 6mercaptopurine-associated hepatic sinusoidal obstruction syndrome (hSOS) during the maintenance treatment phase. Diagnosis of hSOS was considered if new isolated or disproportionately low platelet count was observed (platelet count $< 75x10^9/L$) without accompanying (or proportionately severe) neutropenia and anaemia [35]. Thrombocytopenia was typically moderate (platelet count between 55 and $75x10^9/L$), was not observed prior to start of the maintenance treatment phase, developed within 6-8 weeks of continuous 6-mercaptopurine treatment and recovered to normal levels 2 - 3 weeks following discontinuation of the drug. Enlargement of the liver and spleen was uncommon (2 of 8 & 1 of 8 patients respectively). No patient had jaundice (serum bilirubin levels within normal limits) and levels of serum aminotransferases were only mildly elevated (2 - 5 times above baseline, as is commonly observed in patients on 6-mercaptopurine). Ultrasound liver studies performed in 3 patients showed no anatomical findings

of concern. Five of 8 patients (63%) were older than 10 years. In all patients, the dose of 6-mercaptopurine was reduced (to between 25 and 50% of protocol-recommended doses) and methotrexate dosing was intensified (125 - 150% of recommended doses). Ursodeoxycholic acid was administered in all patients, given its reported therapeutic benefit in hSOS.

Adaptive dosing to achieve maximum tolerated antimetabolite dose has to be balanced against the risk of neutropenia-associated infection, deeper immune suppression, and non-haematological toxicities.

While the maximum tolerated doses of 6-MP and MTX are given by adaptive dosing [36] [21], occurrences of neutropenia or thrombocytopenia, need to be kept under check. The severity of neutropenia and thrombocytopenia leads to reduction of doses of 6-MP and MTX, or halting of the two drugs altogether. Several studies have shown that it is desirable to have neutropenia episodes during dose escalation, for better survival outcomes [16].

Schmiegelow has advocated the need for treating to toxicity during maintenance chemotherapy to prevent relapse. In a study of 122 children with ALL followed for 84 months, they found that children with a cumulative withdrawal of 6-MP or MTX for more than 10% of the time, had an increased risk of relapse [16]. In contrast Welch and Lilleyman cautioned that dose escalation may not result in increased cumulative median doses of anti-metabolites. In a study of 88 gender matched children with ALL, Welch and Lilleyman studied dose escalation during MT. They cautioned that dose escalation may not result in increased cumulative median doses of anti-metabolites. They found that children who had dose escalation, compared to those who did not, ended up with similar cumulative median doses of drugs; however, those with dose escalation ended up spending

more time off of 6-MP [37]. This study was limited to only six months and did not look at survival, or relapse, as endpoints.

2.3.2 Compliance to Treatment Protocol for Prescribing Chemotherapy Doses

Toxicity-guided dose adjustment protocols, require strict compliance for good outcomes. Dose adjustment to achieve optimal myelosuppression, is the physician's responsibility. Several groups have reported compliance issues related to dose adjustment [17, 18, 38].

Peeters et al. computed the cumulative doses of chemotherapy drugs for 2 groups of children, those with relapse, and non-relapse. It was observed that the relapsed group had low cumulative doses of chemotherapy drugs, compared to the non-relapsed group [17].

Results from the UKALL VIII trial showed a compliance problem when neutropenia episodes were evaluated for the cohort from the trial - UKALL VIII and UKALL V [18]. It depicted under-prescribing the doses of chemotherapy drugs. The authors in [38] mapped weighted average WBC of children with Down syndrome and ALL, against children with ALL and no Down syndrome, to observe compliance of the treatment protocol. They concluded that less intensive treatment in terms of titration of chemotherapy drugs in children with Down syndrome and ALL, as compared to children with no Down syndrome and ALL, may contribute to poor prognosis for event free survival.

2.3.3 Patient Adherence to Maintenance Therapy

As physicians try to establish and advice maximum doses of chemotherapy drugs; simultaneously, every child has to adhere to the prescribed drugs. As MT is very long, the effects of medication, can be only seen if children are adherent to the prescribed dose.

Investigating risk of relapse to the exposure of 6-MP; Bhatia et al., in her study, reported higher risk of relapse, for non-adherent children as compared to children adherent to weekly doses of 6-MP, by the means of an electronically monitored adherence system [39]. The authors reported 2.7 fold increase risk of relapse, in non-adherent children. In another study by Bhatia et al., they showed a decline in adherence rate, measured electronically, from 95.0% to 91.8% across five months, for children undergoing MT [40]. There were 20.5% children with $< 90\%$ adherence to medication, at the end of the study.

2.3.4 Principles of Maintenance Therapy

Sustained myelosuppression, maximum tolerated dose of oral chemotherapy through adaptive dosing and adherence are the three vertical pillars of maintenance chemotherapy (Figure 2.2). Outcomes for ALL treatment depends upon the three factors working together hand-in-hand during MT.

Both NOPHO ALL-92 and MRC UKALL X studies have shown that achieving optimal myelosuppression during MT lead, to higher survival rates in individuals with ALL [23] [20]. Several other studies in the past have shown the importance of achieving myelosuppression through adap-

tive dosing and adherence to medication, playing an important role in event free survival rates [21, 22, 41]. Compliance to the protocol for adaptive dosing by physicians is vital for better outcomes [17, 42, 43].

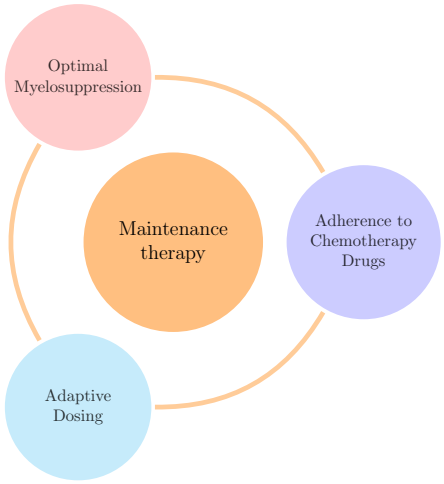


Figure 2.2: Three basic principles of maintenance chemotherapy in ALL treatment

2.3.4.1 Effectiveness of Adaptive Dosing in Maintenance Therapy

The previous three subsections highlight the problems encountered during MT. The problems related to toxicity may be addressed by compliance to treatment protocols with the help of adaptive dosing. Treating to maximum tolerated dose, or intensifying MT is essential, as it affects overall survival of children, and reduces the risk of relapse.

We present a review of various studies reporting treatment outcomes highlighting the importance of MT and how better governance of treatment intensity, has improved the overall treatment outcomes. Pub-Med and Google databases were searched with the following terms to retrieve articles: maintenance therapy, acute lymphoblastic leukaemia, mercaptop-

urine, methotrexate, and treatment outcome. Pub-Med search resulted in 82 searches, out of which 12 relevant search results were selected to report. 5/40 relevant searches were shortlisted to report from the Google search.

All the articles were read and critically reviewed to examine how MT has influenced ALL treatment outcome. Specifically, the following selection criteria were used to include the study in literature review: (i) Duration of MT; (ii) Dose prescribed during MT – 6-MP and MTX. Any study that evaluates mentioned parameters on treatment outcome were selected.

Table 2.2 lists the relevant studies that reported importance of treatment intensity with respect to survival rates in paediatric ALL.

Table 2.2: Literature review of studies showing importance of maintenance therapy intensity on overall survival outcomes.

Sr. No.	Reference	Results	Conclusion
1	Yang KB, Sun XF, Zhen ZZ et al. (2017) [44]	5-year event free survival (EFS) - Intensified therapy group: (76.9 ± 5.8)%; Non-intensified therapy group: (77.9 ± 4.3)%	Intensified MT did not improve the prognosis of patients with advanced lymphoblastic lymphoma
2	Brandalise SR, Viana MB, Pinheiro VR, Mendonça N et al., *Front Pediatr*, (2016) [45]	EFS at 15 years - Group 1 (18 months): 65.8±2.3%; Group 2 (24-month): 66.3±2.3%	Six month shorter duration of MT in ALL children had same overall outcomes as compared to 2-year regime
3	Schrappe M, Möricke A, Reiter A, Henze G et al., *Klin Padiatr*, (2013) [46]	10-year probability of disease-free survival (pDFS) - Group 1 (24-month): 0.78; Group 1 (18-month): 0.70	Shorter MT regime did not prove to as effective as the 24 months
4	Schmiegelow K, Al-Modhwahi I, Andersen MK et al., *Blood*, (2009) [47]	Among 427 thiopurine methyltransferase wild-type patients, those who received higher doses of average 6-MP developed second malignant neoplasm (SMN) as compared to remaining patients	The intensity and duration of MT may influence the risk of SMN in childhood ALL
5	Schmiegelow K, Heyman M, Gustafsson G et al., *Leukemia*, (2010) [48]	Adolescents received lower 6-MP and MTX doses compared to non-adoloscent during MT	The risk of relapse for adolescents with ALL may be associated with compliance to MT
6	Mahoney DH Jr, Camitta BM, Leventhal BG et al., ,*Cancer* (1995) [49]	Estimated 4-year EFS was 66% and was comparable to prior paediatric oncology group protocols	Low dose MTX therapy may be less effective in preventing relapse than higher dose during MT
7	Schmiegelow K, Björk O, Glomstein A et al., *J Clin Oncol.*, (2003) [36]	The relapse risk was 5% in the control group and 19% in the pharmacology group for girls during MT. Relapse risk was not different in pharmacology and control group for boys	Pharmacologically guided treatment to intensify dose with respect to blood counts may not be warranted for girls. For boys, new methods to optimise MT may be required
8	Brandalise SR, Pinheiro VR, Aguiar SS et al., *J Clin Oncol.*, (2010) [50]	Continuous administration of 6-MP/MTX: Overall Survival (OS) - 91.4% +/- 2.2%; EFS 80.9% +/- 3.2%. Intermittent administration of 6-MP/MTX: OS- 93.6% +/- 2.1%; EFS 86.5% +/- 2.8%	The intermittent use of 6-MP and MTX during MT is less toxic, with better EFS. Intermittent schedule for boys had significantly better EFS as compared to girls
9	Veerman AJ, Hählen K, Kamps WA et al., *J Clin Oncol.*, (1996) [51]	At 8 years, EFS rate - 81%; Survival rate - 85%	For children with non-high-risk ALL, the combination of IV medium high-dose methotrexate, triple intrathecal therapy in the first year of MT, and the use of dexamethasone for induction and pulses during maintenance treatment proved to be effective for prevention of central nervous system relapse

Continued on next page

Table 2.2: *Continued from previous page*

Sr. No.	Reference	Results	Conclusion
10	Lobato-Mendizábal E1, Ruiz-Argüelles GJ, *Rev Invest Clin*, (1990) [52]	5 year disease free survival for children receiving full doses of 6-MP/MTX was 65% as compared to 7% for children receiving suboptimal doses during MT	Suboptimal maintenance chemotherapy, due to bone marrow toxicity is an adverse prognostic factor for outcome in treating children with ALL
11	Koizumi S, Fujimoto T, *Int J Hematol.*, (1994) [53]	The 10 year EFS - Intermittent cyclic regimen: 65.4%; Conventional continuous regimen: 36.1%. EFS rate for 811 protocol (1981-1983) - 41.4%, 841 protocol (1984-1987) - 51.4%, 874 protocol (1987-1990) - 54.4%.	Standardized MT should include cyclic administration of intermediate doses 6-MP an MTX
12	Pearson AD, Amineddine HA, Yule M et al., *Br J Cancer*, (1991) [41]	Patients with low 6-MP doses because of neutropenia and those who randomly were prescribed higher MTX doses had a low rate of relapse after the cessation of MT	Prescribing maximally tolerated doses during MT may be associated with an increased survival rates in childhood ALL
13	Schmiegelow K, Nielsen SN, Frandsen TL et al., *J Pediatr Hematol Oncol.*, (2014) [23]	-	Patients receiving suboptimal MT after tolerating starting anti-metabolites doses had poorer outcome as compared to patients with reduce and upwards dose adjustment to achieve myelosuppression
14	Relling MV, Hancock ML, Boyett JM et al., *Blood*, (1991) [21]	Children with cumulative 6-MP dose intensities of 85% had better EFS as compared to children with cumulative 6-MP dose intensities of 70%	Children with higher intensities of 6-MP doses had better EFS as compared to children with low doses of 6-MP
15	Chessells JM, Harrison G, Lilleyman JS et al., *Br J Haematol.*, (1997) [20]	EFS - 634 children with at-least one neutropenia episodes: 75%; 104 children with no neutropenia episodes: 61%	Early intensification of treatment may influences the probability of occurrence of neutropenia and that patients exhibiting myelosuppression have a better chance of prolonged remission during MT
16	Benigna Maria de Oliveira, Maria Thereza Macedo Valadares, Marcilene Rezende Silva et al., *Rev Bras Hematol Hemoter*, (2011) [43]	EFS - Children with MT suspended for a period of more than 2% of the total duration of therapy: 80.3% ± 5.1%; Children with MT suspension for a period of less than 2% of the total duration of therapy: 33.3% ± 13.6%	Adherence to treatment protocols contributes to better treatment results in children with ALL
17	Schmiegelow K, Schrøder H, Gustafsson G et al., *J Clin Oncol.*, [54]	Children with higher values of product of mean erythrocytes MTX (E-MTX) and erythrocytes thioguanine (E-TGN) nucleotides values had higher EFS as compared to low values of product mean E-MTX and E-TGN values	Optimal use of MTX and 6-MP along with its pharmacokinetics information could result in the more cure for children with ALL

2.4 Challenges in Addressing Paediatric ALL Treatment in India

2.4.1 Collaboration and Uniformity in Treatment

According to a study, in 2011, by Kulkarni et al. - over the past four decades, only fourteen studies have reported on ALL treatment in India [11]. Only one successful attempt saw three centres participating and carrying out uniform treatment procedures [55]. In India, out of eight centres that carried out studies on ALL, Tata Memorial Hospital, Mumbai (TMH), alone contributed five studies out of fourteen (4 - stand alone and 1 - multi-centred) evaluating their practice.

Lessons learnt from several studies from TMH have shown improvements in cure rates as compared to other hospitals in India [11] [10]. Two recent studies reporting on survival outcomes, have emphasized on the need for collaborative trials, to determine the standard treatment for paediatric ALL in India [56] [57].

2.4.2 Standard/Modern Treatment

Outcomes in childhood ALL now approach 90% in North America, Europe, and Oceania [7] [8]. This has been achieved with administration of drugs that have been in use, since the 1960s. A key contributor to improved outcome is the introduction of risk-stratified treatment. Risk stratified treatment, involves the use of clinical features at presentation, lymphoblast genetic characteristics, and assessment of early treatment response, to identify children who will require low, moderate, or high intensity chemotherapy, to achieve cure. In the absence of specialised laboratory tests for risk stratified treatment, children in India have been administered

all-purpose therapy of moderate or high intensity. This resulted in excess toxicity, including treatment-related deaths, compelling clinicians to de-intensify critical elements of therapy, which in turn, results in higher rates of relapse. Some of the studies from India have proposed to inculcate modern risk stratification methods [57] [58]. Researchers have also cautioned about treatment toxicity, as a result of deaths [10] [59].

Also, treatment for ALL has been based on institutional protocols, and were not uniform across treatment centres. Further, treatment protocols used at institutions are based on published treatment regimens, which are no longer contemporary. The studies reported in [11] used standard or modified treatment protocols implemented in western countries, where cure rates are high. Berlin-Frankfurt-Münster (BFM), MCP and United Kingdom (UKALL) were the baseline ALL treatment protocols used with MCP, being most common. This non-uniform practice has also resulted in disparity in treatment outcomes and cost.

Several clinicians through their experience in treating ALL patients have focused on the need to adapt new and modern treatment specific, to scenarios in India [57–60]. The ICiCLe initiative attempts to address these disparities, by introducing contemporary risk-stratified therapy as part of a collaborative multicentre treatment protocol, involving major childhood cancer centres in the country.

2.4.3 Accessible Treatment

Further, access to the treatment by patients, deficit of specialized treatment centres, supportive care and financial burden, poverty, and illiteracy have hindered the cure rates in India [56, 57, 60]. Adding to these factors, socio-economic circumstances, treatment disbelievers, alternative therapy,

and environmental determinants lead to abandoning treatment and follow up, in the Indian setup [56] [61]. Delay in diagnosis because of lack of disease knowledge, education, and limited access to primary cancer centres, does not help. Chandy in 1995 proposed a theory to provide individualized therapy to ALL patients in three-tier society by dividing patients based on socio-economic factors of education and income [62]. Menon et al. recommended the idea of - ""twinning" between specialized centres in India and peripheral hospitals". This aimed to create a network to make ALL treatment more accessible for children [63].

2.4.4 Information Gathering

Specific data registries are lacking in the Indian medical set-up for reporting any kind of clinical studies. Aggregating trial data in one place is the need of the hour in India for paediatric ALL [10] [62]. For specific and common childhood diseases like ALL, where multi-fold treatment avenues are untouched, having all the treatment specific information stored and accessible is essential. At one go, such mechanism would give an opportunity for clinicians to achieve better cure rates, and researchers to explore new directions.

2.5 Clinical Decision Support Systems

Clinical decision support systems (CDSSs) are computer based programs that assist health care practitioners in decision making. Over the years, CDSSs were developed with specific purposes such as drug event monitoring, nutrition dosing, antibiotic prescribing, laboratory reporting and alerting, assisting diagnostic services, and documentation support in

clinical settings [64].

2.5.1 CDSS Architecture

The foundation of a CDSS is based on the knowledge base and clinical data. Access to clinical data by a CDSS is achieved with the help of human interaction or electronic medical records. The inference engine or agent, process the clinical data with the help of the knowledge base to solve the given problem. Different researchers give different names to the modules of the CDSS they build. But the underlying functionality of the majority of the modules remains the same [65] [66]. With reference to [65] [66], we present a generic architecture of a CDSS in Figure 2.3 followed by an explanation for each of the components.

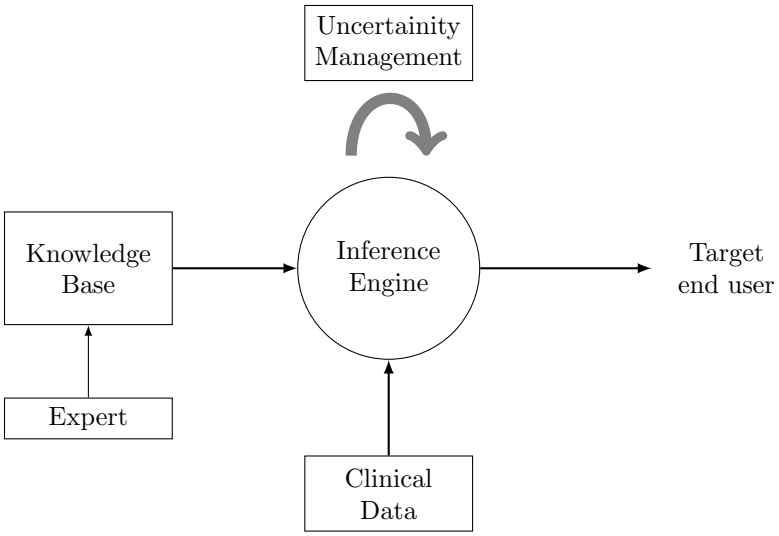


Figure 2.3: Generic Model of CDSS

1. **Clinical Data**: For a CDSS to be functional, it needs clinical data. Source for clinical data may be electronic health records, treatment history, clinical characteristic data, or data entered by a physician

or patient. Depending upon the clinical setting, clinical data may be directly provided to the CDSS or manually entered into the CDSS.

2. **Knowledge Base**: The knowledge base is a standard collection of medical domain knowledge. It is developed with the help of experts or following clinical guidelines. It can be updated as per the requirement of the problem.

3. **Inference Engine**: Once the clinical data is fetched by the system, the inference engine processes it with respect to the knowledge base. The inference leads to generating advice or recommendations, or conclusions depending upon the nature of the design of the CDSS.

   Similar clinical problems may demand different strategies and solutions. This may lead to uncertainty in interpreting clinical data of such problems and needs to be addressed carefully. An uncertainty module would strengthen the working of a CDSS.

4. **Target End User**: Who the end target user is depends upon whether the CDSS is integrated in the clinical environment workflow, or used as a stand-alone system. In case, the CDSS is integrated into the workflow, intermediaries like nurses or electronic health records may use the CDSS instead of the target physicians. Target clinicians, as end users, may use a CDSS in a stand-alone setting directly.

2.5.2 CDSS Features

The clinical effectiveness of a CDSS varies greatly due its design, functionality, and use. A comprehensive evaluation of technical requirements, clinical workflow, and context, are essential to build a CDSS. Sim and

Berlin proposed characterization of CDSS design and functionality, based on the following: (1) context, (2) knowledge and data source, (3) decision support, (4) information delivery, and (5) workflow [67]. Figure 2.4 shows CDSS's features, each of which are discussed below:

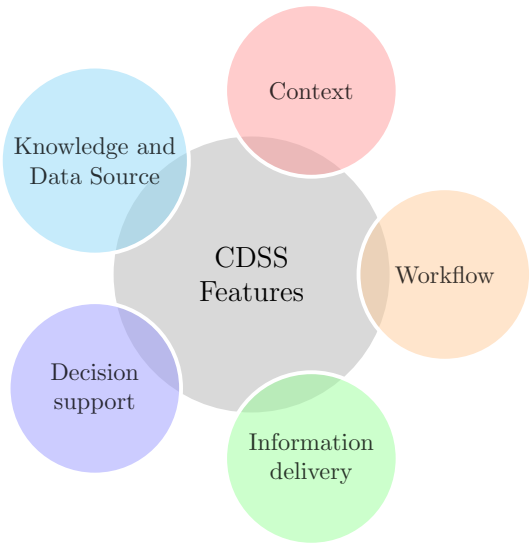


Figure 2.4: Features of a CDSS

1. **Context**: In a clinical setting decision making varies from context to context. In patient or outpatient settings where a CDSS is used, should be known. Understanding which clinical task it accomplishes such as screening, diagnosis, follow-up or assessment is necessary. Finally, the context and the task of a CDSS, influences the clinical work flow.

