**Time from Diagnosis to Treatment as a Prognostic Factor in Adult Patient Newly-Diagnosed with Acute Myeloid Leukemia: A 5-Year Retrospective Study in a Tertiary Institution**

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**INTRODUCTION**

**Background of the Study**

Acute Myeloid Leukemia (AML) is a rare bone marrow cancer resulting from an accumulation of immature, nonfunctional blood cells (myeloblast) in the bone marrow and blood leading to abnormal hematopoiesis. The resultant anemia leads to weakness and pallor; neutropenia leads to increase risk of infection and poor wound healing; and thrombocytopenia leads to spontaneous bleeding. 1,2

Leukemia accounts for 2.5% of all new cancer incidence and 3.1% of cancer related mortality.3AML is the most common form of acute leukemia among adults in the United States, as well as the largest reports of annual death from leukemias.4 In the Philippines, leukemia is among the top 5 causes of cancer mortality, with increasing incidence from 5,795 in 2020 to 7,026 in 2022.5

Historically, AML is defined by the French American British (FAB) system using morphology and immunohistochemical stains to differentiate it from acute lymphoblastic leukemia (ALL).6 In the latest World Health Organization (WHO) Classification, AML is divided into 2 separate groups: AML defined by differentiation, and AML with defining genetic abnormalities with the later confirming the diagnosis regardless of blast percentage. The 20% blast cutoff is maintained to differentiate Myelodysplastic Syndrome (MDS) from AML. Classification of AML requires morphologic, immunophenotyping and molecular genetic analysis.7

**Table 1. 2022 WHO classification of Acute Myeloid Leukemia7**

|  |  |
| --- | --- |
| AML with defining genetic abnormalities | AML defined by differentiation |
| APL with PML::RARA fusion  AML with RUNX1::RUNX1T1 fusion  AML with CBFB::MYH11 fusion  AML with DEK::NUP214 fusion  AML with RBM15::MRTFA fusion  AML with BCR::ABL1 fusion  AML with KMT2A rearrangement  AML with MECOM rearrangement  AML with NUP98 rearrangement  AML with NPM1 mutation  AML with CEBPA mutation  AML, myelodysplasia-related  AML with other defined genetic alterations | AML with minimal differentiation  AML without maturation  AML with maturation  Acute basophilic leukemia  Acute myelomonocytic leukemia  Acute monocytic leukemia  Acute erythroid leukemia  Acute megakaryoblastic leukemia |

Typical treatment of AML involves two main phases, remission induction, followed by consolidation treatment. Induction chemotherapy usually includes cytarabine and an anthracycline, with a possible addition of a third drug if with noted targetable mutations. Consolidation treatment may involve several cycles of high-dose cytarabine or allogeneic stem cell transplantation.8Treatment strategy depends on the patient’s functional capacity and complications from pre-existing comorbidity. Patients who cannot tolerate intensive treatment strategies may be given hypomethylating agent (HMAs) or venetoclax-containing regimens as their treatment regimen with good outcomes.9-11The availability of novel agents against targetable mutation further improves the survival rates. However, the results of tests for these targetable mutations usually only become available in 7 days or more.12

The severity and onset of AML vary from person to person however, it is advised that diagnosis and treatment is started in a timely manner. Identified barriers of treatment includes, but not limited to, clinical delays (infection or optimization of clinical status), high costs of treatment, lack of access to treatment/facilities, unfamiliarity to novel agents, and challenges in treatment of relapse/refractory cases. 13, 14

While various international papers investigating the impact of time delays in AML reveals contradicting results, there are no local studies about the prognostic effect of time from diagnosis to treatment (TDT). 16-22 In this study, we aim to evaluate the relationship between TDT and prognosis of patients newly diagnosed with AML.

**Research Question**

Does TDT affect the prognosis of patients with newly diagnosed acute myeloid leukemia undergoing intensive chemotherapy?

**Objectives**

The main objective of this study is to determine if TDT affects the prognosis of patients with newly diagnosed AML. The specific objectives are as follows:

1. Determine the baseline demographic, clinical, and hematologic profile of newly-diagnosed AML patients, including:
2. Age at diagnosis
3. Sex
4. ECOG status
5. HCT-CI
6. Time from diagnosis to treatment
7. AML type
8. ENL risk 2017 group
9. Use of hydroxyurea and cytarabine pretreatment as cytoreductive agent
10. Baseline WBC (x109/L)
11. LDH
12. Bone marrow blast (%)
13. Karyotype
14. Treatment regimen
15. Allocation to allogeneic stem cell transplantation
16. Determine the clinical outcomes including remission status, early death, event-free survival, and 1-year overall survival
17. Determine the reasons for delay of treatment initiation including clinical delays (infection or nutritional upbuilding), high costs of treatment, lack of access to treatment/facilities, unfamiliarity to novel agents
18. Determine the association between TDT, specific reason of treatment delay, and 1-year overall survival of newly-diagnosed AML patients
19. Determine the association between TDT and remission status, early death, event-free survival, and 1-year overall survival of newly-diagnosed AML patients

