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Folate deficiency in north Indian children undergoing maintenance chemotherapy for acute lymphoblastic leukemia—Implications and outcome

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Abstract

Background: Treatment-related toxicity and mortality are not uncommon during maintenance chemotherapy for childhood acute lymphoblastic leukemia (ALL), especially in the low- and middle-income countries (LMIC). Undernutrition and micronutrient deficiencies are commonly seen in children from LMICs undergoing treatment for ALL. The present study examines the prevalence and clinical implications of folate deficiency in north Indian children with ALL during the maintenance phase of treatment in view of prolonged antifolate treatment and high population prevalence of folate deficiency.

Procedures: Pre-cycle folate levels/deficiency as well as weight for age *z*-score and serum albumin level were determined and correlated with complications of treatment and mortality encountered during the maintenance phase of treatment.

Results: Twenty-nine of 52 children enrolled in the study had folate deficiency at some point during maintenance chemotherapy. Neutropenia (18 of 29 vs. 4 of 23; $P = 0.002$), thrombocytopenia (17 of 29 vs. 4 of 23; $P = 0.005$), febrile neutropenia (17 of 29 vs. 4 of 23; $P = 0.005$), and need for chemotherapy dose reduction (20 of 29 vs. 7 of 21; $P = 0.01$) were more common in folate-deficient children. Maintenance deaths were higher (8 of 29 vs. 1 of 23; $P = 0.03$) and survival lower ($P = 0.02$) in deficient children. In multivariate analysis, hypoalbuminemia ($P = 0.02$) and folate deficiency ($P = 0.01$) were associated with febrile neutropenia, and folate deficiency with maintenance deaths ($P = 0.03$).

Conclusions: Folate deficiency was associated with treatment-related complications and adverse outcome in our patients. The risks and benefits of folate supplementation in deficient children during maintenance chemotherapy need to be explored with properly designed randomized studies in similar settings.

KEYWORDS

ALL maintenance, clinical implications, folate deficiency

1 | INTRODUCTION

Maintenance chemotherapy is one of the most effective interventions in reducing relapse and has contributed significantly toward the excellent outcome of childhood acute lymphoblastic leukemia (ALL).[1] Maintenance chemotherapy is comprised of a comparatively low intensity treatment including oral 6-mercaptopurine and methotrexate as backbone in addition to pulses of steroids, vincristine, and intrathecal methotrexate in many protocols.[1] Despite the low intensity of treatment, considerable drug toxicities are often encountered requiring dose reduction or interruption in therapy and also toxic deaths during maintenance, prompting many study groups to attempt deintensification of therapy during maintenance.[2–4]

Toxicities during maintenance are of special concern in low-income countries due to various reasons including poor nutritional status, lack of optimum supportive care, delay in treatment of infections due to long distance from hospital, and lack of awareness in seeking care on

Abbreviations: ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; LMIC, low- and middle-income countries; MTHFR, methylene tetrahydrofolate reductase; NCI, National Cancer Institute; WAZ score, weight for age *z*-score

time,[2] as children on maintenance are mostly treated on a domiciliary basis. Since the antifolate methotrexate forms one of the mainstays of maintenance chemotherapy, the importance of folate deficiency in predisposition of toxicities during maintenance chemotherapy cannot be underestimated, more so as mutations in the genes of the folate metabolic pathway have already been shown to alter chemotherapy toxicity during maintenance.[5,6] We have previously shown that folate deficiency contributed significantly to a higher incidence of toxicities during induction chemotherapy for childhood ALL,[7] however, the importance of folate deficiency during maintenance chemotherapy needs to be studied, especially in a population with high prevalence of childhood folate deficiency (between 30% and 40%[8]) in a country without mandatory folic acid fortification of food.[9]

2 | METHODS

All children with ALL who were registered for treatment in the Division of Pediatric Hematology-Oncology at King George's Medical University, Lucknow, India (a tertiary care teaching hospital attached to a medical university in north India) from December 2011 through November 2013 and had completed at least one cycle (i.e., 84 days) of maintenance chemotherapy at the time of analysis were included. Though our center mainly caters to the state of Uttar Pradesh, one of the biggest provinces in India, we get patients from adjacent provinces of Uttarakhand, Bihar, and Jharkhand as well. Occasionally, we also get patients from Nepal, a neighboring country.