2. **Knowledge and Data source**: Once the context of a CDSS is known and evaluated; the underlying knowledge of the CDSS is built. The knowledge source for a CDSS is clinical knowledge from established guidelines or experts. The system may have a free a text inputs, or coded inputs, according to a well-established clinical cod-

ing scheme as a representation of the data formats. The challenges present here is the customisation of the evidence base.

3. **Decision support**: Decision making is based on the reasoning method, built into the CDSS. Several reasoning methods have been used in implementing a CDSS such as rule based methods, Bayesian methods, and neural networks [67]. The time taken for decision making by the CDSS is a major factor influencing usage, along with the ease to execute the explicit recommendations suggested by the CDSS. The presence of an interactive response provision, also helps in user compliance.

4. **Information delivery**: As important as decision making is, delivering the information in the right format is fundamental. The delivery mode of the information can be a solicited or unsolicited recommendation with respect to the delivery point of information. A good CDSS needs an interactive and explanatory advice delivery system. Simple and minimal actions, may be integrated to complete the recommended actions by the information delivery system.

5. **Workflow**: While the development process of a CDSS is ongoing, the target or end decision maker, should always be considered such as physician, nurse, generalist, or specialist. At-last the CDSS should be compatible with the institution's workflow, in order to achieve maximum usage and clinical effectiveness.

In order to develop a CDSS, the features or characteristics on the basis of which it is built, should be analysed critically. The adoption of the above characteristics to build a CDSS would deliver an effective system. Shortliffe and Sepúlveda, express similar concerns about building

a successful CDSS [68]. They emphasized transparency in functionality, time efficient, complexity, relevant understanding of the domain, delivery of knowledge, and strong scientific foundations in terms of usability, safety, validity, and reliability.

2.5.3 Reasoning Methods in Decision Support

The heart of decision making, or decision support, in a CDSS is the reasoning method. The reasoning or inference methods used depend upon the nature of the knowledge base, data source, and the intended use of the CDSS. A review by Stojkovska and Loskovska presented common reasoning methods used in CDSS [69]. We present a few of the reasoning methods below:

1. **Rule-based reasoning**: Rule representation in the form of conditions and actions is the mainstay of this reasoning method. Conditions and actions are encoded by the means of IF-THEN-ELSE statements [70]. IF represents a condition on which the incoming data of the CDSS is evaluated. THEN represents an action to be taken for respective IF conditions. An array of such IF-THEN statements are present, representing the clinical knowledge and outcomes or decision to follow. The queried or incoming data for CDSS, will satisfy one of the IF conditions and trigger a THEN action. In case, no condition is satisfied, the end user gets notified accordingly. There are two types of IF-THEN rule base systems, forward chaining and backward chaining.

2. **Case-based reasoning**: Case-based reasoning comprises of a problem, solution, and its results. The life cycle of a case-based reasoning

system has four major steps: (1) retrieve, (2) reuse, (3) revise, and (4) retain [71]. Whenever, a new problem is presented to a case based reasoning system, a match is *retrieved* from the repository of previous cases, to find the most similar case based on domain knowledge.

The case is matched and evaluated on basis of the degree of similarity. This leads to an estimate on the extent of *reuse* of the previous solution of matched cases for the current case. The most relevant solution is *revised* by adapting in terms of testing and repairing the solution. The tested solution is presented as the final solution to the asked case problem. Thereafter, the new processed problem with its solution is *retained* in the case repository for future use.

3. **Probabilistic or Bayesian reasoning**: The field of medicine, many a times works with a degree of uncertainty. Managing the degree of uncertainty comes from previous knowledge gained through years of experience. In a probabilistic or Bayesian reasoning [72] system, the degree of uncertainty is evaluated with the help of probability. The queried problem is evaluated for the evidence from the knowledge base. This is done by computing the probabilities given the occurrence of another event or the condition, from the knowledge base [72].

4. **Machine Learning**: The modern CDSSs developed by many researchers and service providers, are based on machine learning. This reasoning method relies on a learning model. The ground truth clinical data is modelled and made to learn with the help of machine learning techniques or statistical reasoning. The learning of clinical data is divided into two types: (1) supervised learning - clinical data

is mapped with clinical decisions, and (2) unsupervised learning - clinical data has no mapping and the model needs to infer on its own [73].

2.6 CDSS in Paediatric Setting

In paediatric settings, the purpose of CDSSs are similar to the purpose in other clinical settings [74]. Several paediatric clinical settings, have used CDSSs to deliver paediatric specific guidance on care with the help of alerts, computerized provider order entry (CPOE), order sets and clinical practice guidelines [75] [76]. ISABEL, a paediatric CDSS for diagnosis was developed and used suggesting 15 diagnoses for a set of clinical features [76]. MEDITEL, Quick Medical Reference, DXpIain, Iliad and PEM-DXP were other diagnostic CDSSs developed in late 80's for paediatric settings [75].

CDSS support for medication prescribing in the paediatric setting was found to be beneficial in a review study. The study evaluated various modules of CDSS such as CPOE, medication dosing calculators, decision support for medication dosing, order sets, and alert overrides tools that provided treatment and therapeutic recommendations to the physicians [77].

2.6.1 Chemotherapy Medication Errors and CDSSs

Chemotherapy is one of the areas prone to medication errors due to its complexity in any clinical settings [78] [79]. Weingart et al. pointed out that chemotherapy errors occur at the rate of one to four per 1000 orders, which affect 1-3% of oncology patients. The increasing use of oral chemotherapy regimes in various cancer care treatments, pose novel

safety challenges. Implementation of safe practices and standard guideline, and assistance from information technology, could potentially reduce chemotherapy errors [79]. The chemotherapy drug doses are computed based on body surface area, height, and weight of the patient. The drug doses may change over the course of therapy, based on treatment protocol. Such variations and complexity, adds to the inherent problems of medication errors [80].

Oral chemotherapy is prone to medication errors. Oberoi et al. evaluated prescriptions and administered oral chemotherapy drugs in an outpatient setting for children with ALL in India. They concluded prescribing errors of 4.5% per prescription, and 7.4% per patient [81]. Further, administration error was 7.3% per prescription and 14.8% per patient where medication errors wered present.

During a two-month study, Taylor et al., analysed chemotherapeutic medications of 69 ALL children with 172 prescriptions. More than one error, occurred in 17 (9.9%) medication prescriptions, out of which 12 (7.0%) were administration errors while 5 (2.9%) were prescribing errors [82]. Medication errors in terms of prescribed chemotherapy drugs and observation of administration of drugs at home, were computed from 92 home visits for children with leukaemia [83]. As many as 72 errors were detected upon review of the records and observations.

To reduce medication errors by physicians utilization of a CDSS would add value [84] [85]. Rahimi et al. carried out a systemic review to assess effects of chemotherapy prescription using CDSSs on the chemotherapy process [86]. The author reported 3 studies with impact on compliance with chemotherapy protocols. Of these 3 studies, one study had negative effect on compliance with treatment plan, whereas the other two improved

the compliance rate. The review concluded that reduction in medication errors specifically dosage errors, along with time taken for chemotherapy processing, when specifically designed CDSSs for chemotherapy process were used.

2.6.2 LISA: a web-based decision-support system for trial management of childhood acute lymphoblastic leukaemia

Of the 3 studies reported by [86] showing positive impact on compliance on chemotherapy protocols; I would like to discuss one paper relevant to our work, the article by authors Bury et al. who developed a web-based decision support system, to assist physicians in prescribing oral chemotherapy medications during MT in ALL treatment [87].

LISA - Leukaemia Intervention Scheduling and Advice was a decision support system developed and tested for a nationwide clinical trial - UKALL R3. The development of LISA started by developing the knowledge representation with the help of PROforma technology. The various combinations of oral MTX and 6-MP doses, that are prescribed to a child during chemotherapy, were identified and modelled.

An interface to enter haemoglobin, WBC, ANC and PLC values was developed. Upon entering the CBC values, the CDSS would provide a combination of 6-MP and MTX doses, to be prescribed to the child. A context specific justification, a link to the therapy protocol, and clinical guidelines, and a dose calculator window with rounding off of doses was provided. Users were able to override the decision in case required.

Subjects from different institutions were invited to test the system. Time taken to reach dosing decisions was faster for novice subjects. It did

not increase the speed of decisions for experts. When they calculated 144 dosing decisions without the LISA CDSS, there was an error of nearly 23% (33/144). Non-intentional deviation from the protocol occurred 22% of the time, in 32/144 decisions. With LISA, there were no dosing calculation errors or deviation errors from the protocol.

The major highlight of this system was the potential to reduce chemotherapy errors pertaining to calculations and protocol interpretation. Along with this, the time taken to arrive at dosing decisions could make less expert physicians more efficient. Dose adjustments during MT are prone to errors, and uniform physician compliance with the protocol are issues discussed earlier. In view of this, a system similar to LISA in the Indian settings could be beneficial.

The inherent problem of oral chemotherapy in the form of medication errors poses a continuous challenge. A systematic approach to dose calculations and prescribing, could potentially decrease errors. Understanding the clinical guidelines and protocols for dose adjustment, is the first step. Assistance in schematically showing how a medication should be administered, along with the use of a CDSS, may address the problem of medication errors and physician compliance, to dose adjustment protocols.

Chapter 3

Study Setting

This chapter presents details on the study setting, ethical clearances, and study design.

3.1 Study Setting

This work was carried out at Tata Medical Center Kolkata West Bengal, India and Tata Translational Cancer Research Center Kolkata West Bengal, from March 2017, to October 2018. Tata Medical Center, Kolkata (TMCK) is a specialized tertiary care oncology center for eastern India. Tata Translational Cancer Research Centre (TTCRC) is a part of TMCK which focuses on translational research for cancer care in India.

Recently, a retrospective analysis study of flow cytometry based immunophenotyping and genetics data extracted from January 2014 to August 2017, by the flow cytometry laboratory at TMCK was carried out [88]. The authors reported 631 cases of newly diagnose acute leukaemia out of which 334 (52.9%) were ALL. Children <15 years of age with ALL, accounted for 197/334 (58.98%) cases. Most children had B-ALL - 85.78% (169/197) - whereas T-ALL, accounted for 14.21% (28/197) of cases in chil-

dren. While the majority of children with cancer enrolled at TMCK are from West Bengal, and the neighbouring states of Bihar, Jharkhand, and Odisha, there are children also coming from the neighbouring countries of Nepal, Bhutan, and Bangladesh.

3.1.1 ICiCLe-ALL-14/INPOG-ALL-15-01 clinical trial

TMCK and TTCRC are the coordinating centre for ICiCLe-ALL-14/INPOG-ALL-15-01 clinical trial. ICiCLe ALL-14 is a collaborative, multi-centred national, randomised open label phase IV study [33] [13]. It is an intervention trial with a primary aim to standardize ALL treatment across India, and improve outcomes for children with ALL in India. For standard risk, and intermediate risk stratified children, under the age 10 years, randomization is carried out by decreasing the duration of steroids from 5 to 3 weeks, in the test arm. The primary aim with the randomization is to show a decrease in toxicity in the low dose arm [33].

Initially, an in-house study titled - *"ICICLE-1 Study"* was registered at TMCK. Amendments were made to the ICICLE-1 Study and multiple centres started to participate in the study. The study was renamed as ICiCLe-ALL-14 in 2014. In 2016, with more centres across India participating in the study, ICiCLe-ALL-14 was adopted under the Indian Paediatric Oncology Group (In-PoG) [12].

The collaborating centres across India are: All India Institute of Medical Science, New Delhi; MAX Super-speciality, New Delhi; Post Graduate Institute of Medical Education and Research, Chandigarh; Tata Memorial Centre, Mumbai; Tata Medical Center, Kolkata; and Adyar Cancer

Institute, Chennai. All the children diagnosed with ALL at TMCK are registered under the ICiCLe-ALL-14 clinical trial.

3.1.2 Information Recording System for Maintenance Therapy at TMCK

Following completion of induction and consolidation, children undergoing maintenance therapy have two options in terms of follow-up for MT: 1) visit the TMCK MT clinic every 2 weeks (Figure 3.1: arm A) or 2) e-mail the CBC reports to the TMCK MT management team every two weeks (Figure 3.1: arm B). All children would have to come in to TMCK for intrathecal methotrexate once every 12 weeks, as part of the MT protocol.

Children along with their parents from nearby areas, were able to visit TMCK bi-weekly. Children who stayed far away in different states or neighbouring countries, used to e-mail the CBC reports, and physicians e-mailed back the weekly dosage advice.

Figure 3.1 depicts the work flow for children undergoing MT at TMCK.

Access and ability to view the MT information for any child at one go, is essential for physicians because this contains blood profile information, along with drugs prescribed by the team for 96 weeks. It is crucial to record information in a systematic way.

Maintenance clinic information is recorded at two different places, with two separate formats, when patients visit the hospital (Figure 3.1: arm A). First, are the handwritten ***maintenance sheets***. Maintenance sheets are hand-written sheets used by the physician to record the information over a period of 2 years. These sheets are retained by families during the entire duration of therapy. Figure 3.2 shows a maintenance sheet used at TMCK

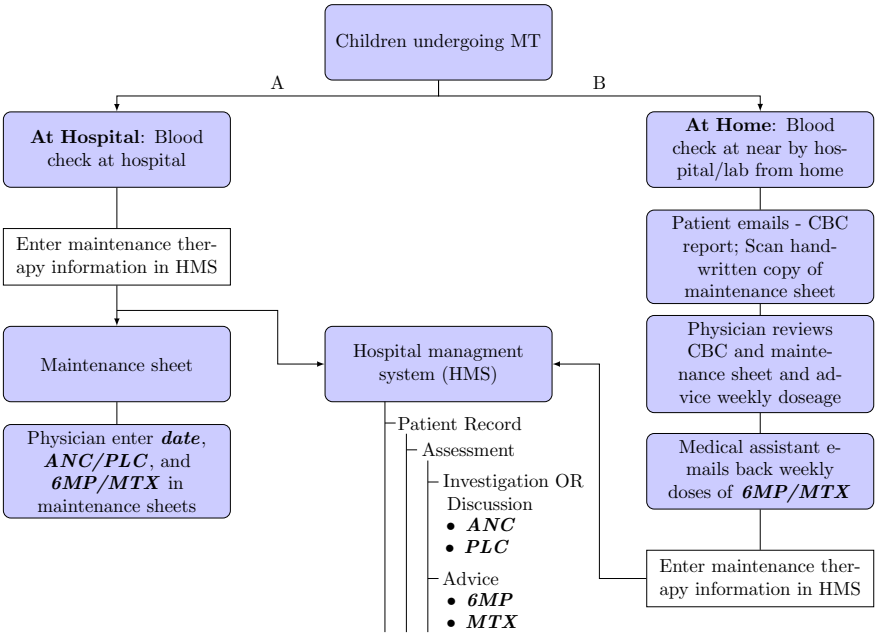


Figure 3.1: Flowchart describing maintenance therapy work-flow for children undergoing maintenance therapy at Tata Medical Center, Kolkata.

for recording MT information. There is no electronic access to these sheets so they are not available in the clinic for review.

Figure 3.2: Maintenance sheet used for recording information during maintenance therapy at Tata Medical Center, Kolkata.

Physicians fill maintenance sheets for children at each visit to the hospital with date of visit, absolute neutrophil and platelets counts, followed by weekly 6-MP and MTX doses, in respective cells of the sheet. Physicians also keep a note of week/date on which IT MTX was given in each cycle, and also of oral antibiotics. At the beginning of each cycle - cycle number of MT is noted down in the "Maintenance Cycle" field of the sheet. Other fields such as - Name, Date of Birth, and MR No, Patient Weight (kg), Patient Height (cm) and SA (m^2) are entered at the beginning of MT. Subsequently, updated height and weight are recorded at the beginning of each new cycle.

Simultaneously, the second approach, for that visit is a free text entry, made in the ***hospital management system*** (HMS). HMS at TMCK is an in house software system built by Tata Consulting Services, India, and is used to manage various hospital services including medical, administrative, and financial services.

There is no separate module for MT in the current HMS system. The entry made in the HMS is in free text, and includes the clinical examination in the assessment section, accompanied by the prescribed dose of 6-MP and MTX, and steps on how to consume the oral tablets throughout the week. The complete blood count done at TMCK is captured in a separate lab section in the HMS. The current visits absolute neutrophil and platelets counts are auto populated into the investigation section of the assessment sheet. If a child has blood work done outside of TMCK then the complete blood count including the ANC/PLC counts have to be manually entered by the physician. This is accompanied by prescribed dose of 6-MP and MTX, as well as steps on how to consume the oral tablets throughout the week, in the advice section of the assessment sheets.

In case, the children are not able to visit the hospital, CBC reports along with hand-written sheets are e-mailed to the maintenance clinic management team, by the children or their parents (Figure 3.1: arm B). On the next day of maintenance clinic, a team consisting of doctors and health care assistants review all the e-mailed CBC reports. The CBC report along with previous prescribed doses of 6-MP and MTX from the e-mailed hand written sheets or HMS, are checked to prescribe the new weekly dose, and e-mailed back to the children and their parents. Thereafter, a note of e-mailed ANC/PLC/6-MP/MTX values is made in the child's HMS record, in the assessment sheet.

3.2 Ethical Issues and Clearance

The Tata Medical Center-Institutional Review Board granted clearance for the ICiCLe study, reference number *EC/TMC/12/13* in October, 2013. The study is registered with the Clinical Trials Registry - India with reference number - CTRI/2015/12/006434 [13].

Additional ethical clearance for the retrospective cohort study from children enrolled in the ICiCLe-ALL-14 was obtained from the Institute Ethical Committee, of the Indian Institute of Technology Kharagpur in February 2019, with a reference number - IIT/SRIC/DR/2019; Appendix IV.

3.2.1 Consent

Once the children register for ALL treatment at TMCK, the clinical trials unit team members along with the physicians, and principle or co-principle investigator-tor of the ICiCLe-ALL-14 trial, explain the study to

the children and their parents. Children and their families are asked about their willingness to participate in the study. This included informing them about use of childrens' data related to treatment, diagnosis, and monitoring therapy, to carry out various research studies in order to develop better treatment strategies. Consent forms in English, Hindi, and Bengali are available for the children and their parents.

3.3 Retrospective Study of Maintenance Therapy at TMCK

We carried out a retrospective cohort study for the group of children who completed MT from February 18^{th} 2016, to September 27^{th} 2018 at TMCK. The data collection procedure started in July 2017, and continued till October 2018.

During this period several visits to TMCK were made for data collection, understanding MT, and the dose adjustment protocol. We were permitted to visit the maintenance therapy clinic which runs at TMCK every Thursday. The ICiCLe-ALL-14 protocol was studied with the help of expert physicians, to understand the rules for regulating MT. This helped us in understanding the maintenance therapy information, and aided in the data collection and analysis process.

3.3.1 Patient Selection for Data Collection

Prior to the development of our data collection procedure, we spent a lot of time with the staff of the MT clinic, to understand how data is collected, stored, and updated. Members of the clinical trial unit, assisting

the maintenance clinic, kept a note on children completing MT. The data managers checked on the children who would complete MT on a given MT clinic day. Thereafter, either data mangers or ourselves, approached the childrens' guardians for the hand written maintenance sheets, to convert them to digital form for our work.

3.3.2 Understanding the Dosing Decisions for Maintenance Therapy

Data was obtained from two sources: (1) handwritten maintenance sheets and (2) the hospital management system. Maintenance sheets had weekly or bi-weekly information on visit date, absolute neutrophil counts, platelet counts, 6-mercaptopurine and methotrexate doses. Access to hospital management system at TMCK, was granted to us to complete the data collection process. The entire data collection procedure is explained in the next chapter.

We reviewed the InPOG-ALL-15-01 (ICiCLe-ALL-14) protocol Appendix 14: "***Guidelines for anti-metabolite dosing during maintenance for all patients***" with the oncologists to understand the rules for regulating MT [33]. It became clear, that these guidelines are just a skeleton of the requirements for MT, and a detailed state diagram and flowchart would advance the requirement for uniformity, in dosing for MT. After many iterations with the oncology team dose adjustment rules for MT were designed, to build the automated dose advice method which is presented in Chapter 8.

Chapter 4

Objective 1: To Develop a Single Data Repository for Maintenance Therapy from Paper and Electronic Based Records

This chapter describes the methodology for data collection, information extraction, and data management to create a data repository for maintenance therapy.

4.1 Background

Before data collection began, we spent a lot of time understanding the work flow, of the maintenance therapy clinic. We discussed workflow with physicians, data managers, staff, and patients.

Maintenance therapy clinic at Tata Medical Center Kolkata (TMCK) is a stand-alone clinic dedicated for children undergoing MT. The clinic operates once a week. During the clinic, a team examines the child, assesses toxicity issues, adherence to medications, and reviews other health

complaints and makes sure the leukaemia is in remission.

A total of 223 children were treated for ALL at TMCK from March 2013 to October 2016. As of February 22^{nd} 2019, 212 out of 223 children had completed MT. Four children abandoned the treatment, and 5 were still in treatment. The status of 2 children is unknown. During the entire course of a child's maintenance therapy, several clinicians prescribed the 6-MP and MTX doses. The paediatric oncology group for ALL treatment at TMCK consists of 12-15 doctors, with different levels of experience and expertise. The group is comprised of consultants or senior physicians, fellows, and junior physicians.

We collected MT information for children who completed MT for ALL from February 18^{th} 2016 to September 27^{th} 2018. All the children were enrolled under the ICiCLe ALL-14 clinical trial. From January 4^{th} 2018 to October 25^{th} 2018, 41 maintenance clinics were conducted at TMCK. On average 44 children visited each clinic, which was being held on Thursdays. The number of children at each MT clinic was 38 to 49.

MT clinic comprise of children who have undergone induction and consolidation treatment for ALL at TMCK, and other children with ALL who may have undergone treatment elsewhere. In addition, there are also children who had relapse.

In the MT clinic physicians review longitudinal data for children using handwritten sheets. This process is time consuming and slow, and also found to vary in terms of completeness, of the information recorded.

4.2 Data Collection

As mentioned in the previous section, a total of 223 children were treated for ALL at TMCK from March 2013 to October 2016. As of February 22^{nd} 2019, 212 out of 223 children completed MT. We collected MT information for children, who completed MT for ALL from February 18^{th} 2016 to September 27^{th} 2018. All the children were enrolled under the ICiCLe-ALL-14 clinical trial. MT information for *56 children* was collected. Following are the sequential steps followed to collect the data.