**Literature Review**

AML results in the accumulation of immature, nonfunctional myeloblast in the bone marrow and blood leading to signs and symptoms of anemia, neutropenia and thrombocytopenia. Historically, it was considered as one of the hematologic emergencies due to its high mortality rate, requiring prompt initiation of treatment.

AML treatment strategies vary significantly, affecting the outcomes of patients. Approximately 60-70% of adults with AML can expect to achieve complete remission (CR) following induction therapy. 28 In a study focusing on older adults (age >65), complete remission rates were about 50% for those receiving standard intensive induction. 29 Relapse rate is approximately 60% within five years for those not undergoing allogeneic hematopoietic stem cell transplantation (Allo-HCT). 30 For patients achieving CR, the two-year overall survival rate was reported at 32%, significantly higher than non-responders(6%). 32 Treatment-related mortality (TRM) is significant in intensive treatment, particularly among older patients. Younger adults had a TRM rate of about 25%, notably higher than that of cohorts without treatment (12%). 31

In a retrospective analysis, patients treated off-study (patients who received treatment outside a formal clinical trial setting due to medical, and logistic reasons) showed a decreased overall survival (OS) compared to those receiving standard intensive therapy. A total of 365 patients were analyzed, with patients categorized into two groups: newly diagnosed AML and relapsed/refractory AML, and further divided into groups treated according to clinical trial protocols and those not treated due to various reasons (medical, logistics). Among newly diagnosed patients CR without MRD is significantly higher for those treated on study (61%) compared to those off study (35%). Overall CR rates were also higher for on-study patients (86%) versus off-study patients (64%). On-study median OS was 2 years with median relapse-free survival (RFS) of 12 months. However, patients treated off study for medical reasons had significantly poorer outcomes with a median OS of 8months and median RFS at 7 months. 33

In 2021, a retrospective study in a tertiary hospital in the Philippines focused on the clinical outcomes of adult Filipino patients diagnosed with AML. The study included 395 patients, predominantly female (54%) with a median age of 42 year old, receiving the standard intensive chemotherapy followed by subsequent intermediate to high-dose cytarabine for post-remission therapy. The median OS for the cohort was 10 months. Successful induction chemotherapy is important for survival. Patients who achieve and maintain remission have significant outcomes. Better survival outcomes was influenced by younger age, good performance status, and accessible health care; while early relapse, adverse cytogenetic risk profile, presence of other health conditions, infection and limited treatment regimens resulted in lower survival rates. 34

The prognosis of AML patients is heavily influenced by age, genetic factors, initial disease characteristics, response to treatment and overall health status. Those who receive appropriate treatment generally have better outcomes compared to untreated individuals, who face rapid disease progression and significantly lower survival rates. With the advent of novel agents that addresses targetable mutations improving the survival outcomes of these patients, the question of whether waiting for these results be more beneficial for these patients arises.1,2,12,14

A study by Sekeres, et. al. includes 1,317 patients from two institutions between 1994 and 2005. The median age of patients was 60 years (age 17-87 years), with varying cytogenetic risk distribution: 8% favorable, 66% intermediate, and 26% unfavorable. The median time from diagnosis to treatment was 4 days (range 1-78 days). Younger patients (under 60 years) generally experience better outcomes with a CR of 67%, and a median OS of 68 weeks, while older patients (60 years and older) had a CR rate of 55% and a median OS of only 33 weeks. The study found that longer TDT negatively impacts both complete remission (CR) rates and overall survival (OS) rates in patients under 60 years. In statistical analyses, longer TDT was significantly associated with worse CR and OS outcomes in younger patients but did not show a significant impact on survival for older patients.16

In addition, a Swedish-population based study utilizing data from their AML Registry with 2,374 patients showed that two-thirds of patient who had a TDT of 5 days had significantly better outcomes compared to those with delays. The two-year survival rate for patients treated immediately was 47.5%, while it dropped to 36.0% and 37.9% for those treated after 6-10 days and 11-15 days, respectively (p < 0.0001). The rate of achieving CR was also higher in the immediate treatment group at 80%, compared to 70% for delayed treatment (P < .001). However, there was no significant difference in early death rates within 30 or 60 days post-treatment initiation across different timing groups, suggesting that while immediate treatment improves long-term survival, it does not affect short-term mortality.19