Serum folate level was estimated by electrochemiluminescence (using Cobas e 411 analyzer) prior to each cycle of maintenance. Serum was obtained by centrifugation of blood immediately on collection and was stored at −20°C until analyzed. Folate deficiency was defined as serum folate level less than 4 ng/ml.[10]

Methylene tetrahydrofolate reductase (MTHFR) 677 and 1,298 genotypes of all the study subjects were also determined by the polymerase chain reaction–restriction fragment length polymorphism technique. Dietary pattern (vegetarian or nonvegetarian), socioeconomic status according to modified Kuppuswamy's scale, distance of home from our center were also recorded for all patients at registration. Pre-maintenance chemotherapy nutritional assessment included weight for age *z*-scores (WAZ scores) and serum albumin measurement. Malnutrition was defined as WAZ score of <−2 and hypoalbuminemia as serum albumin <3.5 g/dl. Maintenance chemotherapy in our cohort comprised weekly oral methotrexate (20 mg/m^2) and daily oral 6-mercaptopurine (75 mg/m^2) in addition to pulses of vincristine and dexamethasone every 4 weeks. Intrathecal methotrexate was also administered at the start of each 84-day cycle.

Complications during maintenance chemotherapy were monitored using the standard National Cancer Institute Common Toxicity Criteria version 4 (NCI-CTC v.4). Adjustment for dosages of methotrexate and 6-mercaptopurine were made based on absolute neutrophil count (ANC; targeting an ANC between 1,000 and 1,500/mm^3) and platelet counts (targeting platelet count above 75,000/mm^3) prior to the beginning of each cycle, as well as in-between cycles should there be low counts or other clinical indications. This study was approved by the institutional ethics committee and written informed consents were obtained from the parents/care givers at the time of inclusion.

Statistical analysis was performed using SPSS version 16.0 for Windows (Statistical Package for Social Sciences, SPSS, Inc., USA) and GraphPad Prism (version 3.0; GraphPad software). Descriptive statistics was used to compute central tendencies, dispersions, and frequencies. Intergroup comparisons between different MTHFR genotypes as well as between children with normal folate and folate deficiency were made using Student's *t*-test for continuous variables and Mann–Whitney U-test for nonparametric data. Categorical variables were analyzed using chi-square and Fischer's exact tests. Multivariate analysis using binary logistic regression was used to deduce the strengths of association of the possible contributory factors and the adverse outcomes. Difference in survival between children with and without folate deficiency was computed by survival analysis using log-rank (Mantel–Cox) tests and presented as Kaplan–Meier curves. *P*-values less than 0.05 were considered as statistically significant.

3 | RESULTS

Fifty-two patients underwent at least one cycle (84 days) of maintenance chemotherapy when last analyzed. The baseline characteristics of the enrolled children are presented in Table 1. Mean number of cycles of follow-up in this cohort was 3.2 ± 0.56. Cumulative duration being equivalent to 189 cycles of maintenance (84 days/cycle).

Seventeen patients were folate-deficient at the start of maintenance of whom 7 patients normalized their folate status during subsequent cycles, whereas 12 patients developed deficiency while on maintenance after starting off with normal levels. Folate deficiency was seen at least once in 29 patients while 23 patients had normal folate levels throughout the period of study. Among the 189 cycles of maintenance chemotherapy studied, 48 cycles (25%) in 29 patients recorded a precycle folate deficiency.

Folate deficiency at the start of or during maintenance was not associated with dietary pattern ($P = 0.5$), socioeconomic status ($P = 0.09$), malnutrition ($P = 0.7$), or hypoalbuminemia ($P = 0.54$). Females, however, had a higher incidence of folate deficiency compared to males enrolled in the study (9 of 10 vs. 20 of 42; $P = 0.03$). Though there was no association between folate deficiency and socioeconomic status or dietary habit, it was noted that at all assessment points the mean folate levels were lower in patients from low socioeconomic status as well vegetarians; however, none of these differences reached statistical significance.

Anemia, neutropenia, and thrombocytopenia during the study period were encountered in 40 (21%), 63 (32.8%), and 44 (23.1%) cycles, respectively. Febrile neutropenia was seen in 41(21.5%) of the cycles. Doses of oral chemotherapy had to be reduced due to cytopenia (thrombocytopenia and/or neutropenia) in 50 of 189 cycles (26.3%). Interruption of chemotherapy (more than 7 days off oral chemotherapy) was needed in 38 of 189 cycles (20%).