STEP 1 - The Clinical trials unit (CTU) - a team responsible for management of "ICiCLe-ALL-14" clinical trial data, assisted us in the data collection process. Initially, the CTU team provided us with photo copies of hand-written sheets for 10 children who had completed maintenance therapy. Thereafter, the team used to intimate us during their routine check-ups on children, who would be completing maintenance therapy, and visiting the maintenance clinic. Subsequently, with the help of CTU team members, we collected 46 more handwritten sheets till October 31^{st} 2018. Sheets were photo-copied, or scanned after assent from parents, and returned back to them. Handwritten maintenance sheets were converted to a digital form. Personal identifiers of children was redacted, in order to maintain anonymity.

STEP 2 - Height, and weight of the child at the start of maintenance chemotherapy was extracted either from the digitized maintenance sheet or hospital management system.

STEP 3 - CBC reports, in the form of excel sheets, for each child

was extracted from HMS. These sheets included patient's date of visit to the hospital, ANC, PLC, WBC, and other CBC parameters. Python scripts were written to extract required information from the CBC reports. Specific information such as date of visit, ANC, and PLC was extracted for our work. CBC excel sheets were kept with us for future use. Additionally, we calculated cumulative week number from entire MT duration, cycle number, and week numbers in each cycle, with the help of semi-automated Python scripts.

STEP 4 - 6-MP and MTX prescribed doses were manually extracted from digitized maintenance sheets. These entries were compiled against the date of visit, ANC, and PLC entries from STEP 2. Now, the gathered data consisted of date of visit, maintenance week number, ANC, PLC, 6-MP, MTX, and IT MTX. This constituted the raw data for our work, which was further completed, by adding ANC, PLC, 6-MP, and MTX missing entries, found in digitized sheets.

STEP 5 - The problem of missing data emerged for visit date, ANC, PLC, 6-MP, and MTX in three situations: (1) in maintenance sheets during children's visit to the clinic, (2) in maintenance sheets in subsequent visit when the child did not visit the clinic in previous visit, and (3) in HMS when child or guardians had e-mailed the CBC reports. To solve the problem of missing entries, when the physician did not make a note in the hand written maintenance sheets or e-mailed counts, we used the HMS. Every visit's ANC, PLC, 6-MP, and MTX, whether blood count check done at the hospital, or e-mailed, gets recorded in HMS by the physicians. For each child, we checked the missing value of ANC, PLC,

6-MP, and MTX for a given date, when the child visited the maintenance clinic. Missing entries were noted down, if found.

STEP 6 - We, further, scanned the curated data to find either of the ANC, PLC, 6-MP, and MTX entries missing from our data set. The presence of visit date, ANC, PLC, and missing values of 6-MP or MTX on hand written maintenance sheet was due to the fact that blood count checks were done elsewhere. Physician forgot to record the doses in the HMS of that particular week, or on hand written sheets in the next visit to the hospital. In such scenarios, an assumption was made after discussing with physicians. For a given missing entry of 6-MP or MTX, we noted the previous recorded entry of 6-MP and MTX, given the admissible ranges of ANC and PLC counts.

STEP 7 - We also found multiple visit entries, which belonged to the same week. Occurrence of such entries were because a child may have visited the clinic twice or more in a week for medical problems, which may or may not have been due to MT. In these cases, MT medications were re-cheeked and re-prescribed, if required, and new entries were recorded in hand written sheets. After discussing with physicians, we considered the 1^{st} full entry, consisting of date of visit, ANC, PLC, 6-MP, and MTX and discarded the other values.

STEP 8 - For each child, we checked if all the entries are distributed within a time span of 4 weeks, in terms of visit date in the gathered information. We reviewed HMS, for the presence of a visit date entry, between two visit dates entries, with more than 4 weeks. Such entries

with all the maintenance data, ANC, PLC, 6-MP, and MTX were added to the data set. In case no entry was found, the entries were kept as it were.

STEP 9 - Finally, we included details of disease characteristic, treatment outcome, and treatment response for each child.

Figure 4.1 Flow diagram for data collection process for each patient from our cohort.

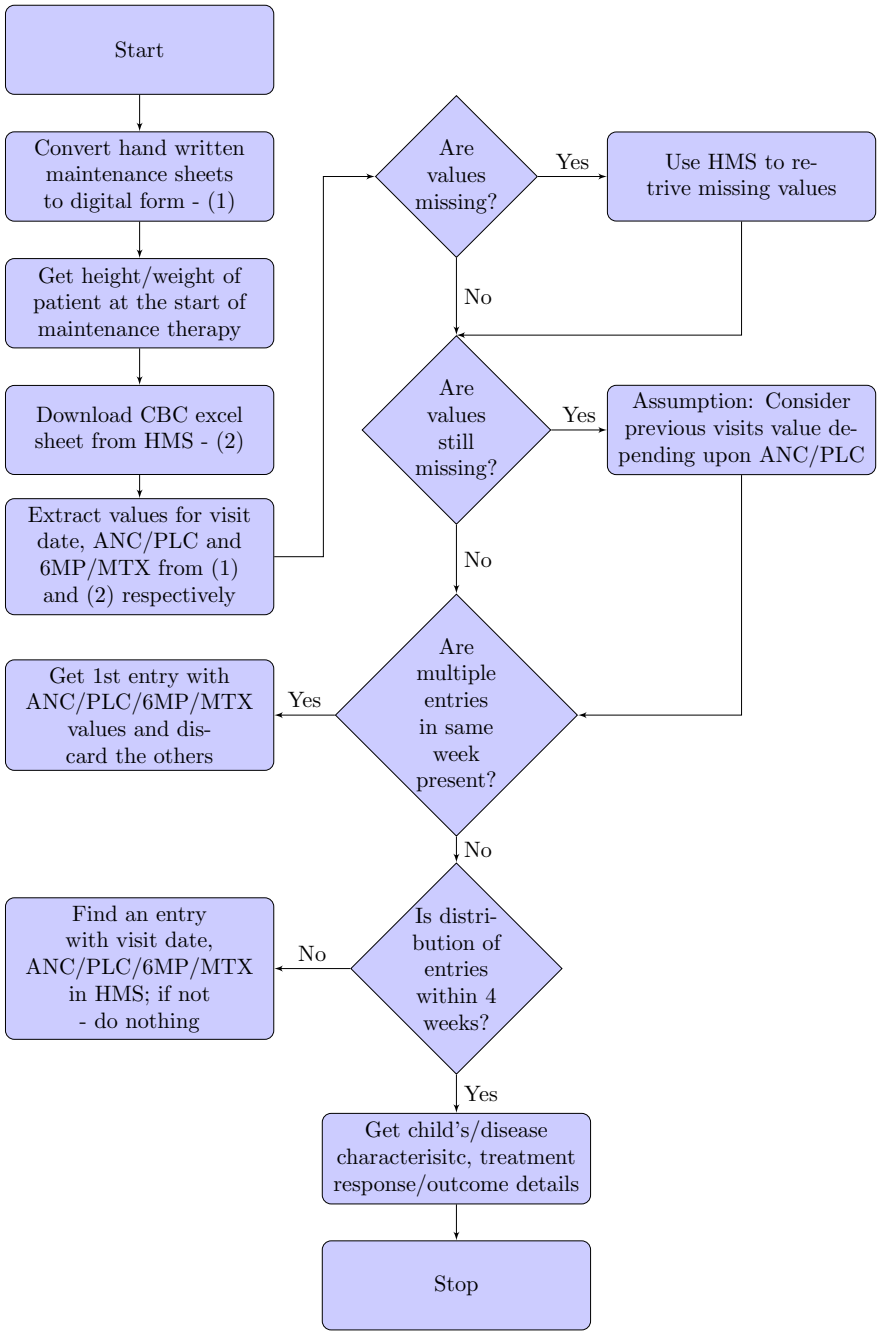


Figure 4.1: Flowchart describing data collection process for each child's maintenance therapy information in our cohort.

4.3 Data Management

To ensure correctness of collected information, a data verification processes was followed. Proof reading of entered data was done against the data from hand written sheets and digitized copies. Proof reading was re-done for the entered data against the HMS extracted data. TTCRC provided us with the HMS extracted data. We examined patient IDs for duplicates. Errors were removed by auditing blank, or negative entries and different date formats to establish completeness.

Hand written maintenance sheets, and scanned digital copies collected from the children included personal identifiers. Identifiers were masked by hand on the hand written maintenance sheet copies. We used Adobe Acrobat Pro software, version 10.1.16, to redact the personal identifiers on digital copies. This ensured anonymity. Anonymized digital copies were encrypted using password with the help Adobe Acrobat Pro software which was followed by archiving. Archived files were password encrypted for portability and storage purpose and future use.

For our work, the entire data was stored in CSV[†] format files. Data was entered manually or by semi-automated methods. Semi-automated methods would process the Microsoft excel or CSV sheet with some manual inputs, to extract the required data and store it in CSV format. Python. a high level programming language was used for creating semi-automated methods for our work. We used Python version 2.7.12.

[†]Comma-separated values (CSV) file format is a delimited text file format to store values. The values are stored in a tabular format with comma separated. Source: *https://en.wikipedia.org/wiki/Comma-separated_values*

4.4 Data Visualization

We documented blood work information along with the oral dosages of weekly 6-MP and MTX for the 96 weeks of chemotherapy. During the entire duration of MT it is not easy for any physician to look at the longitudinal data for a child, to monitor his or her therapy progress and the physician's dose adjustments. In such a scenario, it is convenient to have a visual representation to get on update on all ANC, 6-MP, and MTX values from the start of MT for the duration of the child's MT. We developed such a data visualization method.

The dose adjustment process for 6-MP and MTX is time dependent, with respect to ANC values. Physicians need to take into account the previous prescribed doses for current recommendation of doses. To visually inspect the MT data, we plot a line graph representing ANC, 6-MP and MTX against time in weeks. We also mark the indicators for ANC showing the target treatment range between which the ANC values should be maintained by the physician, by regulating the weekly 6-MP and MTX doses. This visual representation aids the physicians in monitoring all the dose adjustment decisions, which are based on ANC values.

4.5 Results

4.5.1 Data Description

We stored collected maintenance therapy information in CSV-format. For each child, MT information was recorded as a set the following parameters: patient id, height. weight, maintenance cycle, week number during each cycle, ANC, PLC, dose of 6-MP, dose of MTX and date of visit to

the hospital. Table 4.1 shows the fields with abbreviation used to store the information.

Table 4.1: Fields used for data collection process for each patient and their abbreviations.

Fields	Abbrevations
Patient Id	MR_Number
Height (in cm)	*ht*
Weight (in kg)	*wt*
Absolute Neutrophil Count	*ANC*
Platelet Count	*PLC*
6-Mercaptopurine	*6-MP*
Methotrexate	*MTX*
Date of Visit to Hospital	*date*

4.5.2 Visual Representation of Maintenance Therapy Information

We visually inspected the MT information. Figure 4.2 shows a visual representation of ANC with desired target range marked and prescribed chemotherapy schedules.

Figure 4.2 shows a visual representation of longitudinal information for 4 children from the cohort of 56 children who have completed MT. Y-axis represents three different parameters: ANC, 6-MP, and MTX. The numerical range for ANC and MTX varied from as small as 5 for MTX, to as high as 10,000 for ANC. To capture the small variations in prescribed MTX doses as well as the variations of ANC, we used log10 transformation on the y-axis. X-axis represented time in weeks for MT.

All the four children (A, B, C, and D) in the Figure 4.2 have completed the 96 week of MT. The upper left graph for the first child (A) is an example where the ANC values were within the targeted therapeutic range

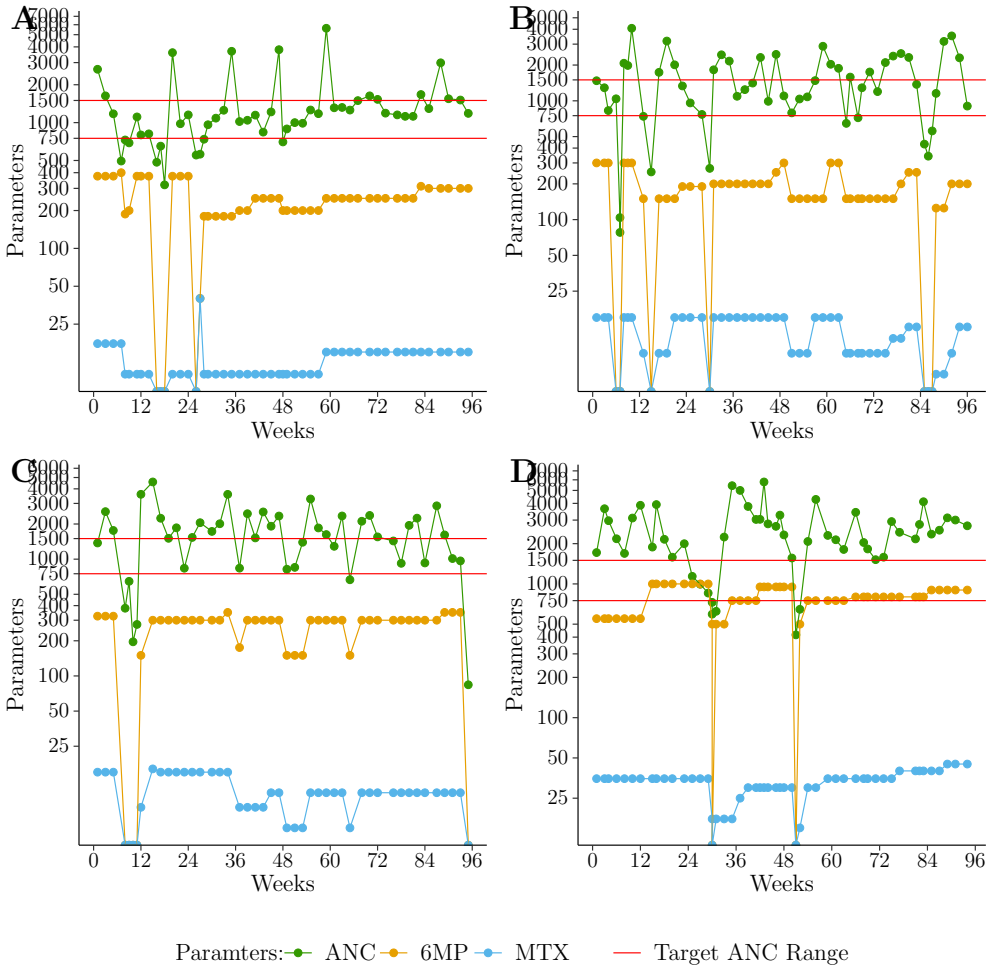


Figure 4.2: Line graph (A, B, C, and D) shows longitudinal information of MT for 4 children from the cohort over 96 weeks.

to sustain myelosuppression. However, the antimetabolites were not re-started with full capacity of 100% dose after the doses were halted near week 26. In graph B, the ANC values were within the target range nearly half of the time. Here, we can observe neither the doses were re-started at 100%, nor they were increased beyond 100% throughout the MT duration.

In addition to this, the doses were never increased beyond 100% dose throughout the treatment period. For child C, the ANC values were outside the desired range for most of the time with only two instances with dose

increase beyond 100%. For child D, although the patient had dose increase episodes, myelosuppression was not sustained with ANC values outside desired range throughout the treatment period.

The line graph may be considered as a very good representation of MT information to visualize MT progression for a child. The physician during every visit of a child, would be able to check on how ANC values have changed from the start of MT, with respect to the prescribed chemotherapy drugs.

4.5.3 Patient Characteristics

Maintenance therapy sheets consisted of longitudinal data for 96 weeks comprising ANC, PLC, 6-MP and MTX entries. The sheets were handwritten by the physicians on every child's visit to the hospital. Most of the children visited TMCK frequently and the rest followed up through e-mails. For 56 children, a total of 2,704 entries either for MT visits to the hospital, or e-mail were gathered. Each entry had maintenance cycle, visit date, ANC, PLC, 6-MP, and MTX. The median number of entries for each child in the cohort was 48.5 [IQR: 46-51].

The cohort of 56 children aged between 1.5-15.5 years with median age of 5.58 [IQR: 3.56-9.42] years. The minimal residual disease status was categorized into two groups based on the numerical definitions of blast cells. Positive MRD was defined as more than or equal to 1 blast cell in 10,000 cells (MRD positive: $>= 10^{-4}$). Negative MRD was defined as less than 1 blast cell in 10,000 cells (MRD negative: $< 10^{-4}$).

Initial risk stratification was based on the NCI Risk Group and based on WBC count and age of the child. This was followed by day 8 risk stratification, based on assessment after 7 days of steroids. Finally, stratification

at day 35 was done. It was based on the assessment after the induction phase of ALL treatment, which considers bone marrow remission, remission of bulky organs, and MRD status. Children were then classified into SR, IR, or HR. Regardless of the final risk group, every child underwent the same maintenance therapy protocol. Patients' characteristics are shown in Table 4.2.

Table 4.2: Characteristics of Children with ALL completing maintenance chemotherapy

	All Patients
Total Visits	2,704
Median (IQR)	48.5 (46-51)
Patients (N)	56
Male (%)	31 (55.35%)
Female (%)	25 (44.64%)
Age at Diagnosis (years)	
Median (IQR)	5.58 (3.56-9.42)
Presentation WBC Count (n=55)	
Median (IQR)	13.23 (9.4-39.5) x $10^9/L$
Lineage	
T-ALL	11
BCP-ALL	45
MRD Status (n=46)†	
Positive (>= 10^{-4})	5
Negative (< 10^{-4})	41
Risk Group	
Standard Risk	17
Intermediate Risk	17
High Risk	22
Relapse Status‡	
Yes	8
No	48

† 10 patients did not have MRD status because of T-cell Lineage. MRD status was not evaluated for T-cell lineage till March, 2018 at TMCK.
‡ Last follow-up status for treatment outcome till October 31^{st}, 2018.

4.6 Discussion

Maintenance therapy is an essential part of paediatric ALL treatment and the span of 2 years of MT, needs to be administered cautiously. Doctors, as well as children along with their parents, need to participate actively to carry out the treatment successfully. We observed and investigated the data recording problems faced at TMCK during MT for children.

Firstly, the data recording process in HMS is not prototyped or in order. Consultation, advice, CBC parameters, and prescribed dose is recorded in free text form. Moreover, there is no provision to observe the previous or longitudinal data for a child in one go. The physician needs to pull out records based on date of visit to the hospital, to check the MT information. As the chemotherapy dose regulation is time dependent, and based on ANC and PLC, a better choice would be to have an alternative, to extract the MT information during each child's check up by the physician.

Secondly, maintenance sheets are one of the best possible solution to record MT information. Recording the information on the sheets, requires diligence for meaningful inferences to be drawn.

The above mentioned second issue, leads to the problem of missing values, while we gathered retrospective information for our work. As mentioned, in the first issue, scattered information in the HMS was very tedious to extract from the patient's record in the HMS. We had to follow a set of actions in order to achieve completeness of information. One had to look up both HMS, and the maintenance sheets to get the information, which was a tiresome job. A potential solution to overcome such problems are (1) a separate module for MT in HMS and (2) automated system for recording information. The HMS module should have a specific format to

record the MT information which would ease the job of the physician. It would also bring uniformity in recording of the MT information by different physicians. Moreover, it would be simple and clear for new physicians to understand the work flow.

We introduce a new visualization method to monitor children's progress during MT. At a given point of time, physicians would be able to check how a child is responding to the prescribed chemotherapy drugs, during MT. This would also aid physicians to observe their dose adjustment regime, during the course of MT. It would save a lot of time for physicians in the clinic, as physicians need not go through the HMS records or MT sheets. We propose the integration of this visualization method of MT information, in terms of line graph with a HMS module for MT.

The data gathered from this data collection procedure had limitations. The children were not selected randomly from the cohort of 212 children who completed MT from March 2013, to October 2016. Children visited the hospital with their parents, either during MT or once every three months after completion of MT. Above this, every child had a different completion date for MT. Due to this, it was not possible to obtain the maintenance sheets randomly.

4.7 Conclusion

We gathered maintenance therapy information for a cohort of 56 children who completed MT by collecting records and accessing the HMS. The records were digitized, anonymised, and archived in order to ensure data security and confidentiality. Maintenance therapy information specifically ANC, PLC, 6-MP, and MTX doses, date of visit to the hospital, height,

weight for each child was extracted from the records and HMS. To collect the mentioned information a set of rules was adhered to achieve completeness of information. A visual representation in the form of a line graph is proposed, to aid physicians in monitoring a child's MT progression.

Chapter 5

Objective 2 - Retrospective Cohort Study of Children who Completed Maintenance Therapy from February 2016 to September 2018 (31 months) at Tata Medical Centre Kolkata to Understand Existing Dosing Practice and Toxicity

This chapter is a retrospective analysis of maintenance therapy from the cohort. This chapter is divided into two sections: 1) Section I - analysis of dose escalation and neutropenia events; and 2) Section II - analysis of dosing decisions during maintenance chemotherapy.

5.1 Analysis of Dose Escalation and Neutropenia Events

5.1.1 Background

Although more than 90% of children achieve remission during the induction phase of ALL treatment, MT is required for sustained remission [89–91]. A combination of oral 6-MP and MTX are prescribed over the two years of MT, to achieve complete remission. Dose adjustment is required during MT [15, 20, 36]. Dose adjustment of anti-metabolites are tailored to ANC or WBC. Adjustment may be to increase, decrease, continue, or halt the doses of 6-MP and MTX, based on the child's blood-work.

Cyto-toxicity is an unwanted secondary effect of 6-MP and MTX anti-metabolite therapy [92]. The intensity of the two anti-metabolite drugs are monitored carefully due to the risk of cyto-toxicity and immuno-suppression [93].

Anti-metabolite dose escalation needs to be carried out carefully to achieve optimal myelosuppression. Dose escalation, however, may result in toxicity or severe myelosuppression. *Toxicity or episodes of severe myelosuppression where* $ANC < 500 \times 10^6/L$ *is called severe neutropenia.* Severe neutropenia may lead to dose reduction or stoppage of the anti-metabolite drugs. Some groups advocate raising the anti-metabolites doses, with an aim to observe severe neutropenia episodes [21, 37, 94] because they argue that children with severe neutropenic events during MT, have decreased risk of relapse [22] [20].