Alsouqi, et. al. further analyze data from 55,985 patients diagnosed with AML using the National Center Database from 2004 to 2018 shows that in patients under 60 years old, a 5-day delay in chemotherapy initiation was associated with worse long-term survival (HR 1.05 95% CI 1.01-1.09.) Survival decreased significantly with longer delays in treatment initiation. In contrast, patients 60 years old and older did not exhibit a significant impact on long-term interval due to treatment delays.20

However, a 2013 study from France involving 599 patients treated with induction chemotherapy showed a different result. The median age of participants were 58 years (range 16-83 years), with 60% aged 60 years and younger. The median TDT was 8 days, with significant differences based on age, WBC count and other factors. The analysis revealed that TDT did not significantly impact OS or response rate in the multivariate analysis (p = 0.4095). Factors such as age over 60 years, secondary AML, high WBC count, and performance status were more influential on survival outcomes. Of note, patients with a TDT of less than 5 days did not show improved outcomes when compared to those who have longer TDTs.17

A study by Röllig, et. al. also showed comparable results. It analyzed data from 2,263 patients with newly diagnosed AML in the German Study Alliance Leukemia-Acute Myeloid Leukemia registry. The median age of participants was 59 years, (range 50-68) with a mix of genetic risk profiles according to the European LeukemiaNet (ELN) 2017 classification. Median TDT was 3 days (interquartile range, 2-7days). Unadjusted two-year OS rates were similar across different TDT groups: 51% for 0-5 days, 48% for 6-10 days, 44% for 11-15 days, and 50% for >15 days (P = .211). In multivariable analysis, the hazard ratio for TDT as a continuous variable was 1.00 (P = .617), indicating no significant association between TDT and survival.18

Most recently, Baden, et. al. analyzed 1,012 patients from 2 distinct cohorts (138 patients from the Study Alliance Leukemia database and 717 patients from the global health network TriNetX) undergoing venetoclax-based therapy. The study population is older at 68 years, with comorbidities common in the older adults such as frailty, cardiovascular and renal disease. The analysis found no significant correlation between TDT and OS rates. Remission rates are also comparable among the different timing groups.21

A systematic review done last 2023 included data from 17 studies comprising a total of 5,000 patients diagnosed with AML. The meta-analysis showed no significant association between the TDT and OS (hazard ratio [HR] = 1.01, 95% confidence interval [CI]: 0.99-1.03). Various subgroup analyses were conducted based on age, cytogenetic risk and treatment regimen also showing no consistent impact of treatment delay on survival.22

With all these robust studies with differing results done international, a search for local studies about the impact of TDT in the prognosis of AML patients revealed no results.

**Significance of the Study**

This study holds considerable significance in contributing to an in depth understanding of the disease’s prognosis. There are limited local studies on newly diagnosed AML patient here in the Philippines. This study is the first of its kind to be conducted at University of the Philippines-Philippine General Hospital (UP-PGH). The investigation may shed light into impact of the time interval between diagnosis of the disease to initiation of definitive treatment, on whether we can wait for molecular studies to further individualized patients’ treatment or should we be aggressive in starting chemotherapy while waiting for these additional studies.

Moreover, it is crucial to consider that the healthcare system faces challenges such as limited beds for admission for induction chemotherapy, which can delay treatment initiation. These constraints may complicate decision-making regarding the urgency of starting therapy. The findings will also add to the body of medical knowledge and can serve as a useful tool for those who want to learn about the disease. This information can aid in the creation or revision of existing treatment protocols, ensuring that patient care is both effective and timely.

The Philippines is considered one of the resource limited countries where access to healthcare and medications are insufficient. Despite the substantial advancement in the treatment with AML, with the introduction of multiple novel and target-specific treatments available internationally not readily available in the country, this study aims to determine if the TDT affects the prognosis of newly diagnosed AML patients.

**METHODOLOGY**

**Study Design**

This study is a single center, retrospective, non-interventional, analytical cohort study aimed to assess if the prognosis of newly diagnosed AML patients undergoing initiation chemotherapy is affected by the TDT. As a retrospective, analytical study, review of medical records of the all newly diagnosed adult AML patients seen at UP-PGH outpatient hematology clinics or admitted at the hospital’s service and private wards from January 1, 2020 to December 31, 2024.

**Study Setting**

This study will be conducted at UP-PGH, a tertiary referral with a 1,500-bed capacity catering to a large number of leukemia patients, it also has one of the few institutions offering hematology training in the country.