The MT protocol defined in ICiCLe-ALL-14, recommends a starting dose of 60 $mg/m^2/day$ and 20 $mg/m^2/week$ for 6-MP and MTX respec-

tively [33]. Readjustment of anti-metabolites bi-weekly, based on ANC, is recommended to keep ANC values between $(750 - 1,500) \times 10^6/L$ for all children. Dose increase is recommended if the ANC is stable over an entire cycle or for $ANC > 1,500 \times 10^6/L$ at-least two times in six weeks. An increase in 6-MP dose is followed by a dose increase in MTX, either in two, or four weeks.

The idea during MT is to treat to tolerance by using the maximum tolerated dose. Physicians need to dose escalate, in order to find the maximum tolerated dose for the child. In view of this, the current part of this chapter investigates dose escalation episodes for the cohort, along with severe neutropenia episodes. We analysed the proportion of severe neutropenic episodes, across 8 cycles, in children who had a dose escalation, and compared them to children who had no dose escalation.

5.1.2 Methods

We retrospectively looked at a cohort of 56 children with ALL who completed maintenance chemotherapy from February 18^{th} 2016 to September 27^{th} 2018, at TMCK. During this period, the children in the cohort had a total of 2704 complete blood counts, which were available for analysis. In this section, we define and derive terminologies to analyse the dose escalation activity for the cohort.

We define severe neutropenia event, anti-metabolite dose escalation, and time to first anti-metabolite dose increase event as follows:

- ***Toxicity Event is defined as severe neutropenia***: For a given visit, if $ANC \leq 500 \times 10^6/L$.

- ***Anti-metabolite Dose Escalation Event***: Dose prescribed at

the first visit for the child was called the hundred percent (100%) dose. The *hundred percent anti-metabolite dose* was defined as the product of the hundred percent 6-MP and MTX dose. If a prescribed anti-metabolite dose at any given visit was more than 100%, an anti-metabolite dose increase event was noted. We give a small derivation below for the factor defined for anti-metabolite dose increase.

- ***Time to First Anti-metabolite Dose Increase Event***: This is defined as time, in weeks, taken to observe the first increase in anti-metabolite dose.

5.1.2.1 Derivation of Factor for Anti-metabolite Dose Increase

Next, we derive the factor for the dose escalation event. Let x, y, and z represent 100% or starting dose of 6-MP, MTX, and the anti-metabolite dose (6MP*MTX). Let δ be the operator denoting the change in any of the drugs prescribed, as compared to the drugs prescribed during the first visit for a child. We assume, δx and δy as the change in 6-MP and MTX dose. ***Dose Escalation*** or ***dose increase (DI)***, for 6-MP and MTX are defined as

$$DI_{6MP} = x + \delta x \tag{5.1}$$

$$DI_{MTX} = y + \delta y \tag{5.2}$$

We know that anti-metabolite dose is defined as the product of 6-MP and MTX. From equations (5.1) and (5.2), we may write dose increase for anti-metabolite dose as

$$DI_{6MP*MTX} = DI_{AnMtb} = (x + \delta x) * (y + \delta y) \tag{5.3}$$
$$= xy + \delta x * y + \delta y * x + \delta x * \delta y$$

z can be expressed in terms of the product of x and y; in other words $z = xy$. Therefore, equation (5.3) may be written as

$$DI_{AnMtb} = z + (\underbrace{\delta x * y + \delta y * x + \delta x * \delta y}_{\substack{\text{Factor for} \\ \text{Anti-metabolite Dose Increase}}}) \tag{5.4}$$

The equation (5.4) shows the factor by which the anti-metabolite dose increase may be considered.

The ICiCLe-ALL-14 protocol suggests incremental increase in 6-MP should be followed by an incremental increase in MTX but not simultaneously. So, on a given visit, we may have a change in either 6-MP or MTX. This means $\delta x = 0$ or $\delta y = 0$ has to be true for any given visit. This reduces the factor further to either $(\delta x * y)$ or $(\delta y * x)$. Considering the reduced factor, now, the dose may have an increment either for $(\delta x * y)$ or $(\delta y * x)$.

For our analysis, we consider the maximum of $\delta x * y$ and $\delta y * x$ for following reasons:

1. If there is an increase in z based on one of the factors - $(\delta x * y)$ or $(\delta y * x)$, comparing z with $z + maximum(\delta x * y, \delta y * x)$ value would be able to capture the incremental increase based on either of the factors.

2. Expert physicians, after analysing information collected on the cohort, hinted at a sub-optimal dose practice for the cohort. They also

indicated dose increase during a given visit was not up-to the required mark. The incremental increase in the doses of the anti-metabolites varied across all the children. To capture all dose increase of the anti-metabolites, expert physicians suggested to capture the smallest of dose increase.

Hence, we considered the least possible incremental increase factor of anti-metabolite dose for analysis. Once we find a dose increase record, we update z with the dose increase entry denoted as z_{new}. This value, z_{new} is then compared to $z_{new} + maximum(\delta x * y, \delta y * x)$. This iterative procedure is followed to capture all the dose increase episodes.

Next, we decide upon the values of δx and δy. Children were prescribed 50mg 6-MP tablets. The minimum quantity at times, suggested by the physician in the maintenance clinic, was one-fourth of the 50 mg table; that is 12.5 mg. For MTX, it was 2.5 mg. As a result, we considered *12.5* and *2.5* as change in dose of 6-MP and MTX doses respectively.

5.1.3 Results

Severe neutropenic episodes during maintenance therapy may occur due to dose escalation. We investigated dose escalation in the cohort.

5.1.3.1 Dose Increase

We divided the cohort into two subgroups: (1) **subgroup 1** - *children with anti-metabolite dose increase*– that is children with at-least one dose escalation episode– during maintenance therapy; and (2) **subgroup 2** - *children with no anti-metabolite dose increase*– that is children who had no dose escalation at all– during maintenance therapy. 45/56 ($\sim 80\%$) of

children had anti-metabolite dose increase while 11/56 ($\sim$ 20%) children did not.

We evaluated the median time to first dose increase for subgroup 1– children who had at least one episode of anti-metabolite dose increase during MT. We plot a time to event curve to observe the median time to dose escalation in Figure 5.1.

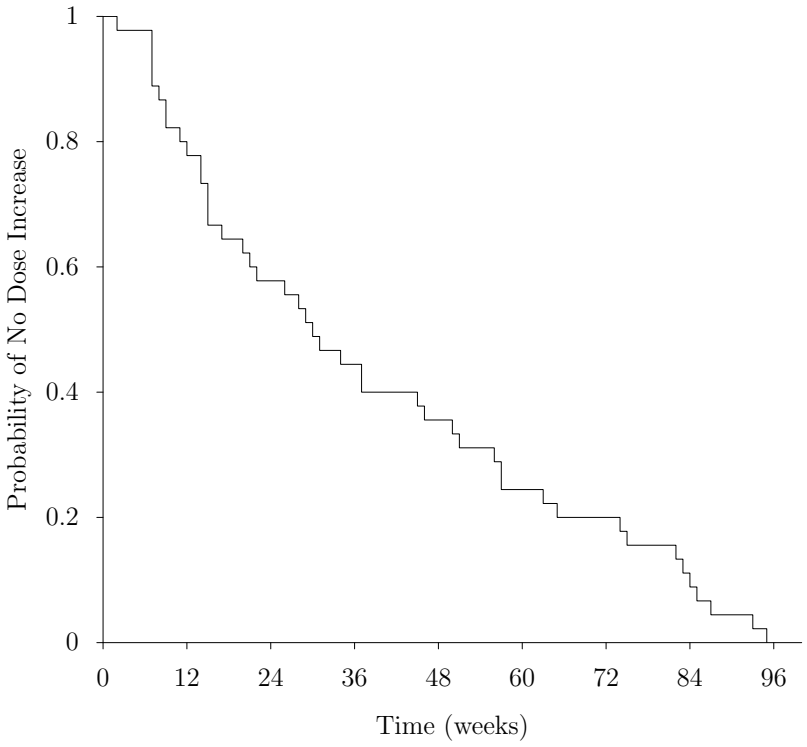


Figure 5.1: Time to first dose increase event in the group - anti-metabolite dose increase (n=45).

Recommended time to first dose increase is 12 weeks. It may so happen that the first dose increase occurs before 12 weeks, depending upon the treatment response by the child. With a conservative approach, by the end of cycle 1, or 12 weeks, there should be a dose increase episode. It is

however observed that the median time to first dose increase was 30 weeks [95% CI:20-51], that is during cycle 3 of MT for the cohort.

5.1.3.2 Toxicity Events

Next, we examined whether difference is observed in the frequency, duration, and timing of neutropenia events, in subgroup 1– children with at least one dose escalation of anti-metabolite– versus the subgroup 2, without anti-metabolite dose escalation.

In each the two subgroups, we computed episodes of occurrence of toxicity. Thirty four of 45 children ($\sim$ 75.5%) experienced severe neutropenia, in the dose-escalation subgroup, compared to 10 of 11 patients ($\sim$ 91%), in the no-escalation group. This difference was found not to be significant (p=0.42, Fisher exact test; Table 5.1). While not statistically significant because of the small sample size, the trend suggests that there may be something inherently different in children who did not have a dose increase, and still had severe neutropenia, possibly related to genetic polymorphisms in the way they metabolize 6-MP and MTX. This warrants further investigation with a larger sample sized powered to investigate this difference.

Table 5.1: Distribution of proportion of children experiencing/not experiencing severe neutropenia events for anti-metabolite dose increase/no increase group

	Anti-metabolite Dose Increase	**No Anti-metabolite Dose Increase**	**Total**
Severe Neutropenia Events (Yes)	34	10	44
Severe Neutropenia Events (No)	11	1	12
Total	45	11	56

We additionally observed the following:

1. **Frequency of severe neutropenia events**: In the dose-escalation subgroup, 69 episodes of severe neutropenia were observed in 45 children (1.5 episodes per child), compared to 28 episodes in 11 children (2.5 episodes per child) in the no-escalation subgroup.

2. **Timing of severe neutropenia events**: In total, there were 97 episodes of severe neutropenia events for the whole cohort, across 96 weeks. The median number of severe neutropenia episodes for the cohort was 2 [IQR:1-2] with a range of 0-9. We further distributed 97 episodes of severe neutropenia across 8 cycles of MT. Figure 5.2 shows a bar graph for the distribution of severe neutropenia events across 8 cycles of MT.

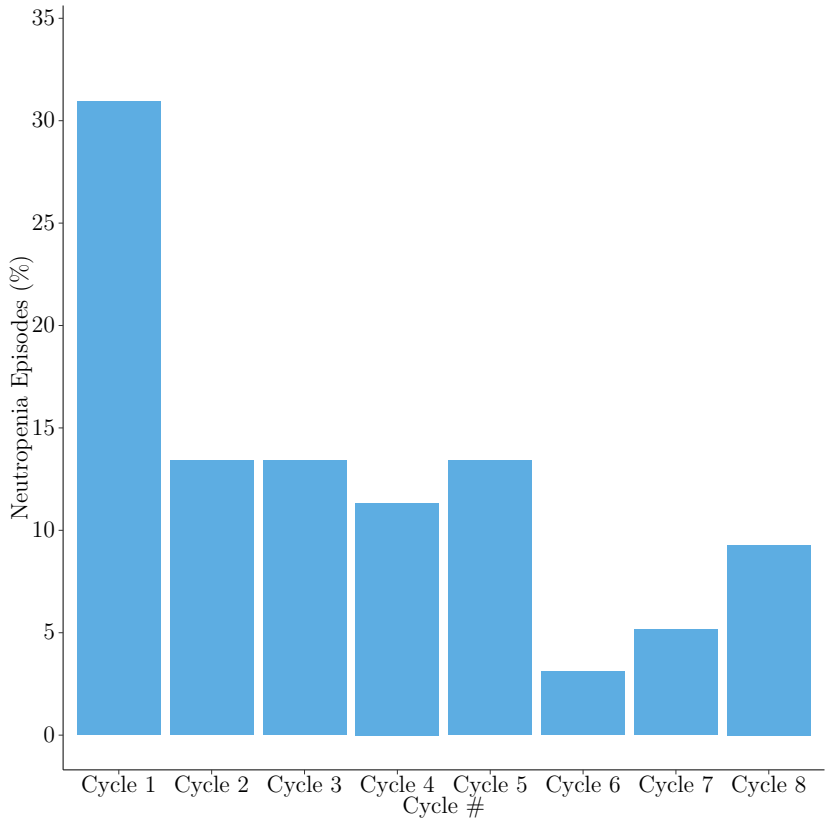


Figure 5.2: Distribution of severe neutropenia events across 8 cycles of maintenance therapy for cohort (N=56).

Around 30% of severe neutropenia events occurred during cycle 1 for the

cohort. Following cycle 1, the occurrence of severe neutropenia never increased beyond 13% in subsequent cycles.

We evaluated the occurrence of severe neutropenia episodes in subgroup 1 and 2 across 8 cycles of MT. Figure 5.3 shows severe neutropenia episodes by subgroup, across the 8 cycles. Severe neutropenia episodes were most frequent in cycle 1, in both subgroups and subsequently never rose beyond 18% in remaining cycles.

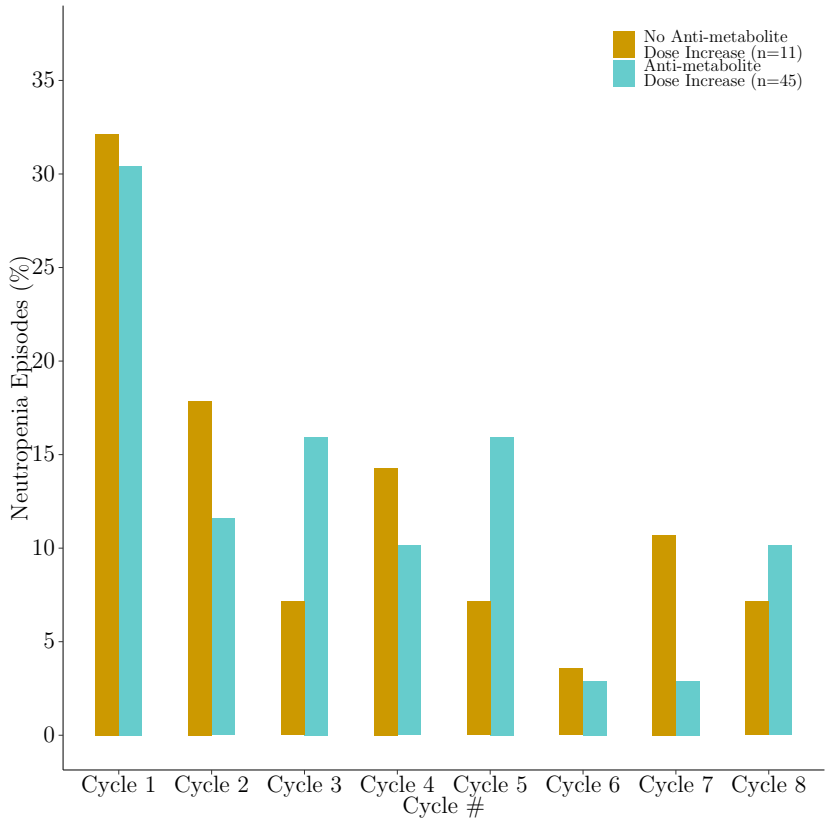


Figure 5.3: Occurrence of severe neutropenia episodes in groups - anti-metabolite dose increase and no anti-metabolite dose increase - across 8 cycles of maintenance therapy.

3. **Duration of severe neutropenia**: Duration of severe neutropenia was defined as the time to recovery of neutrophil count ($> 750 \times 10^6/L$) from onset of severe neutropenia ($\leq 500 \times 10^6/L$). Information was available

in 94 of 97 patients. In 3 patients, severe neutropenia was observed in the last week of maintenance, and information is therefore not available on the time to recovery. The median duration of severe neutropenia in the dose-escalation subgroup was 3 weeks (IQR, 1-3 weeks) compared to 4 weeks (IQR, 3-6 weeks) in the no-escalation subgroup (p=0.10, Wilcoxon test; Figure 5.4).

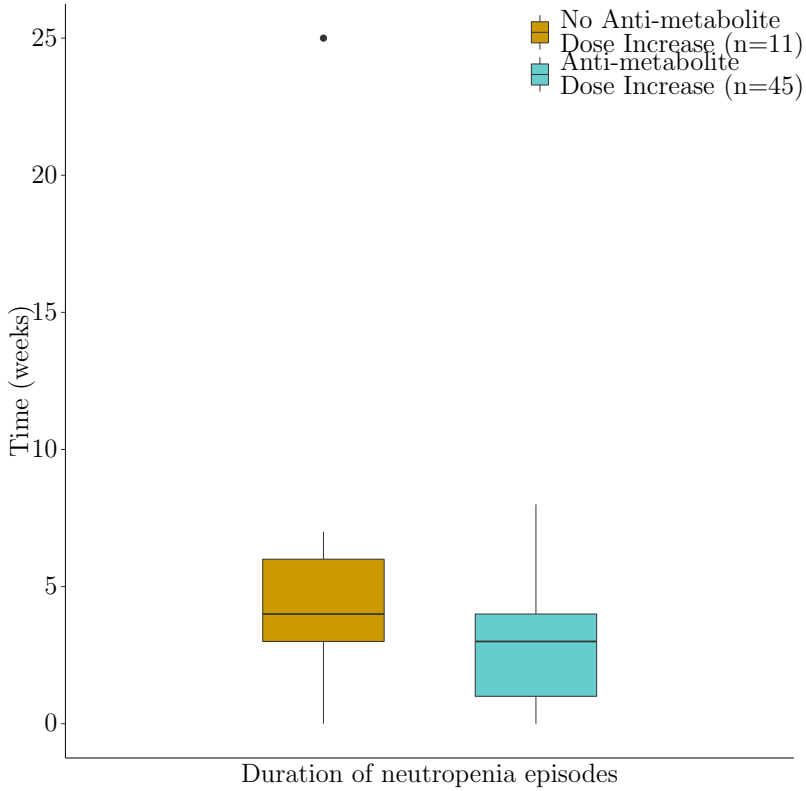


Figure 5.4: Box plot comparing median duration of severe neutropenia episodes for groups - anti-metabolite dose increase and no anti-metabolite dose increase.
Note: Box Plot representation: Box denotes IQR (25%-75%) range; Horizontal line inside the box denotes median value; Whiskers represents 1.5*IQR; black dot represents an outlier.

5.1.4 Discussion

Adaptive dosing plays a vital role during MT to continue remission and sustain bone marrow suppression. It encompasses primarily halting, reducing,

continuing, or escalating the chemotherapy drugs. Dose escalation aims to treat to tolerance. Treating to tolerance is prescribing enough chemotherapy drugs to suppress bone marrow activity adequately with minimal toxicity. Maximum tolerated doses of anti-metabolites are advised. Neutropenia events are tolerated in the process of adaptive dosing, even though the flow of the MT may be affected.

In this section, we analysed the occurrence of toxicity events and dose escalation activity during MT for the cohort. We started with computing the median time to first dose increase. Median time to dose escalation happened at 30 weeks or the third cycle.

A total of 97 severe neutropenia events occurred for the cohort during the period of MT, which ranged from 0-9 for each child. We checked for occurrence of these 97 episodes of severe neutropenia across 8 cycles of MT. Around 30% of episodes - the highest proportion of events - occurred in cycle 1. We further checked for the distribution of these 97 episodes between children who had anti-metabolite dose escalation, and those with no dose escalation. The distribution of severe neutropenia events did not differ between the two subgroups. In both subgroups, the highest proportion of severe neutropenia episodes was observed in cycle 1.

Although the median time to first dose escalation was observed in cycle 3, there were more severe neutropenic events in cycle 1. One of the possible reason for the median time to dose escalation in the third cycle, may be due to presence of 30% severe neutropenia episodes in cycle 1. Another possible reason may be conservative dosing practice, or it may be purely due to some other reason that there was a drop in ANC in cycle 1. Given the distribution of severe neutropenia events in subsequent cycles between the two groups from Figure 5.3, it is difficult to observe any relation between dose escalation and a drop in ANC counts.

A further sub-analysis in the form of comparing duration of severe neutrope-

nia episodes was carried out. We evaluated duration of each severe neutropenia events for both the subgroups and found the statistically not significant (p=0.10 by Wilcoxon test). However, the duration of severe neutropenia episodes was *longer* in *no dose escalation*. This group of children may be genetically sensitive to anti-metabolites.

5.1.5 Conclusion

A drop in absolute neutrophil counts is warranted during adaptive dosing of maintenance therapy. Treating to maximum tolerated dose is desirable for sustaining myelosuppression. The toxicity episodes experienced by the cohort depicted regular fluctuations, irrespective of the dose escalation activity across 8 cycles. The greatest fluctuation was observed in the first cycle, and subsequently stabilised across the course of maintenance therapy. The duration of toxicity events were statistically not different, between dose escalation and no dose escalation subgroup; however, the duration of toxicity events was longer in no dose escalation subgroup.

5.2 Analysis of Dosing Decisions during Maintenance Chemotherapy using Conditional Probability

5.2.1 Background

Compliance to the treatment protocol by prescribers is important and affects treatment outcomes [17] [38]. Physician's level of experience, expertise, and understanding of the treatment protocol are crucial determinants that influences the decision making process of dose adjustment. During the initial phase of MT, physicians are more inclined towards not escalating

the anti-metabolite doses due to concern of toxicity effects [17].

The ICiCLe-ALL-14 trial clinical team, formulated a set of rules for adjusting the anti-metabolites drugs [33]. The rules are tailored to absolute neutrophil counts and platelet counts of the patients, during maintenance therapy. Over the period of 5.5 years from commencement of study trial in March 2013, till October 2018, fine tuning and tweaks to dose adjusting rules were done. Nevertheless, the basic rules remained the same. In view of this, we evaluate the dosing decisions based on the dosing rules defined in the protocol for MT.

5.2.2 Methods

In this section, we describe the process of modelling ANC values and the corresponding physician prescribed doses to evaluate the dosing decision for the cohort, enrolled in the ICiCLe-ALL-14 study. We consider only 6-MP values for our analysis.

The dose adjustment rules suggest among both the drugs - 6-MP and MTX - dose escalation occur for 6-MP, first, which is followed by escalation for MTX in subsequent visits. This implies no dose escalation would ever take place for MTX before 6-MP. Considering this dose escalation criteria, capturing 6-MP dose increase would indirectly entail MTX drug escalation. For dose reduction and stopping, the rules state that actions are to be taken synchronously for both the drugs.

Dose escalation rules consider ANC as a prime factor to increase 6-MP and MTX drugs. For any dose escalation rules, platelet counts were required to be above $75,000 \times 10^6/L$. While for dose reduction or stoppage of dose rules, ANC as well as PLC are considered.

Six primary states depending upon various ranges for ANC and PLC

values were modelled. Next, we modelled physicians' prescribed doses and used conditional probability to check the probabilities of each dosing decision depending upon the ANC values.

Four primary or basic conditions to adjust dose depending upon ANC values were as follows: (1) severe neutropenia, (2) mild neutropenia, (3) target range for ANC, and (4) above target range. The ANC range defined for these conditions are describe in Table 5.2.

Table 5.2: ANC states and their definition

ANC States	**ANC Range** $(10^6/L)$
ANC_Below (B_{ANC})	$0 < ANC \leq 500$
ANC_Reduce (R_{ANC})	$500 < ANC \leq 750$
ANC_Within (W_{ANC})	$750 < ANC \leq 1,500$
ANC_Above (A_{ANC})	$ANC > 1,500$

Two states, namely, (1) moderate thrombocytopenia and (2) mild thrombocytopenia were defined based on platelet counts. Platelet range for these two state are described in Table 5.3.

Table 5.3: PLC states and their definition

PLC States	**PLC Range** $(10^6/L)$
PLC_Below (B_{PLC})	$0 < PLC \leq 50,000$
PLC_Reduce (R_{PLC})	$50,000 < PLC \leq 75,000$

A dose was prescribed for every child by the physician on each visit, depending upon the child's ANC and PLC. We define every dose prescribed as a state.

Before we create the states for physicians' dosing decision, we need to decide upon the prescribed dose ranges. This was done because during the entire duration of maintenance therapy of a child, several physicians were involved in prescribing the doses of 6-MP and MTX. Physicians had

different ways of reporting and prescribing the amount of dose. This created varied values of prescribed 6-MP for a given state of ANC or PLC. In an ideal scenario, once the dose was adjusted, it had to be round off, to the nearest possible consumable amount in milligrams and prescribe to the patients. Further, pharmaceutical stores had only one denomination of the 6-MP tablet. This created more variations in prescribing calculated adjusted dose.

Table 5.4 presents different states defined for physician prescribed dose. The first visit dose prescribed by the physician is abbreviated as FVD.

Table 5.4: Physician's decision state and their definitions

Physician's Decision State	**Definition**
No Dose (ND)	No dose prescribed
Decrease Dose (DD)	$0 < Prescribed\ Dose^{\dagger} \leq [(FVD^{\ddagger}/2) + 12.5]$
Same Dose (SD)	$(FVD - 25) \leq Prescribed\ Dose \leq (FVD + 12.5)$
Increase Dose (ID)	$Prescribed\ Dose > (FVD + 12.5)$

† *Prescribed Dose* is defined as physician prescribed dose on a given visit of maintenance therapy.

‡ *FVD* is defined as dose prescribed by physician on the first visit of maintenance therapy

Between decreased dose and same dose on a scale of 50% to 100% of FVD, there were instances of dosing which could not be explained as per the protocol, where for example instead of the stipulated decrease of 50%, there was a reduction of 30%. We could not categorise these situations into the four defined states above. The range for such uncategorised prescribed doses was $[(FVD/2) + 12.5] < Prescribed\ Dose < (FVD - 25)$. This indicated that the uncategorised doses either may have been prescribed independent of the dosing protocol in the ICiCLe-ALL-14, or had other justifications which we could not capture.

The factor of +12.5 in Increase Dose was considered due to the following reason. The FVD is based on a body surface area of $60mg/m^2$ for 6-MP. Liquid formulations of 6-MP were not available. Physicians prescribed parts of the smallest available tablet of 6-MP, which was the 50mg oral tablet. The smallest prescribed dose was a quarter tablet, or 12.5 mg. We used *12.5* as a factor in our calculations. The body surface area based prescribed doses were rounded off considering *12.5* as a factor. During 6-MP dose prescribing, most of the time rounding off was performed to the lower bound for example, if a child required 420 mg/week, they would be prescribed 400 mg. Due to this, doses were reduce by a factor of more than *12.5*. To capture these variations, we used a factor of *12.5*2* or *25*.

5.2.2.1 Conditional Probability

Let A and B be two events. We assume, the probability of occurrence event B is > 0. The conditional probability A given B OR the probability of occurrence of A such that event B has occurred is defined as

$$P(A|B) = \frac{P(A \cap B)}{P(B)} \tag{5.5}$$

The numerator $P(A \cap B)$ is the joint probability or probability that both the events A and B occur. Thus, conditional probability is a measure of the probability of an event given that another event has occurred [95].

5.2.3 Results

The modelling of ANC, PLC and 6-MP values allowed us to group them into different states. Questions were formulated considering dose adjustment rules, and analysis was performed. A total of 2,704 visit records

with ANC, PLC, and 6-MP were modelled. We found a total of 694/2,704 (25.66%) as unaccounted prescribed 6-MP doses, which could not be categorized into one of the four physician's decision states discussed in Table 5.4.

The dosing rules for the dose adjustment are followed by the physicians during MT clinic. We wanted to evaluate the dosing decisions by the physicians for the cohort. Based on dosing rules, the following questions were framed. We use conditional probability from Equation 5.5 to evaluate the dosing decisions.

1. ***Question***: What was the probability of $ANC \leq 500$ or $PLC \leq 50,000$ when physician's decision was 'No Dose' ?

   Result:

   - A total of 244 records had physician's decision - 'No Dose'. Among these, 151 records had $ANC \leq 500$ or $PLC \leq 50,000$.
   - 151/244 (61.88%)

2. ***Question***: What was the probability of $500 < ANC \leq 750$ or $50,000 < PLC \leq 75,000$ when physician's decision was 'Decrease Dose'?

   Result:

   - A total of 554 records had 'Decrease Dose' decision recorded by the physician. Among these, only 75 records had $500 < ANC \leq 750$ or $50,000 < PLC \leq 75,000$.
   - 75/554 (13.53%)

3. ***Question***: What was the probability of $ANC > 750$ for pre-

vious three consecutive visits when 'Increase Dose' decision was taken by the physician for the current visit?

Result:

- We had a total of 571 records where physician's decision was 'Increase Dose'. Among 571, 328 records had $ANC > 750$.
- 328/571 (66.90%)

Note: For the following three questions the units of ANC and PLC is $\times 10^6$/L.

5.2.4 Discussion

A set of rules were followed to prescribe anti-metabolites drugs for patients during maintenance therapy based on the ICiCLe-ALL-14 protocol. Compliance to dose adjusting guidelines along with adherence to prescribed medication by the patients are two important factors to ensure better outcomes in ALL treatment [17, 23, 38, 39]. Compliance to dose adjusting rules would ensure optimal myelosuppression, if children are consuming drugs regularly. Studies have shown compliance problems to dose adjustment [17,38]. These studies stated that the intensity of anti-metabolites doses prescribed was on a lower side. It may be due to the fact that physicians are conservative when it comes to dose escalation.

We performed an analysis to evaluate concordance of physician dosing decisions with blood count conditions. The current analysis aims to determine frequency of deviation from prescribed dosing rules based on observed blood counts. Dosing decisions included continuation, escalation, reduction or suspension of antimetabolite treatment. We modelled MT

parameters of ANC, PLC, and 6-MP, and used conditional probability to determine the probability for different dosing decisions followed.

Our findings indicate

1. In ∼40% of decisions to suspend antimetabolite chemotherapy, no corresponding low blood counts were observed. Only around 60% of the times therapy was interrupted due to severe neutropenia or mild thrombocytopenia.

2. This is even more striking in decisions to reduce chemotherapy where ∼87% of decisions to reduce chemotherapy doses were made independent of blood count results.

3. Similarly, the decision to increase drug doses were made independent of prescribed rules for dose escalation in nearly a third of cases. Only 328/571 (67%) records had a dose increase activity when required by the protocol.

The findings suggest the following:

1. Non-adherence to dosing rules is observed when prescribing antimetabolite drugs during maintenance chemotherapy. This indicates need for periodic training and evaluation of practitioners and highlights the potential benefit of an automated dose advice system.

2. The findings also suggest the role of physician discretion when prescribing drug doses. For instance, drug doses may be reduced in patients with febrile illness even in the presence of appropriate blood counts. Similarly doses may not be escalated in situations where immediate follow-up is not feasible, for instance when families travel outside for holidays. While physician judgement may be subjective,

discretionary decisions that vary from prescribed dosing rules, would need to be recorded, so as to understand additional factors that influence dosing decisions, explore opportunities to minimise subjectivity in decision-making, and incorporate additional considerations of potential importance, in the dose-advice algorithm.

3. Another observation to note here is that the dosing state, increase dose, captured all the dose increase events for the prescribed dose. The value of the prescribed dose was more than the sum of the first visit dose and the factor 12.5. Our cohort had only two children with BSA values < 0.5. Assuming, a BSA value of 0.5 m^2, weekly 6-MP dose prescribed would be 210mg. The dose escalation activity in ICiCLe-ALL-14 protocol mentions a dose escalation by 25%. With a weekly dose of 210mg, an increase of 25% would be $\sim$ 50 mg. This value is four times the dose escalation factor of 12.5. Given the results from our analysis, we suspect that the number of dose escalation records we found may further reduce if we increase the dose escalation factor of 12.5 for 6-MP, depicting lesser dose increase activity for the cohort.

5.2.5 Conclusion

The dosing decision analysis shows that physicians did not consistently follow the MT protocol outlined in the ICiCLe-ALL-14 study. One reason for the failure in compliance may be because the dosing adjustment process is fairly complex, and physicians involved in prescribing are coming from varied levels of expertise. An automated dosing decision method could assist physicians in dosing the chemotherapy drugs during MT.

Chapter 6

Objective 3: Development of Summary Measures to Analyse Maintenance Therapy Prescriptions and Status of Myelosuppression

In the previous chapter, we saw the dosing practice can be further optimised. Here, in this chapter, we develop analytic methods to aid physicians in understanding the effectiveness of treatment for children undergoing maintenance therapy.

6.1 Background

Maintenance therapy (MT) is a cornerstone of paediatric ALL treatment, with an aim to ensure remission. The conventional 2 year period of MT is governed by prescribing the appropriate amount of 6-MP and MTX drugs.

The aim of maintenance therapy is to achieve remission, with anti-leukaemic chemotherapy drugs, by sustaining optimal myelosuppression.

In view of this, it is suggested to adjust 6-MP and MTX drugs, with discretion. Several prospective randomized trials examined the usage and monitoring of anti-metabolite drugs. Daily dose of 6-MP suggested was within a range of 50-75 mg/m^2 and MT was dosed weekly within a range of 20-40 mg/m^2 together in various clinical trials [15].

Optimal dosing of 6-MP and MTX, involves finding the maximum tolerated dose for myelosuppression for a child, while avoiding severe toxicity [16]. Suboptimal dosing of the antimetabolite drugs during MT, doubles the risk of relapse for the child [17] [18].

Adaptive dose adjustment is challenging [15] [20]. Sub-optimal dosing of MT drugs, has been shown to lead to lower event free survival, for children with ALL [17,38,43]. A study from Brazil showed increased relapse in situations where the dose adjustment protocol was not followed during MT [43].

In this chapter, we develop an analytic method to summarize dose prescriptions, and status of myelosuppression, over the 96 weeks of MT for each child. Further, we analyse the retrospective data for the cohort of 56 children, who have completed MT.

6.2 Analysing Longitudinal Maintenance Therapy Information

The prognostic importance of prescribed antimetabolite doses, or dose intensities, have been studied longitudinally in cohorts [21,23,96,97]. Finding ways to compress the longitudinal data into summary measures to assess the effectiveness of maintenance therapy, has been an important area of work.

We present a brief overview of a few studies that reported the summarised longitudinal MT information, with the help of various summary measures related to MT, in Table 6.1.

Table 6.1: Review of studies showing various summary measure based on MT information

Sr. No.	Reference	Representation of longitudinal MT information
1	Schmiegelow K, Pulczynska M, *Br J Cancer*, (1990) [98]	Average dose of MTX and 6-MP, weight mean WBC, weighted mean serum aminotransferase
2	Schmiegelow K, Schrøder H, Gustafsson G et al., *J Clin Oncol.* , (1995) [54]	Median erythrocytes MTX (E-MTX); median erythrocytes thioguanine nucleotides (E-6TGN); product of median E-MTX and median E-6TGN
3	Schmiegelow K, Ifversen M, *Pediatr Hematol Oncol.*, (1996) [99]	Weighted mean - WBC, ANC, aminotransferase (AT) levels, MTX, 6-MP doses, metabolites in erythrocytes (E-MTX and E-6TGN)
4	Schmiegelow K, Heyman M, Gustafsson G et al., *Leukemia*, (2010) [48]	Average dose of MTX and 6-MP, mWBC, median E-6TGN, median E-MTX
5	Bohnstedt C, Levinsen M, Rosthøj S et al., *Leukemia*, (2013) [38]	mean doses of 6-MP (m6MP) and MTX (mMTX), mean level of neutrophil counts (mANCs), median maintenance therapy white blood cell levels (mWBC)
6	Schmiegelow K, Nielsen SN, Frandsen TL et al., *J Pediatr Hematol Oncol.*, (2014) [23]	Weighted mean white blood cells and weight mean 6-MP
7	Nielsen SN, Grell K, Nersting J et al., *Cancer Chemother Pharmacol.*, (2016) [96]	Weighted mean - WBC, ANC, absolute lymphocyte count (ALC), thrombocyte count (TBC), thioguanine nucleotides incorporated in leukocyte DNA (DNA-TGN), thioguanine nucleotides (TGN), methylated mercaptopurine metabolites in erythrocytes (MeMP), 6-MP and MTX
8	Schmiegelow K, Nersting J, Nielsen SN et al., *Pediatr Blood Cancer*, (2016) [19]	Average oral MTX/6-MP doses, time-dependent weighted mean WBC, ANC, ALC, hemoglobin, thrombocyte counts

Schmiegelow et al. calculated, and plotted the weighted mean for WBC (wmWBC) and 6-MP (wm6MP). They defined weight as the difference between two consecutive dose registrations. They showed that the median wm6MP significantly correlated to the median wmWBC in 538 children who had completed MT in the NOPHO ALL-92 study [23].

In another study by Schmiegelow et.al. [54], mean erythrocytes MTX (mE-MTX) and 6-thioguanine nucleotides (mE-6TGN), and the mean of the product of E-MTX and E-6TGN (mE-MTX.6TGN), was computed to study risk of relapse. Cox regression analysis showed mE-MTX.6TGN, and gender, were the most significant predictors of relapse.

Measures for 6-MP and MTX to evaluate MT intensity were discussed by Nielsan et al. [96]. The authors used mean on-therapy WBC values, to check the status of myelosuppression. They found one group of children continued to have higher WBCs, despite high mean 6-MP/MTX doses showing the challenge of obtaining the target WBC counts.

6.3 Methods

We developed summary measures for maintenance therapy for the data from the retrospective study of children, who had completed maintenance chemotherapy for paediatric ALL at Tata Medical Center Kolkata (TMCK) from February 18^{th} 2016 to October 27^{th} 2018. As mentioned, for each child, the following variables were recorded: age, gender, week #, ANC, PLC, prescribed 6-MP and MTX, absolute lymphocyte count (ALC), and mean corpuscular volume (MCV) for every maintenance therapy visit across the 96 weeks of treatment.

6.3.1 Summarizing Dose Prescriptions and Absolute Neutrophil Counts

In this chapter, we evaluate the effect of anti-metabolites on absolute neutrophil counts. We plot weighted mean anti-metabolite drug intensity, against weighted mean absolute neutrophil count, for each child, to evaluate the child's response to the prescribed anti-metabolite drugs during maintenance therapy. In order to illustrate the effect of anti-metabolites, we derived few terminologies based on the maintenance therapy information.

Children either visited the hospital, or e-mailed CBC report for routine maintenance therapy check-up. For annotation and convenience, we considered an event of e-mailing the counts to the hospital team as a visit, as mentioned in (Chapter 4). We used the date of visit as a time factor, and converted it to week number of MT. Week number could range from week 1 to week 96. The reference or week 1, starting from Monday, was computed for the first visit date of a child to the hospital for MT. The successive dates of visits were converted to week number, with reference to the first week. The week number calculation process was carried out for the whole cohort.

Table 6.2 shows terminology describing variables and notations used.

Table 6.2: Terminology and their notations

Terminology	Notations
Visit # to the hospital	$v_i = \{v_1, v_2, \ldots, v_n\}$
Week # during visit to hospital	$wk_i = \{wk_1, wk_2, \ldots, wk_n\}$
ANC during respective visits	$anc_i = \{anc_1, anc_2, \ldots, anc_n\}$
Platelets during respective visits	$plc_i = \{plc_1, plc_2, \ldots, plc_n\}$
Prescribed 6-MP during respective visits	$6mp_i = \{6mp_1, 6mp_2, \ldots, 6mp_n\}$
Prescribed MTX during respective visits	$mtx_i = \{mtx_1, mtx_2, \ldots, mtx_n\}$

Variables age, gender, ALC, and MCV are not mentioned in Table 6.2. These variables are used directly for analysis.

In Table 6.2, $\boldsymbol{i}$ represents the visit number in question. Visit, $\boldsymbol{v_1}$, represents the first visit to the hospital, at the start of MT for the child. During visit v_1, the child gets a CBC check done. The term $\boldsymbol{wk_1}$ refers to week 1 of 96 weeks of MT. The terms $\boldsymbol{anc_1}$ and $\boldsymbol{plc_1}$ represents ANC and PLC values respectively, corresponding to CBC results for visit v_1. The terms $\boldsymbol{6mp_1}$ and $\boldsymbol{mtx_1}$ denote weekly prescribed doses of 6-MP and MTX respectively, based on anc_1 and plc_1 for v_1 by the physician.

A set $\{\boldsymbol{v_i}, \boldsymbol{wk_i}, \boldsymbol{anc_i}, \boldsymbol{plc_i}, \boldsymbol{6mp_i}, \boldsymbol{mtx_i}\}$ represent the $\boldsymbol{i^{th}}$ visit of MT information for the child. For each child, we had n such visits, where n varies depending upon the number of times the child had MT check-up visits. From our data collection process, we had MT information on 56 children. A total of 2,704 follow-up visits during MT was made by the children in the cohort. Given this, we had 2,704 sets of $\{v, wk, anc, plc, 6mp, mtx\}$.

We use the term $\boldsymbol{weight\ w_i}$, to define the interval between two consecutive visits - visit in question, and next subsequent visit - which is termed as the mathematical weight. The letter $\boldsymbol{i}$ represent the visit in question. The weight, w_i, was computed as the difference between the week numbers for two subsequent visits. For our work, we decided upon 1-8 as the range for w_i. The maximum value of 8 representing time duration of 8 weeks was considered for weight. It is anticipated that the ANC stabilizes within 6-8 weeks from the time of anti-metabolite drugs initiation by the child. Beyond 8 weeks of anti-metabolite drug consumption, the ANC values are not representative enough, to check the effectiveness of anti-metabolite drugs. If the time interval between two consecutive weeks is more than 8 weeks, we discard the visit in question for our calculations. For the i^{th} visit, the weight, w_i, was computed as

$$w_i = wk_{i+1} - wk_i \tag{6.1}$$

Recommended dose RD, was defined as the starting dose of anti-metabolites prescribed by the physicians during the first visit. For each child, the ICiCLe-ALL-14 protocol recommends 6-MP at a starting dose of 60 $mg/m^2/day$, and for MTX which is dosed weekly at 20 $mg/m^2/week$ [33]. In other words, the protocol suggested 60 mg/day for the child with body surface area of *one meter square*. Similarly, the protocol suggests 20 $mg/week$, for the child with body surface area of *one meter square*. The weekly recommended 6-MP and MTX dose was 420 $mg/m^2/week$ and 20 $mg/m^2/week$ respectively. In paediatric oncology practice, however, the recommended anti-metabolites are prescribed with respect to a child's body surface area (BSA). Hence, the prescribed dose of 6-MP and MTX, for each child was computed as $(BSA * 420)$ $mg/m^2/week$ and $(BSA * 20)$ $mg/m^2/week$, respectively.

As per the ICiCLe-ALL-14 protocol recommendations, MT would start only when the child's ANC is above the desired range. The admissible ANC range had to be above $1,000 \times 10^6/L$ to start MT [33]. After the start of MT, the physicians prescribed BSA adjusted anti-metabolite doses. The prescribed dose was rounded off to the nearest dosage strength of pill available. Rounding off was done due to the specific availability of oral tablets of 6-MP and MTX in milligrams. Liquid formulations for these are not available in this setting. The physicians adjusted doses in subsequent visits, depending upon ANC and PLC. The physician suggested dose during each visit, is called the ***prescribed dose (PD)***, in our analysis.

We define ***dose intensity*** $\boldsymbol{d_i}$, as ratio of prescribed dose on i^{th} visit, by prescribed dose on the 1^{st} visit for the child.

$$Dose\ Intensity\ (d_i) = \frac{Prescribed\ Dose\ for\ i^{th}\ visit\ (PD_i)}{Prescribed\ Dose\ for\ 1^{st}\ visit\ (PD_1)} \tag{6.2}$$

Dose intensity for 6-MP and MTX was computed as

$$d\_6mp_i = \frac{6mp_i}{6mp_1} \tag{6.3}$$

$$d\_mtx_i = \frac{mtx_i}{mtx_1} \tag{6.4}$$

Schmiegelow et al. discussed interaction between 6-MP and MTX [93] [23]. The authors pointed out, 6-MP and MTX drugs work in synergy, to suppress the growth of leukaemic cells in paediatric ALL treatment. Different proportions of anti-metabolites doses during MT, using adaptive dosing, helps sustain myelosuppression. Keeping this in mind, we define ***anti-metabolite dose intensity*** (***d_AnMtb***), as the product of dose intensity of 6-MP and MTX. Anti-metabolites dose intensity was computed as

$$d\_AnMtb_i = d\_6mp_i * d\_mtx_i \tag{6.5}$$

Table 6.3 shows the list of variables we derived from equations (6.1), (6.3), (6.4), and (6.5).