**Sampling Design and Sample Size**

This study will utilize a complete enumeration sampling design of all newly-diagnosed adult AML patient seen at UP-PGH outpatient hematology clinics or admitted at the hospital’s service and private wards from January 1, 2020 to December 31, 2024. The population will be derived from the census of the Division of Hematology of the Department of Medicine. The study sample size calculated using the Yamane formula is 67.

N 80

n = -------------- = -------------- = 67

1+N (e)2 1+80 (0.05)2

where: n = sample size

N = population size

e = margin of error

**Study Population**

The study will include adult Filipino patients, aged 19 years old and above, newly-diagnosed with AML (based on the World Health Organization updated criteria as of 2022) consulting at the UP-PGH outpatient hematology clinics or admitted at the hospital’s service and private wards undergoing intensive chemotherapy from January 1, 2020 to December 31, 2024.

*Inclusion Criteria*

Selected patients should fulfill the following criteria: aged 19 years old and above, newly-diagnosed AML patients based on the WHO updated criteria, patients receiving intensive induction chemotherapy, and at least 1 year follow-up. Patients who died any time after treatment started will be included.

*Exclusion Criteria*

Subjects will be excluded from the study if they are < 19 year old; their medical records are missing; they have already undergone intensive chemotherapy prior to first consultation at UP-PGH; diagnosed with acute promyelocytic leukemia; utilization of non-intensive treatment; follow-up survival information < 1 year; or if they are participating in another trial or study that prohibits enrollment to this study.

**Fig 1. Patient selection for enrollment to the study.** APL, acute promyelocytic leukemia.

**Study Duration**

The study will commence once approved by the institution’s ethics committees and will be completed by 3 months.

**Operational Definition of Terms**

1. Time from diagnosis to treatment (TDT) – measured in days, refers to the time interval between the establishment of AML diagnosis (by bone marrow biopsy and/or flow cytometry) and receiving intensive chemotherapy
2. De novo AML – refers to cases of AML that arise spontaneously without any prior hematologic disorders or exposure to chemotherapy or radiation.23
3. Secondary AML (sAML) – refers to cases of AML that develops from a pre-existing hematologic condition, such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) .23
4. Therapy-related AML (tAML) – refers to cases of AML that develops as a consequence of chemotherapy or radiation therapy.23
5. Intensive chemotherapy – refers to treatment strategies involving high doses of cytotoxic drugs given with a goal to achieve complete remission.23
6. Non-intensive chemotherapy – refers to treatment strategies that use lower doses of chemotherapy with goal of disease control and minimal side effects, suitable for patients who cannot tolerate intensive chemotherapy due to age, frailty and other underlying health conditions.23
7. Complete remission (CR) – in NCCN AML guidelines, refers to a treatment response defined by bone marrow blast < 5% in an aspirate with spicules, transfusion independence, absolute neutropenic count ≥ 1 x 109/L, and platelet count ≥100 x 109/L.23
8. Complete remission with incomplete hematologic recovery (CRi) – in NCCN AML guidelines, refers to achieving all CR criteria and transfusion independence with persistence of neutropenia (<1 x 109/L) or thrombocytopenia < 100 x 109/L.23
9. Relapse following complete remission – in NCCN AML guidelines, refers to the reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause.23
10. Primary refractory disease - in NCCN AML guidelines, refers to the inability to attain CR or CRi following exposure to at least 2 courses of intensive induction therapy.23
11. Eastern Cooperative Oncology Group Performance status (ECOG) – refers to a tool assessment of level of function and capability of self-care. It uses 5 points score to assess performance status and is considered simple tool to use in daily clinical practice.24

**Table 2. Eastern Cooperative Oncology Group (ECOG) Performance Status**

|  |  |
| --- | --- |
| Eastern Cooperative Oncology Group (ECOG) Performance Status | |
| Performance Status | Definition |
| 0 | Fully active; no performance restrictions. |
| 1 | Strenuous physical activity restricted; fully ambulatory and able to carry out light work. |
| 2 | Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours. |
| 3 | Capable of only limited self-care; confined to bed or chair >50% of waking hours. |
| 4 | Completely disabled; cannot carry out any self-care; totally confined to bed or chair. |
| 5 | Dead |

1. European LeukemiaNet (ELN) genetic risk classification – refers to the list of genetic characterization at diagnosis with their subsequent risk stratification.25

**Table 3. European LeukemiaNet (ELN) genetic risk classification**

| **Risk category** | **Genetic abnormality** |
| --- | --- |
| Favorable | • t(8;21)(q22;q22.1)/RUNX1::RUNX1T1  • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ CBFB::MYH11  • Mutated NPM1 without FLT3-ITD   • bZIP in-frame mutated CEBPA |
| Intermediate | • Mutated NPM1 with FLT3-ITD   • Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions)   • t(9;11)(p21.3;q23.3)/MLLT3::KMT2A  • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse |
| Adverse | • t(6;9)(p23.3;q34.1)/DEK::NUP214   • t(v;11q23.3)/KMT2A-rearranged  • t(9;22)(q34.1;q11.2)/BCR::ABL1   • t(8;16)(p11.2;p13.3)/KAT6A::CREBBP   • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1)   • t(3q26.2;v)/MECOM(EVI1)-rearranged   • −5 or del(5q); −7; −17/abn(17p)   • Complex karyotype, monosomal karyotype  • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2  • Mutated TP53 |

1. Hematopoietic Cell Transplantation – specific Comorbidity Index (HCT-CI) – refers to the a specialized scoring system to assess the comorbidities of patients undergoing hematopoietic cell transplantation (HCT), predicting non-relapse mortality and overall survival outcomes in patients with hematologic malignancies.26
2. Early Death (ED) – refers to death within the first 30 days from the start of treatment.18
3. Event-free survival (EFS) – refers to the duration of time from the date of initiation of treatment until date of disease associated events: occurrence of relapse, primary refractory disease, death.27
4. Overall survival (OS) – refers to the measured time from diagnosis until the date of death or the last known follow-up.18
5. Hyperleukocytosis – refers to a white blood count >50, 000/µL caused by leukemic cell proliferation in an AML patient
6. Long Treatment Delays – refers to TDT that is more that 15 days.18
7. Extended Treatment Delays – refers to TDT that is more than 50 days.18

**Data Collection**

At the start of the study, participants will be identified using the UP-PGH Division of Hematology census data. A thorough review of subject’s medical record will be done attaining information on the subjects, demographics, clinical profile, relevant medical history and laboratory parameters. All data to be collected in this study will be transcribed using a passcode protected Microsoft Excel document. Data collection and encoding will be done by the primary investigator and a research assistant. Subject information will be kept in a secure office, with access available only to the primary investigator and supervising investigator.

Computerized study information will be stored on a secure network with passcode access. All identifiable information and data will be anonymized through a code number. A master list linking the code number and subject identity will be kept separate from the research data and only members of the research team will have access to the list. The research records will be stored at least five (5) years following the completion of the study, after which, the data will be permanently deleted and remaining physical records will be shredded. Identifiable research data will not be shared with individuals outside of the research and analysis team. The investigators have completed the Good Clinical Practice (GCP) training on the responsible conduct of research with human data.

Upon completion of the study, results will be disseminated through peer-reviewed journals, as well as submission to both local and international research forums and conferences, to enhance scientific knowledge and improve patient outcomes.

**Data Analysis**

The study data will undergo a process of anonymization, coding, and transcription into an Excel spreadsheet, followed by analysis utilizing SPSS software. Categorical data will be presented as counts with their respective percentages. Continuous counts will be presented either as means with accompanying standard deviations or medians with their interquartile ranges, depending on their specific distribution. The study will be using an indictor variable for missingness, and utilize inverse probability weighting for missing data as applicable. Clinical characteristics will be compared using Chi-square test for categorical data and Wilcoxon rank-sum test for continuous data. For overall survival and event-free survival, Kaplan-Meier approach is chosen, using log-rank test for univariate significance testing. Correlation between TDT and end points will be assessed by cross-tabulation for univariable analyses and by logistic regression for multivariable analysis. Survival outcomes and TDT were analyzed using Cox regression for univariable and multivariable analyses. Subgroup analysis will be done based on different treatment regimen used, between age >60 years old and < 60 years old, as well as to assess the influence of different cause treatment delays. The influence of hydroxyurea and cytarabine cytoreduction will be investigated by introducing an interaction term between the TDT and the presence of cytoreductive treatment. Statistical significance will be set at p < 0.05, with 95% confidence intervals (CI).

The study will be using an indictor variable for missingness, and utilize inverse probability weighting for missing data.

**Outcomes**

The primary outcome of this study is to assess the impact of TDT on the prognosis of newly-diagnosed AML patients being treated with upfront chemotherapy. OS will be measured after chemotherapy until the date of death or if the patient did not die during the follow-up period, OS will be censored on the date of last known follow-up.

The secondary outcomes are 1. To determine whether TDT influences the remission status, early death, event-free survival, and overall survival of AML patients; and, 2. To determine whether TDT, specific reason of treatment delay, such as clinical delays (infection or nutritional upbuilding), high costs of treatment, lack of access to treatment/facilities, unfamiliarity to novel agent, affect OS.