Table 6.3: Derived variables and their notations

Derived variables	Notations
Weights (w_i)	$\{ w_1, w_2, \ldots, w_{n-1}\}$
Dose Intensity for 6-MP (d_6mp_i)	$\{d\_6mp_1, d\_6mp_2, \ldots, d\_6mp_{n-1}\}$
Dose Intensity for MTX (d_mtx_i)	$\{d\_mtx_1, d\_mtx_2, \ldots, d\_mtx_{n-1}\}$
Anti-metabolites Dose Intensity (d_AnMtb_i)	$\{d\_AnMtb_1, d\_AnMtb_2, \ldots, d\_AnMtb_{n-1}\}$

Using the derived variables (Table 6.3), and initial variables (Table 6.2), we created summary variables, to analyse all the prescriptions of 6-MP and MTX into a single value for each child. Weighted mean is defined as an average of weighted observations. Weighted mean ANC– ***wmANC*** –was calculated as the mean of weighted ANC values at each visit for the child. Similarly, weighted mean for anti-metabolites dose intensity (***wmAnMtb***) was derived.

For our analysis, Table 6.4 gives the description of weighted mean of ANC and anti-metabolite dose intensity.

Table 6.4: Definition for weighted wean for ANC, 6-MP, MTX, and anti-metabolite dose intensity

Variable	Definition
Weighted Mean ANC ($wmANC$)	$\frac{w_1 anc_1 + w_2 anc_2 + \ldots + w_{n-1} anc_{n-1}}{w_1 + w_2 + \ldots + w_{n-1}}$
Weighted Mean AnMtb ($wmAnMtb$)	$\frac{(w_1 * d\_AnMtb_1) + (w_2 * d\_AnMtb_2) + \ldots + (w_{n-1} * d\_AnMtb_{n-1})}{w_1 + w_2 + \ldots + w_{n-1}}$

Finally, we derive ***time in treatment range (TTR)***. The notion of TTR for our work was borrowed from the study published by Pokorney et al. [100]. Time in treatment range was defined as time a child had spent in the target treatment range during the entire course of maintenance therapy. The target treatment range was defined as ANC of $(750 - 1,500) \times 10^6/L$ based on the ICiCLe-ALL-14 protocol [33].

The ICiCLe-ALL-14 protocol suggests that it is always desirable for a child undergoing MT, to spend the maximum time in the treatment range of ANC $750 - 1,500 \times 10^6/L$, because that represents optimal myelosuppression. The greater the time spent in the target range, the better the chance for relapse free survival. For our work, we computed ***proportion time in treatment range (pTTR)***.

We calculated the total time in weeks that a child spent in the target range, out of total weeks on MT. We then divided the total time spent in target treatment range by total weeks of MT to calculate pTTR. Finally, proportion was expressed in percentage.

In the next section, we compute the above derived summary variables. A graphical representation was developed, to observe an overview on how the over-

all dose adjustment procedure, complemented the status of myelosuppression, and proportion of time spent in the target treatment range for the cohort. We further performed a sub-analysis to investigate if age was related to the problem of medication non adherence during MT.

6.4 Results

We summarized the overall treatment status for each child in terms of myelosuppression with respect to anti-metabolites over the period of MT. A graph was plotted for weighted mean anti-metabolite dose intensity ($wmAnMtb$), against weighted mean absolute neutrophil count ($wmANC$), to check the effectiveness of anti-metabolite dosing. The range of optimal myelosuppression, also known as the target treatment range for ANC, was defined as $(750 - 1,500) \times 10^6/L$. The optimal dose intensity window was labelled as 0.8-1.2 which represents 80% to 120% of PD on first visit. The dose intensity of 1 indicates the first visit dose or 100%.

As doctors had reviewed the MT information for the cohort, they suggested 0.8-1.2 as the range for wmAnMtb that would capture the majority of the doses. With the help of the target treatment range, and ideal dose intensity range indicators, a scatter plot was obtained as shown in Figure 6.1.

Figure 6.1 shows a scatter plot for wmAnMtb vs wmANC for the cohort of 56 children. Each dot represents the summarised longitudinal information, over a duration of 96 weeks of MT, for a child, with respect to wmAnMtb and wmANC. The green colour dots represent children who have not had a relapse, whereas the magenta colour dots represent children who have had a relapse. The ideal scenario for the child completing MT is to reside somewhere in the grey shaded area, or on the right of the grey shaded area, in the graph (Figure 6.1). This would mean ideally, the child was treated with the maximum tolerated doses of the drugs, and thereby had sustained myelosuppression.

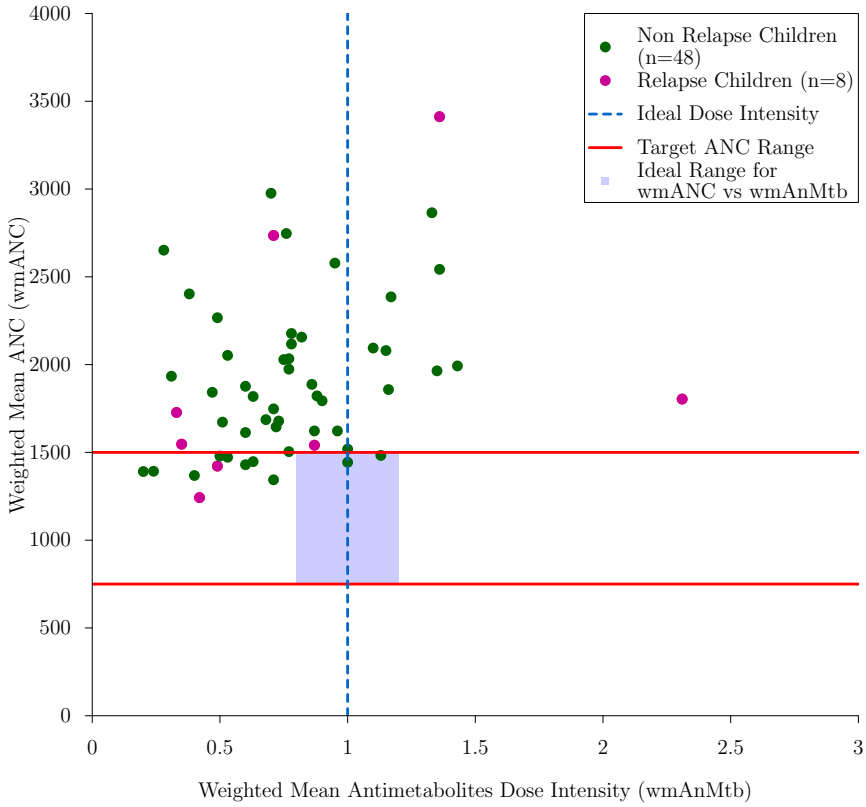


Figure 6.1: Scatter plot showing weighted mean anti-metabolite dose intensity (wmAnMtb) against weighted mean absolute neutrophil count (wmANC) for 56 children who completed maintenance therapy following ICiCLe-ALL-14 protocol.
The target range of $(750 - 1,500) \times 10^6/L$ for ANC is marked with red lines. Ideal range for dose intensity was 80% - 120% (0.8 - 1.2) of starting 100% anti-metabolite dose.

Further, we investigated the scatter plot information by diving the cohort into two subgroups: (1) group of children achieving optimal myelosuppression; and (2) group of children not achieving optimal myelosuppression. Both the subgroups were analysed with respect to anti-metabolite dose intensity within or outside target treatment range. Table 6.5 shows the distribution of the cohort, achieving optimal myelosuppression (Yes/No) against target treatment range (Yes/No).

Table 6.5: Distribution of children among subgroups - sustained optimal myelosuppression (Yes/No) and target anti-metabolite dose intensity (Yes/No)

	Sustained Optimal Myelosuppression (Yes) $(750 < ANC <= 1,500)$	**Sustained Optimal Myelosuppression (No)**	**Total**
Target Anti-metabolite Dose Intensity (Yes) $(0.8 - 1.2)$	2	13	15
Target Anti-metabolite Dose Intensity (No)	10	31	41
Total	12	44	56

Table 6.5 shows that only 2 children achieved targeted optimal myelosuppression, with the anti-metabolite dose intensity in the desired range. The other 10 children had sustained optimal myelosuppression, but the maximum tolerated dose was not prescribed to them. 44 children did not have their ANC in the expected target range. The dose intensity for only 15 children was within the desired treatment target range, while it was outside desired range for 41 children.

Out of 41 children, for 6 children weighted mean antimetabolite dose intensity exceeded 1.2. In all six, weighted mean neutrophil count was higher than $1500/mm^3$, prompting us to speculate that treatment adherence, was perhaps, lower in this group of children.

In view of this observation, we inspected these 6 children, against the rest of cohort. Adherence to anti-metabolites drugs during continuation therapy is essential to improve outcomes however we had limited methods to retrospectively assess treatment adherence [39] [40]. We looked at surrogate measures available to us to assess adherence, the absolute lymphocyte count, and the mean corpuscular volume of red blood cells. We also did a sub analysis of whether age

the six children were older on average than the rest.

The cohort was stratified into two subgroups (1) children with $wmAnMtb > 1.2$; and (2) children with $wmAnMtb \leq 1.2$. We analysed patient characteristic information for these two groups. Records consisting of age, gender, ALC, and MCV were considered for the above mentioned two groups for analysis.

Children adherent to antimetabolite therapy during maintenance, experience red cell macrocytosis [101] [102], characterised by raised, red cell MCV, and lymphopenia [103] characterised by low ALC. Age is reported to influence treatment adherence, with poorer adherence observed in older children [104] [105]. ALC and MCV may be considered as surrogate markers to check adherence to 6-MP. The standard values of ALC and MCV are (1,000-5,000)/micro-litres ($10^{-3}L$) and (75-90) femto-litres (fL) respectively. To check 6-MP adherence, physicians may check ALC and MCV, values of subsequent weeks from the week anti-metabolites were orally consumed.

Children are expected to have high MCV, and low ALC if they have adequate exposure to 6-MP. On the basis of this correlation, we analysed the two subgroups: (1) **subgroup 1** - children with wmAnMtb greater than 1.2; and (2) **subgroup 2** - children with wmAnMtb less than or equal to 1.2.

For each child, we computed the average ALC and MCV over the period of MT. The average values were then computed for subgroup 1 children with wmAnMtb greater than 1.2 and subgroup 2 children with wmAnMtb less than or equal to 1.2

Table 6.6: Distribution of age, gender, mean absolute lymphocyte count, and mean corpuscular volume among groups - $wmAnMtb > 1.2$ and $wmAnMtb \leq 1.2$

	Gender (M:F)	**Age** (IQR:25%-75%)	**Median ALC** (IQR:25%-75%)	**Median MCV** (IQR:25%-75%)
wmAnMtb > 1.2	4:2	8.54 (6.31-12.61)	787 (469.7-1,173.1)	94.03 (90.89-96.66)
wmAnMtb ≤ 1.2	27:23	5.18 (3.54-8.98)	956.6 (795.9-7,085.6)	97.67 (92.94-102.91)

Table 6.6 shows no direct visible trend of low ALC and high MCV, among the two groups showing no conclusive evidence, for medication non-adherence. Statistical test revealed no significant difference in the MCV (p-value=0.25, Wilcoxon ranked sum test), and ALC (p-value=0.36, Wilcoxon ranked sum test) values among the two subgroups.

Further, we analysed age. We plotted a box-plot to observe the distribution of age and formed the following hypothesis

> ***Null Hypothesis*** *(H_0)* : Age of children in subgroup 1 (children with wmAnMtb greater than 1.2), and subgroup 2 (children with wmAnMtb less than or equal to 1.2) is not different.

> ***Alternative Hypothesis*** *(H_1)* : Age of children in subgroup 1 (children with wmAnMtb greater than 1.2), and subgroup 2 (children with wmAnMtb less than or equal to 1.2) is different.

Figure 6.2 shows distribution of age for above mentioned two groups.

We performed Wilcoxon rank sum test to check the association between the subgroups. Analysis provided a p-value of 0.18. With the resultant p-value, we accepted the null hypothesis. This indicated that statistically there was no difference in age. However, median age was higher in the 6 children (median: 8.54 years, full range:[1.5-13.6]) compared to the group treated with lower weighted mean antimetabolite intensity (median:5.18 years, full range:[1.5-15.5]), although formal testing indicated no significant difference, perhaps due to the small numbers. A more detailed investigation of the records would need to be carried out to better understand these six outliers.

Figure 6.3 shows a scatter plot for wmANC against pTTR. It is desirable to

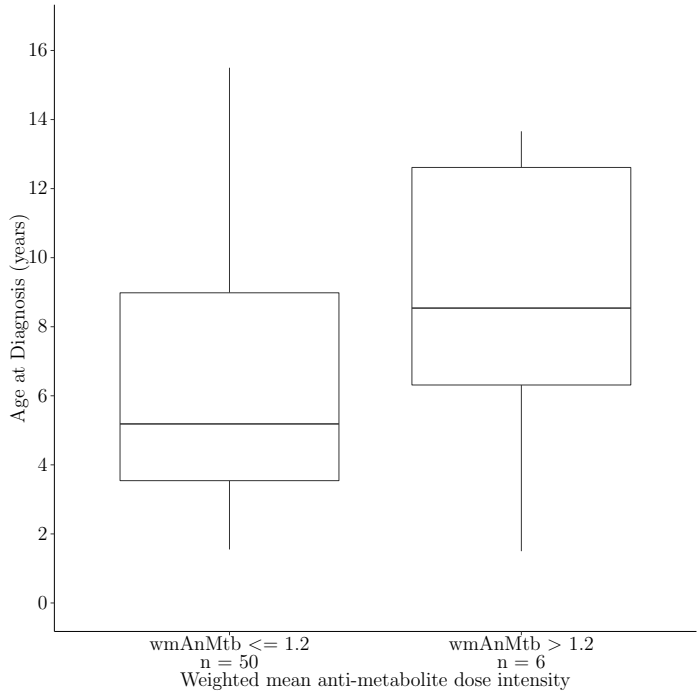


Figure 6.2: Distribution of age by group - wmAnMtb $>$ / $\leq$ 1.2. (N=56).
Note: Box Plot representation: Box denotes IQR (25%-75%) range; Horizontal line inside the box denotes median value; Whiskers represents 1.5*IQR.

have the pTTR as high as possible as it represents the total duration of sustained myelosuppression during 96 weeks of MT. Along with this, the ideal wmAnMtb range lies within 0.8-1.2. From Figure 6.3, we observe that the median pTTR for the cohort was 33.8% [IQR: 20.16%-45.53%], which is far below the expected.

6.5 Discussion

Maintenance therapy is the longest phase of paediatric ALL treatment. Several facets of MT need to be administered during the 96 weeks. Physicians need to be compliant to the dose adjustment protocols, by ensuring children are prescribed the maximum tolerated doses, while closely monitoring myelosuppression.

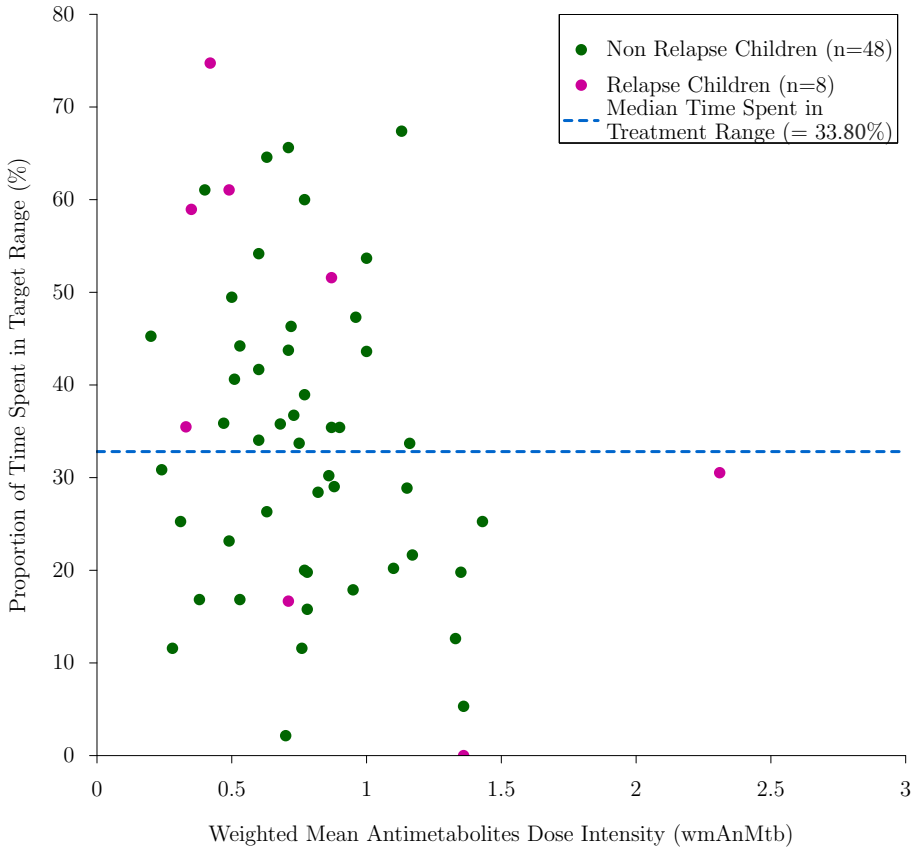


Figure 6.3: Scatter plot showing wmAnMtb against pTTR (%). Median pTTR for the cohort was 33.8% [IQR: 20.16%-45.53%].

The maintenance clinic at TMCK runs once a week wherein the doctor needs to follow-up on very child coming to clinic, and base decisions on longitudinal data over time. Visualisation of longitudinal information on key parameters–ANC, PLC, 6-MP, and MTX doses–at one go, could aid physicians in assessing a child's progress. Numerous visits mean multiple time points, with each time point having CBC, and anti-metabolite information. It becomes difficult to analyse all the time point information at one go.

Concise information on MT for each child, would help the physician better understand the child's progression. This would also save energy, and physician

time. The summary variables discussed in this chapter, aim at representing MT information, in a crisp manner. Along with this, the progression graph showing each visit's ANC, 6-MP, and MTX information as a line graph for each patient, may be used, as discussed in Chapter 4.

The progression graph from Chapter 4 along with wmANC, wmAnMtb, and pTTR variables may be considered as novel ways to represent MT information for each child. These variables convey different information on MT progression. Moreover, wmAnMtb, wmANC, and pTTR, may be considered as a 3-dimensional portrayal to observe MT information. For any child during MT, if MT information has these three attributes, it becomes easy to understand, on how well the child is doing during the treatment. It would also narrate the physicians' compliance, to dose adjustment protocols.

The summary variables were used for the retrospective cohort analysis of children completing MT. This work allowed us to evaluate MT practice at TMCK. Figure 6.1 represents a scatter plot for wmANC and wmAnMtb. We observed only 12/56 children had sustained myelosuppression, over the period of 96 weeks. However, only 2 out of 12 children who sustained myelosuppression, had dose intensity in the target range. The proportion of time spent in treatment range by the cohort was 33.8% [IQR: 20.1%-45.53%]. This was below what is optimal, given children need to spend the maximum time, in the desired treatment range.

41/56 (73.2%) children did not have anti-metabolite dose intensity within the desired range. 6 out of 41 (14.6%) children who had dose intensity level higher than 1.2 were investigated for treatment adherence. The possibility of treatment adherence come from the fact that these 6 children should have sustained myelosuppression. Median age group for these 6 children was higher (8.5 years [IQR: 6.3-12.6)] as compared to the rest of cohort (5.2 years; IQR: [3.5-8.9]) though due to the small numbers it did not appear statistically significant.

6.6 Conclusion

MT information for a child at different time points is tedious to analyse concurrently. The summary variables, along with the progression graph, integrated with a hospital management system of a cancer care centre, could aid physicians in making dosing decisions–especially, a cancer care centre such as TMCK, where on average 44 children visited the clinic during the first 10 months of 2018 for MT check-up, and physicians had less than 10 minutes on an average dedicated for each child.

The retrospective cohort analysis using the summary variables shows potential for improving dosing practice. A possible solution to the problem of dose adjustment as shown in this chapter would be modelling the dose adjustment protocols and developing an automated dose advice method.

Chapter 7

Analysis of Practice Following Introduction of Analytic Methods in the Clinic

The results from the analytic methods discussed in Chapter 6 were reviewed with the team of physicians responsible for ALL maintenance treatment at Tata Medical Center Kolkata (TMKC). The summary graph of wmAnMtb vs. wmANC, and wmAnMtb vs. pTTR, for the cohort of 56 children was discussed. The results showed a further opportunity to optimise the maintenance therapy by treating the children to maximum tolerated doses. The importance of compliance to dosing rules was reviewed with the team, once again. In this chapter, we discuss analysis of dosing practice, in a new cohort, following this intervention.

7.1 Methods

Maintenance therapy information was collected by Ms. Sanjali Mitra interning at Tata Translational Cancer Research Centre Kolkata, for a newer cohort from January 1^{st} 2019, to February 19^{th} 2019. The newer cohort commenced MT between June 1^{st} 2017, to January 31^{st} 2018, and

had completed a median of 5 cycles [IQR:5-7] of maintenance therapy, at the time of analysis on May 20^{th}, 2019. The completeness of information was performed, as discussed in Chapter 4.

The MT information collected on the new cohort consisted of date of visit, ANC, PLC, prescribed doses of 6-MP and MTX, and relapse status. Other information such as demographic characteristics, MRD status, risk group, and lineage was not collected.