**Ethical Considerations**

This research will be submitted for ethical review to the Institutional Review Board (IRB) of the UP-PGH, which oversees studies involving human subjects. A waiver for informed consent will be requested from the UPMREB panel based on the following criteria: (1) the research poses minimal risk and does not involve procedures, such as medical interventions, that typically require informed consent; (2) granting the waiver will not negatively impact the rights and welfare of participants; (3) it would not be feasible to conduct the research without this waiver, in accordance with the National Ethical Guidelines for Research Involving Human Participants 2022. This request is justified by the study's minimal risk nature, which involves only the review of medical records. Although this study will include vulnerable populations, such as the elderly, indigenous individuals, unemployed persons, those living in poverty, and patients receiving emergency care; there will be no direct interaction between physicians and patients, nor will there be any follow-up with participants. Additionally, participants will not receive any direct benefits or non-material compensation for their involvement in this study.

The primary investigator will oversee the data collection process, with the addition of a research assistant to provide support as needed. Clear and comprehensive instructions will be given by the lead investigator to the research assistant to ensure compliance with privacy and confidentiality standards as outlined in the Data Privacy Act of 2012 and the National Ethical Guidelines for Health and Health-Related Research 2022. To protect participant identities, numeric codes will be utilized. De-identified data, represented by these codes, will be entered into a secure electronic spreadsheet. All records will be handled confidentially in accordance with the Data Privacy Act of 2012. Case reports and encoded digital files will be encrypted and password-protected using Microsoft Excel, ensuring they do not contain any personal identifiers, and will be securely stored in the research division's office for a duration of five years. The disposal of research data will follow a systematic process involving de-identification and erasure, in line with the Data Privacy Act of 2012. Breaches of confidentiality can lead to significant legal, ethical, and reputational repercussions, including fines and loss of trust or funding. To mitigate these risks, researchers implement secure data management practices and restrict access. In the event of a breach, the issue will be reported to the PGH Data Privacy Officer for immediate action to minimize harm to affected individuals and prevent recurrence. Findings from this study will be disseminated through academic publications, conferences, and presentations.

**Conflict of Interest**

There are no conflicts of interest for the authors concerning this manuscript.

**Dummy Tables**

**Table 4. Patient and treatment characteristics of patients and according to TDT groups**

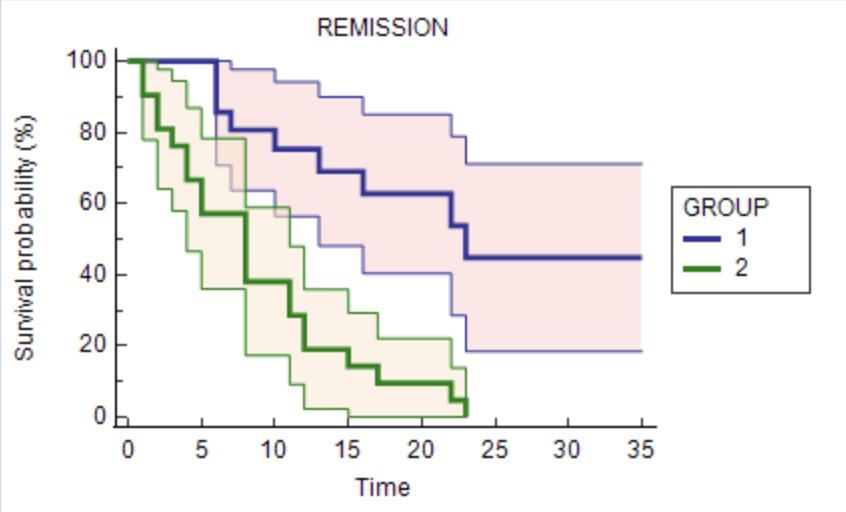
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **All patients,**  **n** | **TDT, 0-5d, n** | **TDT, 6-10d, n** | **TDT, 11-15d, n** | **TDT, >15d, n** |
| **Age at initial diagnosis, y** |  |  |  |  |  |
| Mean (SD) |  |  |  |  |  |
| Median (IQR) |  |  |  |  |  |
| **Female sex, no./no. available (%)** |  |  |  |  |  |
| **ECOG status 0-1, no./no. available (%)** |  |  |  |  |  |
| **HCT-CI score 0-2, no./no. available (%)** |  |  |  |  |  |
| **ELN risk 2022 group, no./no. available (%)** |  |  |  |  |  |
| Favorable |  |  |  |  |  |
| Intermediate |  |  |  |  |  |
| Adverse |  |  |  |  |  |
| **AML type, no./no. available (%)** |  |  |  |  |  |
| De novo AML |  |  |  |  |  |
| sAML |  |  |  |  |  |
| tAML |  |  |  |  |  |
| **Cytoreductive agent pretreatment , no./no. available (%)** |  |  |  |  |  |
| Hydroxyurea |  |  |  |  |  |
| Cytarabine |  |  |  |  |  |
| **TDT, d** |  |  |  |  |  |
| Mean (SD) |  |  |  |  |  |
| Median (IQR) |  |  |  |  |  |
| **WBC, x109/L** |  |  |  |  |  |
| Mean (SD) |  |  |  |  |  |
| Median (IQR) |  |  |  |  |  |
| **HL, no./no. available (%)** |  |  |  |  |  |
| **LDH, U/L** |  |  |  |  |  |
| Mean (SD) |  |  |  |  |  |
| Median (IQR) |  |  |  |  |  |
| **Bone marrow blast, %** |  |  |  |  |  |
| Mean (SD) |  |  |  |  |  |
| Median (IQR) |  |  |  |  |  |
| **Karyotype, no./no. available (%)** |  |  |  |  |  |
| Abnormal, including complex |  |  |  |  |  |
| Normal, including complex |  |  |  |  |  |
| **Treatment regimen, no./no. available (%)** |  |  |  |  |  |
| 7+3 |  |  |  |  |  |
| HIDAC +/- Doxo |  |  |  |  |  |
| HAM |  |  |  |  |  |
| **Allogeneic SCT, no./no. available (%)** |  |  |  |  |  |
| AlloSCT in CR1 |  |  |  |  |  |
| AlloSCT salvage |  |  |  |  |  |
| **Cause of delay of treatment, no./no. available (%)** |  |  |  |  |  |
| Infection |  |  |  |  |  |
| Nutritional upbuilding |  |  |  |  |  |
| Cost of treatment |  |  |  |  |  |
| Lack of access |  |  |  |  |  |
| Unfamiliarity to treatment |  |  |  |  |  |

**Table 5. Treatment outcomes CR/CRi, ED,, and 1-year OS of all patients stratified for TDT group and age </= 60 years vs > 60 years**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **All patients,**  **n** | **TDT, 0-5d, n** | **TDT, 6-10d, n** | **TDT, 11-15d, n** | **TDT, >15d, n** |
| **All patients** |  |  |  |  |  |
| CR/CRi, no./no. available (%) [CI] |  |  |  |  |  |
| ED, no./no. available (%) [CI] |  |  |  |  |  |
| RFS, no./no. available (%) [CI] |  |  |  |  |  |
| OS, no./no. available (%) [CI] |  |  |  |  |  |
| **Age </= 60 y** |  |  |  |  |  |
| CR/CRi, no./no. available (%) [CI] |  |  |  |  |  |
| ED, no./no. available (%) [CI] |  |  |  |  |  |
| RFS, no./no. available (%) [CI] |  |  |  |  |  |
| OS, no./no. available (%) [CI] |  |  |  |  |  |
| **Age > 60 y** |  |  |  |  |  |
| CR/CRi, no./no. available (%) [CI] |  |  |  |  |  |
| ED, no./no. available (%) [CI] |  |  |  |  |  |
| RFS, no./no. available (%) [CI] |  |  |  |  |  |
| OS, no./no. available (%) [CI] |  |  |  |  |  |

**Table 6. ORs for achievement of CR/CRi, ED and HRs for RFS, OS**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Complete Remission | | | Early Death | | | Event-free Survival | | | Overall Survival | | |
|  | OR | 95% CI | p-value | OR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value |
| TDT |  |  |  |  |  |  |  |  |  |  |  |  |
| **ENL risk group** |  |  |  |  |  |  |  |  |  |  |  |  |
| Favorable |  |  |  |  |  |  |  |  |  |  |  |  |
| Intermediate |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse |  |  |  |  |  |  |  |  |  |  |  |  |
| **Age,**  **per 10 y** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Log2 of WBC in x 109/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Log2 of LDH in x U/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| **AML type** |  |  |  |  |  |  |  |  |  |  |  |  |
| De novo AML |  |  |  |  |  |  |  |  |  |  |  |  |
| sAML |  |  |  |  |  |  |  |  |  |  |  |  |
| tAML |  |  |  |  |  |  |  |  |  |  |  |  |
| **ECOG 0-1** |  |  |  |  |  |  |  |  |  |  |  |  |
| **HCT-CI >2** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Cause of delay of treatment,** |  |  |  |  |  |  |  |  |  |  |  |  |
| Infection |  |  |  |  |  |  |  |  |  |  |  |  |
| Nutritional upbuilding |  |  |  |  |  |  |  |  |  |  |  |  |
| Cost of treatment |  |  |  |  |  |  |  |  |  |  |  |  |
| Lack of access |  |  |  |  |  |  |  |  |  |  |  |  |
| Unfamiliarity |  |  |  |  |  |  |  |  |  |  |  |  |