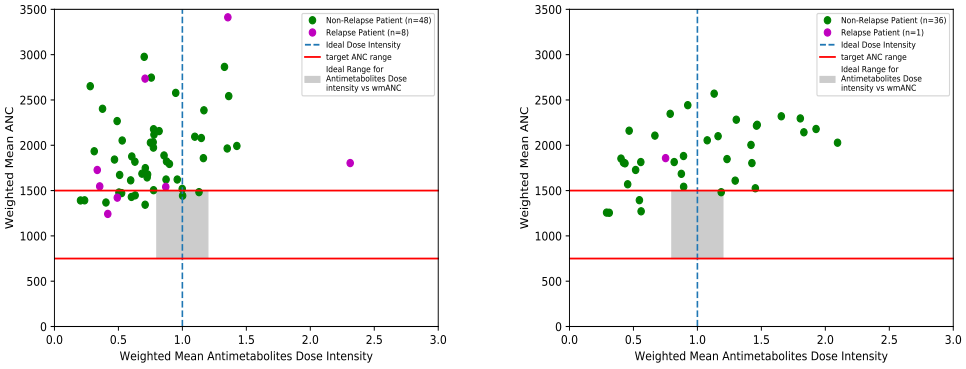
An analysis of the median time to first dose escalation, occurrence of severe neutropenia events in children who had dose escalation, versus those who had no dose escalation, and duration of severe neutropenia events, were studied and analysed. The two sample t-test was used, to compare mean values of wmAnMtb for both cohorts. The two proportion z-test was used, to compare the proportions from the original and the new cohort, to analyse the proportion of children with wmAnMtb ≥ 1, and to analyse the proportion of children experiencing severe neutropenia, in the two cohorts. A Cox proportional hazards regression model was used, to compare median time to dose escalation event, for both the cohorts.

7.2 Results

There were 37 children in this new cohort that had started maintenance therapy from June 1^{st} 2017 to January 31^{st} 2018. We used the analytic methods from the previous chapter, to check the effectiveness of MT following the intervention.

Figure 7.1 (a) shows the graph for wmAnMtb vs. wmANC for the original cohort (OC), and the Figure 7.1 (b) shows the same graph, for the newer cohort (NC). The x-axis represents wmAnMtb dose intensity,

which is plotted against wmANC on the y-axis. Each dot in the graph represents the summarised information for 6-MP and MTX, with respect to ANC for a child over a duration of start of MT and time of analysis (May 20^{th}, 2019). The green colour dot represents children who have not had a relapse, whereas the magenta colour represents children who have had a relapse. The red horizontal lines, represent the upper and lower limits of the desired target treatment range of ANC –750-1,500 $\times 10^6/L$– and the dotted blue line, represents the 100% or starting dose, of anti-metabolites.



(a) Original cohort **(b)** New cohort

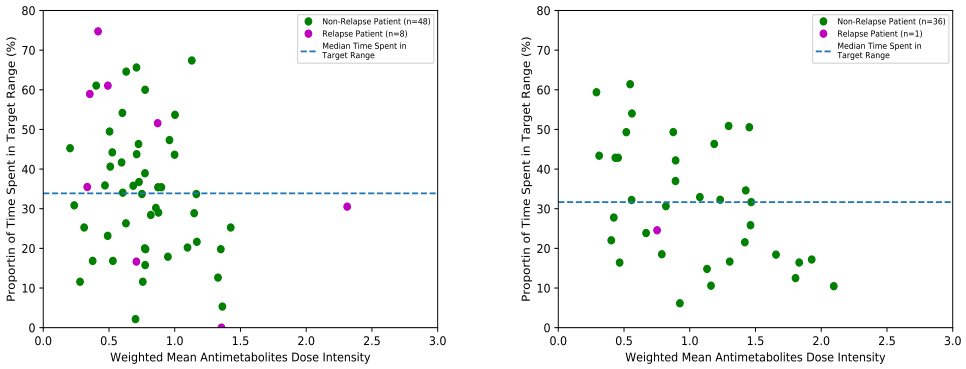
Figure 7.1: Comparison of (wmAnMtb vs wmANC) analysis for original vs new cohort.
Note: One data point is missing from newer cohort to adjust the x-axis scale

We started with checking the number of children with dose intensity, wmAnMtb greater than 1. In the OC, 23% (13/56) of children had ≥ 1. In the NC, 49% (18/37) had wmAnMtb ≥ 1 by cycle 5 (p-value=0.02). The effect of intensive dosing was observed with more children being prescribed higher dose intensities of antimetabolites, in the newer cohort. The average wmAnMtb value for the NC was 1.08, and was higher, as compared to the value of 0.78 for the OC (p-value=0.005).

In the new cohort, most children did not fall within the target range of wmANC (750-1,500 $\times 10^6/L$), even with the higher dose intensity through

cycle 5. As you can see in Figure 7.1 (b) most of the green dots are beyond the upper limit of the red line. Only 5/37 (13.5%) children had wmANC values within the target range, of these one child had a dose intensity greater than 1. Most children, 32/37 (86%) had wmANC greater than 1,500 $\times 10^6/L$ by cycle 5.

The proportion median time in the target treatment range for the children in the newer cohort, was $\sim$ 31.6 weeks [IQR:18.12-42.85; full range:6.15-61.40] compared to $\sim$ 33.8 weeks [IQR:20.16-45.53; full range:0-74.74] weeks for the older cohort (Figure 7.2). (*Note*: The figures provided are with respect to proportions. We computed the proportion by taking denominator as the time for which the patient has completed MT (OC) or time of analysis (NC). Once, we had the proportions, we computed median and IQR for the proportions and reported for both the cohorts.)



(a) Original cohort **(b)** New cohort

Figure 7.2: Comparison of (wmAnMtb vs pTTR) analysis for original vs new cohort.
Note: One data point is missing from newer cohort to adjust the x-axis scale

We computed the median time to first dose increase for the two cohorts. The median time to first dose increase was observed in the 25^{th} week, cycle 3, for the newer cohort. This was 5 weeks earlier as compared to the older cohort, where it occurred at week 30. This is a modest change of

uncertain clinical significance which warrants further long term follow-up (p-value=0.06).

We compared the proportion of children experiencing severe neutropenia in the original cohort and in the new cohort. The proportion of children experiencing severe neutropenia in the NC was 26/37 (70.2%), in the older cohort it was 78.5% (44/56). This difference was not statistically significant (p-value=0.5). Table 7.1 and Table 7.2 summarise the information on dose increase and severe neutropenia in the two cohorts of children. Frequency of severe neutropenia episodes was similar in both the cohorts. The OC had a frequency of 1.7 episodes per child (97/56), as compared to 1.35 episodes per child (50/37) in the newer cohort.

Table 7.1: Dose increase and severe neutropenia events original cohort (n=56).

	Dose Increase	No Dose Increase
Severe Neutropenia Event (Yes)	34	10
Severe Neutropenia Event (No)	11	1

Table 7.2: Dose increase and severe neutropenia events new cohort. (n=37).

	Dose Increase	No Dose Increase
Severe Neutropenia Event (Yes)	18	8
Severe Neutropenia Event (No)	10	1

Finally, we computed the duration of severe neutropenia episodes in the two subgroups: (1) children who had dose escalation, and (2) children who had no dose escalation. In the NC, we found the duration of neutropenia to be 5 weeks (median), in the children who had no dose escalation, and 1 week (median), for children who had dose escalation. *This was similar to the OC, where duration of neutropenia was longer in children who were in the no dose escalation subgroup.* Table 7.3 and Table 7.4 summarise the duration of severe neutropenia in the two cohorts.

Table 7.3: Duration of severe neutropenia episode in dose increase and no dose increase group for original cohort (n=56).

	Median [IQR]
Dose Increase	3[1-4]
No Dose Increase	4[3-6]

Table 7.4: Duration of severe neutropenia episode in dose increase and no dose increase group for new cohort (n=37).

	Median [IQR]
Dose Increase	1[0-4]
No Dose Increase	5[3-6]

Table 7.5 summarises the measures discussed in this chapter for the two cohorts: antimetabolite dose intensity > 1, time to first dose increase, proportion of time in the target treatment range, number of children with severe neutropenia episodes, and the total number of severe neutropenia episodes.

Table 7.5: Comparison of various indicators between original and new cohort.

	Original Cohort (n=56)	**Newer Cohort** (n=37)	**p-value**
# children with anti-metabolite dose intensity ≥ 1	13 (23.1%)	18 (48.6%)	***0.02***
Time to first dose increase episodes (weeks) (median)	30	25	0.06
Proportion of time in target treatment range (median)	$\sim$ 32.8	$\sim$31.7	-
# children with severe neutropenia episodes†	44 (78.5%)	26 (70.2%)	0.50
Total number of severe neutropenia episodes	97	50	-

† Please refer to Table 7.1 and Table 7.2

7.3 Conclusion

These analytic methods present an effective way to analyse the treatment status for children undergoing MT. We presented the results of the analytic methods for the original cohort, to the team of physicians. We presented specifically the graphs discussed here in Figure 7.1 (a) and Figure 7.2 (a). Following this intervention, physicians once again reviewed the dosing rules as a group. We collected new retrospective MT information on 37 children, who commenced MT from June 1^{st} 2017, to January 31^{st} 2018

In this chapter, we analysed the doing practice for the new cohort. Intensive dosing was observed in the new cohort, and more children were prescribed higher doses of anti-metabolites, as compared to the original cohort. At the end of cycle 5, however, this intensive dosing did not translate into seeing more children with wmANC within the range of $750 - 1,500 \times 10^6/L$. Some of the possible reasons may be as follows:

- A possible opportunity for further dose increase during the dose regulations.
- Non-adherence to prescribed anti-metabolites drugs by the children.
- Absolute neutrophil count may be a crude indicator of anti-metabolite dosing during MT. This argues for identification of additional markers based on pharmacological monitoring of 6-MP, to aid during dose regulations for individuals.
- The data is limited to 5 cycles only, and the full impact of maintenance dosing is not yet available with increased dose intensity prescribing.

The median duration of severe neutropenia episodes are longer in the non-escalation subgroup in both the cohorts (Table 7.3 and Table 7.4). Perhaps the non-escalation subgroup is sensitive to standard 6-MP and MTX doses, due to constitutional genetic polymorphism, resulting in a reduced ability to metabolise 6-MP and MTX. Testing of polymorphism in drug metabolism genes, may additionally aid in dosing practice.

We face a number of limitations in this analysis. The new cohort data consisted of 5 cycles only, as compared to the full 8 cycles for the original cohort. The data collection procedure is one of the major roadblocks.

Systems have yet to be implemented to collect maintenance therapy information in a systematic manner in one place, so we were limited in our capacity to collect demographic information for the new cohort. This analysis shows preliminarily, that visual summaries of MT information, can impact physician prescribing behaviour. Future studies need to look at the design and frequency of interventions with physicians, and follow-up impact on physician compliance with dosing protocols, during maintenance therapy.

Chapter 8

Objective 4: Development of an Automated Dose Advice Method to Aid 6-MP and MTX Dosing During Maintenance Therapy

The analytic methods presented in the previous chapter give a mechanism to evaluate the effectiveness of maintenance therapy. This chapter describes the development of an automated dose advice method, to assist physicians in dosing of 6-MP and MTX during maintenance therapy.

8.1 Background

ALL treatment requires dose regulation during the entire course of MT. Delivering optimal therapy by monitoring blood counts, and prescribing the maximum tolerated doses of 6-MP and MTX are the mainstay of MT. Myelosuppression, and toxicity have to be balanced by maintaining ANC within a defined range, while escalating the dose of antimetabolites, across the 96 weeks of MT. Prolonged treatment interruptions due to toxicity

are not desired during MT. Intensive monitoring, and accurate dose adjustment tailored to ANC, are essential during MT. It is challenging for physicians, to comply with the complex nature of dose adjustment rules during MT.

For better treatment outcomes, compliance to dosing protocols, is essential. The problem of compliance to ALL treatment protocols has been pointed out in many studies as previously discussed. Peeters et al studied prescription patterns of maintenance therapy in a cohort of 212 children with ALL, from the Hospital for Sick Children, in Toronto. They found that physician failure to adhere to the recommended protocol during MT, was associated with higher rates of relapse, in a homogenous group of children with standard risk ALL [17]. Children who had relapsed had received significantly lower cumulative doses of MTX during MT, compared to those who did not.

Bohnstedt et al. in two different studies looking at data from 538 children found that children with ALL and Down syndrome, had an increased risk of bone marrow relapse. The data suggested this in part, may be due to physician unwillingness to optimize the intensity of MT in children with Down syndrome and ALL [42] [38].

Oliveria et al., retrospectively evaluated mean prescribed 6-MP, and MTX doses in a cohort of children from Brazil [43]. They were concerned that one of the reasons for increased relapse of ALL, in developing countries, is because of failure to follow protocol during MT. They observed a better event free survival, for children with higher chemotherapy interruptions, due to toxicity and median leukocyte count $< 3,500 \times 10^6/L$, as compared to the children with less therapy interruptions, and median leukocyte count $> 3,500 \times 10^6/L$. They concluded that the chemotherapy

intensity to achieve myelosuppression, may not have been adequate, as a result of compliance failure to therapeutic protocols.

Dosing protocols may be complex. The retrospective study discussed in Chapter 5, showed that physicians had difficulty following the dosing protocol, and there is opportunity to improve compliance. In addition, the retrospective analysis using graphical analysis, showed a conservative dosing practice, with problems related specifically to dose escalation.

In view of this, we developed an automated dose advice method, to assist physicians during MT. The data points to develop the methods were taken from ten patients randomly selected from the cohort. Working closely with an expert paediatric oncologist we iteratively compared dosing decisions made by ADAM, and the expert physician, and made changes to the system to come up with the final version.

8.2 Method

This section describes various conditions, and actions during MT. We coded the actions based on the conditions defined in the ICiCLe-ALL-14 protocol for dose adjustments, with inputs from expert paediatric oncologists.

We started by spending a lot of time in MT clinic at TMCK with physicians, staff, and patients, to understand the dosing decisions required during MT. Table 8.1 delineates terminology and their definitions used during MT.

Table 8.1: Terminology and their definitions used during MT

Terminology	Definition
Maximum Tolerated Dose (MTD)	Highest dose of 6-MP and MTX administered without interruption for a 6-week (42-day) period
Neutropenia	
Severe	ANC $\leq 500 \times 10^6/L$
Moderate	ANC $= (501 - 750) \times 10^6/L$
Thrombocytopenia	
Moderate	PLC $\leq 50,000 \times 10^6/L$
Mild	PLC $= (50,001 - 75,000) \times 10^6/L$
Dose decreases	
Dose reduction	6-MP and MTX at 50% of MTD
Dose interruption	6-MP and MTX administration halted
Recovery of blood counts	
Following dose reduction	To MTD when ANC $\geq 750 \times 10^6/L$ and PLC $\geq 75,000 \times 10^6/L$
Following dose interruption	To MTD when ANC $\geq 750 \times 10^6/L$ and PLC $\geq 75,000 \times 10^6/L$
6-MP dose escalation†	
'2 of 3' ANC rule	If ANC $\geq 1,500 \times 10^6/L$ in 2 of 3 blood count checks over 6 weeks, with blood counts tested every 2 weeks
MTX dose escalation†**following 6-MP dose escalation**†	
14 days	If ANC 2 weeks after 6-MP dose escalation is $\geq 1,500 \times 10^6/L$
28 days	If ANC 2 weeks after 6-MP dose escalation is $< 1,500 \times 10^6/L$

Continued on next page

Table 8.1 – *Continued from previous page*

Terminology	Definition
Dose reset to new 100%	Reset of start dose to a new 100% dose (as % of $1.0 \times BSA$ dose) following 3 consecutive attempts at dosing on $1.0 \times BSA$ dose OR Dose reset may also be at physician discretion

† dose escalation may be from 100% to 125%, 125% to 150%, 150% to 175%

Dose adjustment conditions, and actions were discussed with paediatric oncologists. All the conditions had respective actions, which were then coded to aid in algorithm development. Table 8.2 describes the coded actions and their conditions.

Table 8.2: Anti-metabolite dose change conditions and their actions

Code		Condition	Action
A	1	6 weeks of uninterrupted dosing at 100% 6-MP and MTX Dose	6-MP dose escalation (100% to 125%)
	1.1	Either 14 days or 28 days after A1	MTX dose escalation (100% to 125%)
B	1	6 weeks following A1.1, if '2 of 3' ANC rule **met**	6-MP dose escalation (125% to 150%)
	1.1	Either 14 days or 28 days after B1	MTX dose escalation (125% to 150%)
	2	12 weeks following A1.1, if '2 of 3' ANC rule **not** met	6MP dose escalation (125% to 150%)
	2.1	Either 14 days or 28 days after B2	MTX dose escalation (125% to 150%)
C	1	6 weeks following B1.1/B2.1, if 6 weeks following A1, if '2 of 3' ANC rule **met**	6MP dose escalation (150% to 175%)
	1.1	Either 14 days or 28 days after C1	MTX dose escalation (150% to 175%)

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Table 8.2 – *Continued from previous page*

Code		Condition	Action
	2	12 weeks following B1.1/B2.1, if '2 of 3' ANC rule **not** met	6MP dose escalation (150% to 175%)
	2.1	Either 14 days or 28 days after C2	MTX dose escalation (150% to 175%)
D	1	Following Recovery of blood counts	Return to MTD
	2	Following 6 weeks of uninterrupted dosing at MTD for 6MP and MTX	MTD 6MP dose escalation†
	2.1	Either 14 days or 28 days after D2	MTD MTX dose escalation†
E	1	Severe neutropenia and/or moderate thrombocytopenia	Dose interruption
	2	Moderate neutropenia and/or mild thrombocytopenia	Dose reduction
F	1	Following E1 or E2 on ≤ 3 consecutive occasions from start of therapy	Return to 100% BSA dosing
	2	Following E1 or E2 on > 3 consecutive occasions from start of therapy	Dose reset to new 100%

† dose escalation may be from 100% to 125%, 125% to 150%, 150% to 175%

Once, we had all the actions, and the conditions, each dose combination of (6-MP and MTX) which is observed, after an action is completed, was converted into a state. Transitions from each state to other possible states, were identified from Table 8.2. All the possible transition states were computed for each state. A possible state diagram representing all the states, and their transitions is presented in Figure 8.1.

The state diagram involves uni-directional, and bi-directional arrows. The bi-directional arrow for a state, represents a state transition from the state in question, to the resultant state, and vice-versa. For the unidirectional arrow, the transition is specific from the state in question, to the resultant state. Loops represent the change in state, to the same state.

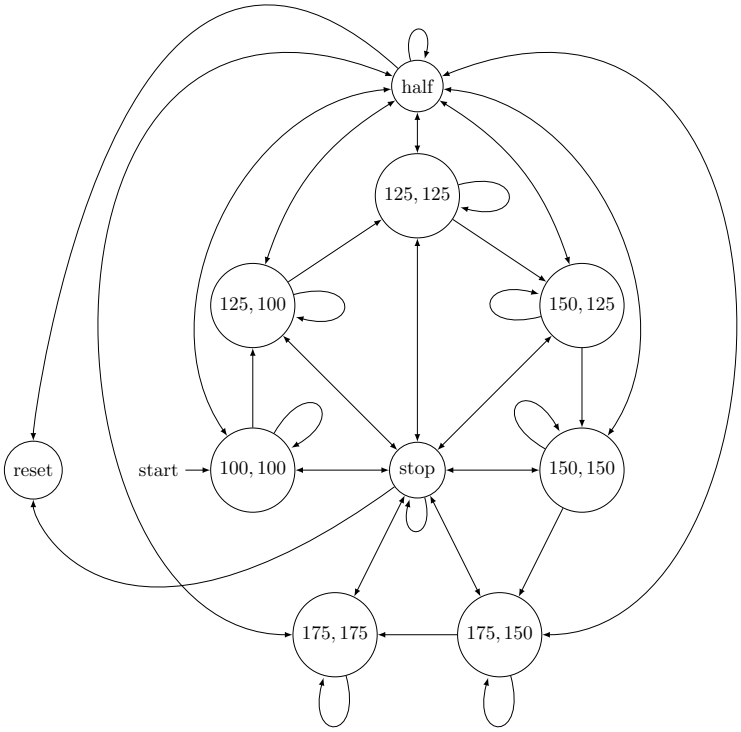

Figure 8.1: State diagram showing different states representing dosing decision during maintenance therapy.
Each state represent combination of (6-MP, MTX) dose prescribed in %.
Note 1: "stop": (6-MP, MTX) *Dose interruption*; "half": (6-MP, MTX) *Dose reduction*; "reset": *Dose reset* at physician discretion. Please refer to Table 8.2 for the definitions of *Dose interruption*, *reduction*, and *reset*.
Note 2: Final (end) state for the state diagram is not represented as the end state may vary due the child's MT progress.

For example, a loop on (6-MP, MTX: 100%, 100%) state means same dose will be given on transition or next visit.

The final state in the the state diagram is not shown in Figure 8.1. Depending upon the progression of the child's MT, and the physician's decisions, the final state may vary. For example, due to several interruptions in MT, the child may reach a dose of (6-MP, MTX: 150%, 150%) by the completion of MT, whereas another child may have less interruptions and reach a dose of (6-MP, MTX: 175%, 175%) at the end of MT. The final state for the first child would be (6-MP, MTX: 150%, 150%), and for the

second child (6-MP, MTX: 175%, 175%).

Such scenarios produce different final states. With this information, we developed an algorithm mimicking the dose adjustment protocol, which we named the ***automated dosing advice method*** (***ADAM***). The algorithm takes a child's information – height, weight, and patient ID, at the beginning of algorithm execution. This is followed by the ANC, and PLC counts, for the latest visit as inputs. The algorithm results in the 6-MP and MTX in percentage, to be given to the child with a description of the rule that was followed to come to the conclusion.

Finally, we carried out an analysis by comparing the automated method's output with that of the expert physician. We randomly selected all retrospective data of ten children from the cohort. The ANC and PLC values for these ten children were extracted. The median number of visits for these ten children was 50 [IQR: 47.25-51.75]. A total of 497 data points for ten children were present.

The doses of 6-MP and MTX actually prescribed were removed. For each child information on each visit date, ANC, PLC, cycle, and body surface area was given to the expert physician. The physician prescribed 6-MP and MTX doses based on the rules of the ICiCLe protocol, in an effort to create an ideal data set. This dose prescription exercise was carried out for four months from August to November 2018 for the 497 data points collected. We carried out the following iterative steps for our analysis:

Iteration 1

- The expert physician assigned the values of 6-MP and MTX doses to the data points represented by ANC, and PLC, by following the same protocol as discussed above. The resultant dosing decision points by the physi-

cian were termed as prescribed doses. Simultaneously, the dosing decisions for the data points of 6-MP and MTX were evaluated by ADAM, and termed as predicted doses.