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**Figure 2. Sample Kaplan-Meier curve**

**Data Collection Sheet**

Patient Code: TDT-AML \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Age upon diagnosis (years) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Sex  Male  Female

ECOG status  1  2  3  4  5

HCT-CI score  0-2  >2

ENL risk 2022 group

 favorable  intermediate  adverse

AML type  de novo  sAML  tAML

Use of Cytoreductive Agent pretreatment

 Hydroxyurea  Cytarabine

Date of diagnosis \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Day 1 of chemotherapy \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

TDT \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

WBC upon presentation \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ x109/L

LDH \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ U/L

Bone Marrow Blast \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_%

Karyotype \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Treatment Regimen \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Allogeneic SCT  in CR1  salvage

Cause of delay in treatment

 infection

 nutritional upbuilding

 cost of treatment

 lack of access

 unfamiliarity

Treatment response

 CR

 CRi

 Primary Refractory Disease

Survival

RFS \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ days

OS \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ days

**Gantt Chart**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | September 2024 | October 2024 | November 2024 | December 2024 | January 2025 | February 2025 | March 2025 | April 2025 | May 2025 |
| Literature review |  |  |  |  |  |  |  |  |  |
| Finalization of the study protocol |  |  |  |  |  |  |  |  |  |
| Technical and ethical review |  |  |  |  |  |  |  |  |  |
| Data collection |  |  |  |  |  |  |  |  |  |
| Data analysis |  |  |  |  |  |  |  |  |  |
| Manuscript writing |  |  |  |  |  |  |  |  |  |
| Review and revision |  |  |  |  |  |  |  |  |  |
| Finalization and submission the study |  |  |  |  |  |  |  |  |  |

**Study Budget**

Funding of the study will mainly be out-of-pocket from the principal investigator:

|  |  |
| --- | --- |
| **ITEM** | **Total (PHP) in 9 month(s)** |
| Personnel and Services  *Statistician* | 15,000.00 |
| Data collection form and other office supplies | 3,000.00 |
| **TOTAL** | **18,000.00** |

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**APPENDIX I. Supplemental Tables**

**Table 7. Hematopoietic Cell Transplantation – specific Comorbidity Index**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **0 points** | **1 point** | **2 points** | **3 points** |
| History of arrhythmia | None | Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias | -- | -- |
| Cardiac dysfunction | None | CAD\*, CHF, MI, or EF ≤50% | -- | Heart valve disease (except mitral valve prolapse) |
| Inflammatory bowel disease | None | Crohn disease or ulcerative colitis | -- | -- |
| Diabetes | None or diet-controlled | Treated with insulin or oral hypoglycemics | -- | -- |
| Cerebrovascular disease | None | CVA or TIA | -- | -- |
| Psychiatric disturbance | None | Depression or anxiety requiring psychiatric consult or treatment | -- | -- |
| Hepatic dysfunction | None | Chronic hepatitis (bilirubin >ULN to 1.5× ULN, or AST/ALT >ULN to  2.5× ULN) | -- | Liver cirrhosis (bilirubin >1.5× ULN, or AST/ALT  2.5× ULN) |
| Obesity ([BMI](https://www.mdcalc.com/calc/29) ≥35 kg/m2) | No | Yes | -- | -- |
| Infection | None or antibiotics only on day 0 | Requiring continuation of antimicrobial treatment after day 0 | -- | -- |
| Rheumatologic disease | None | -- | SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica | -- |
| Peptic ulcer | None or not requiring treatment | -- | Requiring treatment | -- |
| Renal dysfunction | None or serum creatinine ≤2 mg/dL (177 µmol/L), not on dialysis, and no prior renal transplant | -- | Serum creatinine >2 mg/dL (177 µmol/L), on dialysis, or prior renal transplant | -- |
| Pulmonary dysfunction | None or mild | -- | DLco\*\* and/or FEV₁ 66%–80%, or dyspnea on slight activity | DLco and/or FEV1 ≤65% or dyspnea at rest or requiring oxygen |
| Prior solid tumor | None or nonmelanoma skin cancer | -- | -- | Treated at any point in the patient’s history |