Whenever, a dose escalation went beyond 1.75 times of the starting dose, the dosing procedure by ADAM was halted. Due to this, the total number of data points validated by ADAM were 421/497. The remaining 76 data points were not considered for further analysis.

- Next, we compared the prescribed doses by the expert physician against ADAM's predicted doses to get the number of mismatched dosing decisions.
- The variations in predicted, and prescribed doses were discussed with the expert physician. ADAM's reasoning logic was rectified in cases where the dosing protocol was not followed. The prescribed and predicted values were compared to check the performance of ADAM.

Iteration 2

- After, the errors were rectified, we evaluated the predicted, and prescribed doses. Both the results were compared once again to check the performance of ADAM.

Willmott discussed the measures to evaluate the performance of any model developed [106] [107]. Based on the difference between the observed and predicted values, that is difference measure, the *root mean square error (RMSE)* can be used. RMSE represents the magnitude of error, a model may produce. RMSE is used to evaluate, and understand how accurately

the developed model predicts the actual output. It is always desirable that the RMSE converges to a value of 0. RMSE is computed as

$$RMSE = \sqrt{\frac{1}{n}\sum_{t=1}^{n}(Y_t - \hat{Y}_t)^2} \tag{8.1}$$

For our work, Y_t represents the prescribed dose values by the expert physician whereas $\hat{Y}_t$ represents the predicted doses by ADAM. The letter n represents the number of observations.

In addition to RMSE, a new measure - *index of agreement (IOA)*, represented as d - was discussed by Willmott. This measures a degree to which the model's prediction are free from error or predicted values are accurately estimated as observed value. The value of d ranges from 0-1, where 0 represents complete disagreement, and 1 represents complete agreement between predicted and observed values. The value of d is computed as follows

$$d = 1 - \frac{\sum_{t=1}^{n}(\hat{Y}_t - Y_t)^2}{\sum_{t=1}^{n}(|\hat{Y}_t - \bar{Y}_t| + |Y_t - \bar{Y}_t|)^2} \tag{8.2}$$

$\bar{Y}_t$ in Equation 8.2 represents mean of prescribed doses, and other notations are the same as defined in the RMSE equation (Equation 8.1).

8.3 Results

ADAM's predicted output was validated against the expert physician's prescribed doses. The comparison of predicted, and prescribed outputs was performed over two iterations, and is presented in Table 8.3. It also shows the number of mismatched data points from iteration 1 and 2 with RMSE and the index of agreement value.

In Table 8.3, the first column represents the subject number whose data was evaluated, delineated as 1-10 for the ten childrens' data. Column 2-7 represents results from iteration one. Column 2 and 3 show number of mismatch decision points for 6-MP and MTX respectively, after comparing ADAM's predicted output, and the expert physician's prescribed dose. RMSE and IOA for mismatch points with respect to 6-MP and MTX are mentioned in column (4,5) and column (6,7) respectively.

Once the modifications, and errors were rectified in ADAM, iteration 2 was carried out. Column 6-9 consists of results for iteration 2. Column 8 and 9 shows number of mismatch results, and RMSE in column 10 and 11 for 6-MP and MTX respectively. Column 12 and 13 represents value for IOA.

Table 8.3: Comparison of number of mismatched data points, RMSE, and IOA for prescribed and predicted doses.

	Evaluation of prescribed and predicted doses (Iteration 1)						**Evaluation of prescribed and predicted doses (Iteration 2)**					
Subject	**# Data Points Mismatch for 6-MP**	**# Data Points Mismatch for MTX**	**RMSE (6-MP)**	**RMSE (MTX)**	d_{6-MP}	d_{MTX}	**# Data Points Mismatch for 6-MP**	**# Data Points Mismatch for MTX**	**RMSE (6-MP)**	**RMSE (MTX)**	d_{6-MP}	d_{MTX}
1	3	3	11.32	11.73	0.981	0.978	2	0	3.75	0	0.998	1
2	0	1	0	4.29	1	0.987	0	0	0	0	1	1
3	21	27	17.36	19.48	0.953	0.943	3	2	5.79	5.46	0.994	0.995
4	23	23	49.38	46.50	0.662	0.654	1	1	2.43	0.41	0.998	1
5	11	6	22.73	21.37	0.952	0.954	1	0	3.47	0	0.999	1
6	1	0	1.8	0	1	1	1	0	1.8	0	1	1
7	5	5	9.41	10.21	0.986	0.983	0	0	0	0	1	1
8	26	19	19.02	15.68	0.962	0.971	0	0	0	0	1	1
9	3	11	7.12	12.67	0.995	0.983	0	2	0	2.91	1	0.999
10	7	2	7.12	12.67	0.995	0.983	2	1	4.66	4.17	0.997	0.998
Average	10	9.7	14.85	15.08	0.947	0.946	1	0.6	2.21	1.29	0.998	0.999

After iteration 1, we found errors in ADAM's knowledge base where the states, and their actions were encoded. The inference module to interpret the conditions for the respective states were also rectified. After the error rectification process, we re-evaluated the prescribed doses, by comparing physician decisions against the predicted doses suggested by ADAM. An average root mean square error value of more than 10% occurred when the prescribed doses, were checked against the predicted doses in iteration 1. It came down to less than 3% after the prescribed doses were rechecked for time, and count errors. The IOA parameter after iteration 2, had a value of 0.99 for both 6-MP and MTX indicating excellent prediction capability of ADAM.

We found two types of errors that were prominent during validation of prescribed, and predicted doses. First, "the days error". This was a dosing error by the expert physicians which occurred due to miscalculation in computing the difference in days between two visits. The second, is a "counts error". This was due to miss-reading of counts while making dosing decisions. The differences in the results were discussed with the expert. The changes were accepted by the physician for the above mentioned two errors, after iteration 2.

8.4 Discussion

One of the problems that presents a challenge during MT phase of ALL treatment is compliance to the treatment protocol by physicians. Studies have shown better survival outcomes when the intensity of treatment is greater specifically for dosing of 6-MP [17,20,38,43]. Children who received more intense doses of antimetabolite drugs during MT, as compared to

children who received less, have had decreased risk of relapse.

We developed an automated dose advice method to assist physicians in dosing 6-MP, and MTX drugs during MT. ADAM was designed as a decision support method recognizing the above mentioned problems. All the dosing guidelines were discussed with expert physicians, to build the method. The output produced by ADAM directly presents the combination of 6-MP and MTX to be prescribed. The output is in the form of percentage that needs to multiplied by the starting doses of 6-MP and MTX with respect to BSA.

The method was designed with the involvement of an expert paediatric oncologist, and validated with MT data, from 497 decision points in 10 randomly selected children from the cohort. The difference in predicted and prescribed values was evaluated with the help of a difference measure, the RMSE and IOA. The ADAM results were in concordance with the expert physician's prescribed output with average RMSE less than 3%. IOA showed very high concordance in terms of predicting the values for dose as same as prescribed by the expert physician with a value of greater than 0.99 for both, 6-MP and MTX.

Another point to notice is the IOA value for subject 4 in iteration 1. The value of d is 0.66, which suggests a huge difference between the predicted and prescribed values. In other words, the IOA is sensitive to huge differences or extreme values, of predicted and observed values, due to squared differences.

We could not compute an appropriate sample size to evaluate the ADAM performance as it was the first or pilot study to evaluate only ADAM's performance. A prospective study to evaluate ADAM would require a desired power value along with the alpha value, and results for

mean and standard deviation from the pilot study.

The RMSE value of 3% or the deviations observed in results were due to errors by the expert physicians made during arithmetic calculation for time elapsed between visits or misreading of the ANC, and PLC values. A potential reduction in number of arithmetic calculations, and protocol compliance deviations was observed by ADAM, as compared to the expert physician.

Apart from assisting the physicians in dosing during MT, another possible advantage of using ADAM is storage of MT information. Handwritten paper based records to maintain MT information dose not allow for analysis of effective MT over time. As ADAM requires previous dosing history along with visit dates along with the current counts, all the information is stored within the ADAM database. The use of hand written maintenance sheets could be minimised or eliminated.

In terms of limitations of the presented method, only one expert physician was involved in developing, and prescribing the doses for 10 children's test case data. The method could have been more robust with participation of more expert physicians in validating more number of test cases. This would have in turn increased the number of validation test cases data.

We have also developed a method to graphically display the distribution of oral tablets that needs to be consumed on a daily basis by the child. The method would assist parents to administer the doses of 6-MP and MTX on a daily basis. The module is not discussed as a part of this thesis work, and not yet integrated with ADAM. It is proposed as future work.

8.5 Conclusion

Treating to maximum tolerated dose is desirable for sustained myelosuppression, during MT. The physicians need to comply with dose regulation guidelines, while treating to tolerance. A potential issue of physician compliance was observed in past studies, along with the retrospective cohort analysis, presented by us in previous chapters. Chemotherapy medication error is another concern during MT. We present ADAM to address these concerns during MT. The analysis for ADAM's predicted doses, presented in this chapter would ensure the dosing guidelines compliance, and reduction in chemotherapy medication errors, in terms of prescriptions, and administration of doses.

Chapter 9

Conclusion and Future Work

9.1 Conclusion

Clinical decision support system (CDSS) can help physicians follow chemotherapy protocols and prevent chemotherapy related medication errors [86] [85]. In order to be effective, the design of a CDSS needs to be in line with the requirements of the users, and their environment. Flexibility in terms of decision making, and management of uncertain circumstances encountered during maintenance therapy need to be supported by a CDSS.

The CDSS has to have a graphic interface that effectively displays the chemotherapy protocols in context. One potential area where a CDSS may be helpful is in dosing of medications.

Automating the process of adjustments of dosages in a CDSS could reduce calculation errors. Documentation, and reporting errors add to the problem of medication errors. A pre-defined protocol for prescribed medication through a CDSS could further aid in dosing.

Alerts, reminders, and indicators during use of a CDSS aid physicians during decision making. The efficient display of information and the graphical trends help the user better understand the chemotherapy progress. Specific conditions related to toxicities, initial treatment observations, and

drug sensitivity could be provided by CDSSs.

The focus of our work is to develop new methods to summarise, and analyse retrospective MT information in order to develop a CDSS that would assist physicians during MT clinic. The CDSS could aid in dosing, monitoring the progress of the child's MT, and support the physicians' compliance with the dosing guidelines.

In view of this, we looked into following four primary objectives presented in Chapter 1:

- **Objective 1** - To develop a single data repository for maintenance therapy from paper and electronic based records
- **Objective 2** - Retrospective cohort study of children who completed maintenance therapy from February 18^{th} 2016, to September 27^{th} 2018 (31 months) at Tata Medical Centre, Kolkata to understand existing dosing practice and toxicity
- **Objective 3** - Development of analytic methods to understand effectiveness of maintenance therapy
- **Objective 4** - Development of an automated dose advice method (ADAM) to aid 6-MP and MTX dosing during maintenance therapy

The work was carried out at Tata Medical Center (TMCK) and Tata Translation Cancer Research Centre Kolkata, West Bengal, India from March 2017, to October 2018. A retrospective cohort study for the group of children who completed MT from February 18^{th} 2016, to September 27^{th} 2018 at TMCK was carried out. The data collection procedure started in July 2017, and continued till October 2018. The information on MT with variables - absolute neutrophil counts, platelet counts, date of visit

to the hospital, 6-MP, and MTX was gathered. We used hand written maintenance sheets, and hospital management system for collecting the data. A total of 2,704 entries were collected on MT variables for the cohort.

Chapters 4, 5, 6, and 8 provide the methodology followed to carry out the above objectives. They also present the results and observations which are discussed in details. We summarise below the major observations and conclusions corresponding to each of the above research objectives.

1. We found that the MT information recording process is not organised enough to a level wherein the records could be retrieved in order to analyse the information. Lack of such facilities hinders the monitoring of the treatment. It also prohibits the clinicians to determine, and update the treatment regimens based on numerous factors related to the patients.

2. The line graph displaying longitudinal information on ANC, 6-MP, and MTX give an idea on how the child is progressing during MT. Also, physician compliance to guidelines can be checked.

3. The retrospective cohort analysis showed that the median time to first episode of dose escalation occurred in the 30^{th} week that is during the third cycle of the MT. The severe neutropenia episodes were maximum, 30%, during the first cycle of the therapy for the cohort thereafter stabilising in next seven cycles. There was no statistically significant difference in either occurrence of neutropenia events or duration of neutropenia episodes between children who had at-least one episode of dose increase compared to children who did not have any dose increase episode. Hence, it was difficult to difficult to ob-

serve any relation between dose escalation and a drop in ANC counts. However, the duration of severe neutropenia episodes was longer in no dose escalation. This group of children may be genetically sensitive to anti-metabolites.

4. The physicians' dosing for the cohort was evaluated using conditional probability. Further opportunity to optimise MT was concluded with respect to prescribing antimetabolite drugs.

5. We develop analytic method by summarising the longitudinal MT information on ANC, 6-MP, and MTX by computing weighted means. The graphical representation of these summary variables would enable the clinical team to observe the progress of children undergoing MT, and check for physicians' compliance to dosing guidelines. Time spent in the treatment range was another parameter that summarised the amount of time spent within the desired therapeutic range. Three summary variables (1) weighted mean absolute neutrophil counts, (2) weighted mean anti-metabolite dose intensity, and (3) proportion of time spent in treatment range presents a 3 dimensional information on MT. This would assist the clinical team to provide better MT treatment.

6. The results from analytic methods were presented to the team of physicians at TMCK. Following this intervention, we evaluated the dosing practice for a new cohort. We saw dosing intensity was increased and better as compared to original cohort, but there is a further opportunity to optimise dose regulation practice.

7. We developed an automated dose advice method (ADAM) that could assist the clinician in dose prescribing during MT. ADAM

outperformed the expert physician while recommending the oral chemotherapy drugs.

The broader focus of our work is to build a clinical decision support system (CDSS). Usually, a CDSS encompasses knowledge base, inference engine, and an uncertainty management block. The ADAM method presented in the Chapter 8 provides a knowledge base, inference engine, and a database support to store the values. The knowledge base of ADAM has the decision making rules encoded based on the ICiCLe-ALL-14 dosing protocols along with inputs from the paediatric oncologists. ADAM also includes a inference engine which processes the incoming clinical data of ANC, PLC, and visit date for the child. The information is stored in the comma separated value (csv) format which serves as a database.

The uncertainty management for chemotherapy drugs dosing includes the deviation from the dosing protocol by the physicians. For the current version of ADAM, it does not take into consideration other relevant factors apart from ANC, PLT, 6-MP and MTX. The deviation in decision making is from the physician's side. However, if the physicians find the current version of ADAM usable and helpful in the clinic in real time, we may include other information such as toxicity, surrogate markers for 6-MP dose adherence such as absolute lymphocyte counts, and mean corpuscular volume. The provision to deviate from ADAM's suggestion also could be developed.

Apart from this, we could collect the CDSS decision over a certain period of time. This data may have deviations from rules-based decision. We could add a fuzzy logic base or machine learning decision making to address the uncertainty management in decision making. Overall, CDSS

should be able to provide decision support, flexibility, patient safety, automation, standardisation, usability, and reliability.

We believe the analytic methods, and ADAM integrated in a CDSS is capable of assisting, and improvising MT in the clinic. In order to achieve the desired results, the systems needs to be evaluated rigorously in a clinical setting.

In terms of limitations, the number of children in the cohort is less than the actual population that is observed at TMCK. As MT lasts for two years and thereafter, the children come to the hospital once in three months, it was difficult to obtain the MT information. In addition, MT information was not recorded in a systematic manner. Due to this, it was difficult to retrieve MT information of large number of children to carry out any study.

The number of children completing MT every month varied, and there was no systematic method to retrieve MT information to perform any study. This led to a bias during selecting the patients for the cohort which was not done randomly. We or the clinical trials unit team at TTCRC had a prior information on children completing MT based on which the MT information was collected.

The analytic methods developed with the help of summary measures, wmANC, wmAnMtb, and pTTR, needs to be used prospectively in large studies in measuring effectiveness of MT, to check these methods and measures are valuable in long term. The validation of ADAM was performed on 424 decision points. Although the performance of the method was better than the expert, a further validation on more decision points would provide robustness to the method. Further, ADAM should be tested against the dosing decisions from different expert with different levels of experience.

The graphical interface for the ADAM needs to be developed. The shell base interface may not be user friendly to some users and lead to user dissatisfaction. The cognitive load of the developed interface must be evaluated before the usageof CDSS is proposed in a clinical setting.

9.2 Future Work

The results from this dissertation are the individual modules that are essential to build a CDSS. The analytic methods using summary measures would give continuous progress and updates on an individual's response to the therapy. The regulation the bi-weekly doses, to assist physicians, would be carried out with the help of ADAM. Figure 9.1 shows a proposed CDSS with the different modules, and features that are needed.

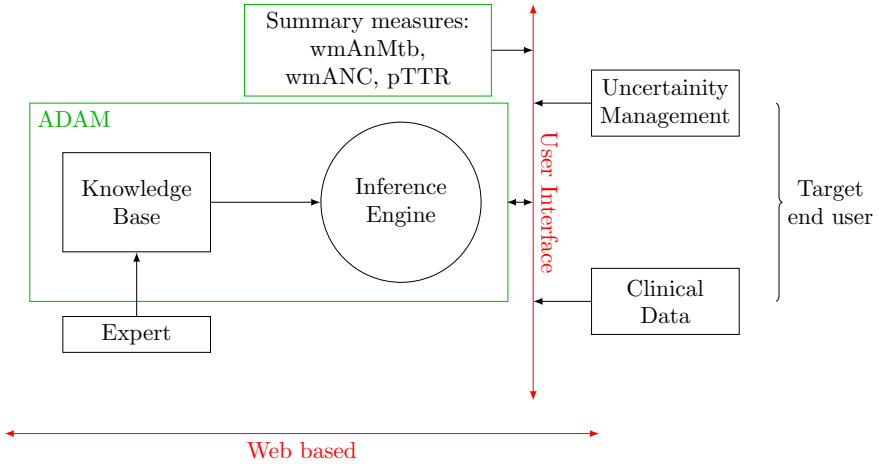

Figure 9.1: Proposed CDSS with various modules. ***Note***: Green color indicates output from this dissertation; Red color indicates future work

.

The user interface for the ADAM needs to be developed with the help of discussions with expert physicians, and cognitive researchers for it's ease

of use. The interface should allow the physicians to enter the clinical data fluently with clear understanding of the context. At the same time, the longitudinal data along with progression graph should be displayed on the screen. This would give physicians a better understanding of the past treatment, the child has undergone.

The prescribed dose suggestions by the ADAM should be presented with longitudinal data, progression graph, and summary measures. This would aid physicians to make a decision on doses to be prescribed. Figure 9.2 shows a basic or initial version of interface built for the CDSS.

(a) (b) (c) (d) (e) (f)

Figure 9.2: Proposed interface in the form of various forms to enter and visualise clinical data for the CDSS (basic version)

Sub-figure: (a) user login page; (b) new user (doctor) registration page; (c) new user (patient) registration page; (d) form to enter weekly blood count details along with other MT therapy infomration for a child; (e) suggestion for prescribed doses of 6-MP and MTX for the physicians; (f) summary of weekly doses for current visit along with weekly distribution of 6-MP tablets to be consume by the children.

The problem of medication adherence during MT is reported in the literature [40] [39]. As MT is very long, the effects of medication can be only seen if children are adherent to the prescribed doses. To address the problem of medication adherence, we proposed an android based mobile pill reminder application. Figure 9.3 shows a basic version of the proposed

application which is under development.

Figure 9.3: Basic version of proposed android based mobile application for prescribed dose reminder.
Sub-figure: (a) user login page; (b) choose the appropriate user and language; (c) enter the prescribed dose of either for 6-MP or MTX depeding upon the tablet selection; (d) check the distribution of the tablets weekly; (e) respond to notification of tablet consumption.

The application would be installed on mobile phones available with parents or children. Once the user creates accounts, they would be able to enter the prescribed weekly doses of 6-MP and MTX in respective fields of the application. It would show the weekly distribution of the doses that needs to be consumed by the children. A reminder on specified time set by the user would remind the parents or children to take the

required amount of 6-MP and MTX tablets. The application would ask the user to respond to a notification of whether the tablets were consumed or not. The response would be saved internally in the phone which can be later retrieved manually from the phone or sync to web-based server.

We believe a web enabled CDSS along with pill reminder application could assist in optimising MT, and overcome the current challenges present during MT. The proposed medical informatics solutions could be possibly use to support the ICiCLe-ALL-14 clinical trial nation wide, and improvise the health care delivery for children with ALL in India.

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Contributions

- Manuscript: **Mungle T** et.al., *Novel Methods to Analyse Maintenance Chemotherapy Information in Children with Acute Lymphoblastic Leukaemia*. (In preparation, to be submitted in the journal - Pediatric Blood & Cancer)
- Abstract: **Mungle T** et.al., *Automated Dose Advice Method to Aid 6-mercaptopurine and Methotrexate Dosing During Maintenance Therapy* (In preparation, to be submitted in conference - $XIII^{th}$ SIOP Asia 2020, March 27-29, Mumbai, India)
- Presentation on *Decision Support System for Supervision of Maintenance Therapy* at PHOCON 2017, 24-26 November, 2017, Kolkata, India
- Grant:

  Applying Artificial Intelligence to Improve Outcomes for Children Undergoing Maintenance Chemotherapy for Acute Lymphoblastic Leukaemia in Low Resource Settings under the Scheme for Promotion of Academic and Research Collaboration (SPARC); SPARC/2018-2019/P639/SL, Dt.15-03-2019; MHRD, New Delhi, India. (Sanctioned Amount: *72.4 Lakhs*)

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- **Mungle, T.**, Tewary, S., Arun, I., Basak, B., Agarwal, S., Ahmed, R., Chatterjee, S., Maity, A.K. and Chakraborty, C., 2017. Automated characterization and counting of Ki-67 protein for breast cancer prognosis: A quantitative immunohistochemistry approach. *Computer Methods and Programs in Biomedicine*, 139, pp.149-161.
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- Maity, M., Dhane, D., **Mungle, T.**, Maiti, A.K. and Chakraborty, C., 2017. Web-Enabled Distributed Health-Care Framework for Automated Malaria Parasite Classification: an E-Health Approach. *Journal of Medical Systems*, 41(12), p.192.
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