Neutropenia, seen in 22 patients, was more common in children with at least one episode of folate deficiency (18 of 29 vs. 4 of 23;

TABLE 1 Characteristics of children (n = 52) on maintenance chemotherapy for ALL

Mean (±SD) age	7.0 ± 3.3 years
Gender	
Male	42
Female	10
Socioeconomic status	
Upper + middle	24
Lower	28
Distance from home	
<100 km	17
>100 km	35
Immunophenotype	
B-ALL	43
T-ALL	9
MTHFR genotype	
677	CC-34, CT-18
1,298	AA-25, AC-17, CC-10
Dietary habit	
Vegetarian	17
Nonvegetarian	35
WAZ score	
≥-2	33
<-2	19
Serum albumin	
≥3.5 g/dl	37
<3.5 g/dl	15
Folate deficiency	
Yes	29
No	23
Cumulative duration on maintenance	568 months
Total cycles of maintenance	189
Cycles beginning with folate deficiency	48 (25%)

WAZ, weight for age z-score.

$P = 0.002$). Thrombocytopenia, seen in 21 patients, was more frequent in children with folate deficiency (17 of 29 vs. 4 of 23; $P = 0.005$). Similarly, febrile neutropenia was also common among the folate-deficient children (17 of 29 vs. 4 of 23; $P = 0.005$). Hepatitis during maintenance seen in 14 of 52 patients was, however, not associated with folate deficiency (6 of 29 in folate-deficient children vs. 8 of 21 in children with normal folate status; $P = 0.21$; Table 2).

Need for reduction of chemotherapeutic dosage was significantly more common in children with folate deficiency (20 of 29 vs. 7 of 21; $P = 0.01$). Similarly, the mean duration off-chemotherapy was also greater in children with folate deficiency compared to children with normal folate status (15.24 ± 18.05 vs. 6.71 ± 12.29 days; $P = 0.05$; Table 2).

Univariate analysis did not identify association of the complications including cytopenias, transfusion requirement, chemotherapy interruption/dose reduction, or febrile neutropenia with any other risk factors studied (socioeconomic status, NCI risk group, gender, immunophenotype, malnutrition, and hypoalbuminemia). Multivariate analysis, however, revealed a significant association of febrile neutropenia with folate deficiency and hypoalbuminemia (Table 3).

In total, nine deaths were encountered during maintenance, eight of which occurred during cycles beginning with folate deficiency ($P = 0.03$), an association that remained significant in the multivariate model of analysis ($P = 0.03$; Table 3). Six of these nine patients died after being admitted to our hospital with neutropenia and sepsis, three of these patients required fluid and inotropic support on arrival to our center. The remaining three died at home, two of them following fever and one had a sudden unexplained death (probably following intracranial bleed as the child complained of headache prior to death). No association between other risk factors including distance of hospital from home and death could be found in either univariate or multivariate analysis. Log-rank (Mantel–Cox) test showed a significantly lower survival in children with folate deficiency compared to the folate-sufficient children (chi-square = 4.85; $P = 0.02$; Fig. 1) during the period of follow-up.

MTHFR genotypes were unrelated to absolute folate levels or deficient status of the children studied. Moreover, MTHFR genotypes were

TABLE 2 Folate deficiency and complications encountered during maintenance chemotherapy

Complication	Folate-deficient children (n = 29)	Folate-sufficient children (n = 23)	*P*-value
Anemia	11 of 29	5 of 23	0.24
Neutropenia	18 of 29	4 of 23	0.002*
Thrombocytopenia	17 of 29	4 of 23	0.005*
Febrile neutropenia	17 of 29	4 of 23	0.005*
Hepatitis	6 of 14	8 of 23	0.17
Dose reduction of chemotherapy	20 of 29	7 of 21	0.01*
Interruption of chemotherapy	15.24 ± 18.05 days	6.71 ± 12.29 days	0.05
PRBC requirement (units)	1.11 ± 1.94	0.47 ± 1.08	0.88
Platelet requirement (units)	1.14 ± 3.15	0.62 ± 1.59	0.99
Maintenance deaths	8 of 29	1 of 23	0.03*

PRBC, packed red cell.
*Statistically significant association.

TABLE 3 Binary logistic regression for association of various risk factors with febrile neutropenia and treatment-related deaths during maintenance chemotherapy

	Febrile neutropenia			Treatment-related mortality		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
NCI risk group (HR vs. SR)	0.96	0.22–4.22	0.95	0.27	0.05–1.50	0.13
Immunophenotype (T vs. B)	1.13	0.14–8.97	0.91	6.49	0.32–132.4	0.22
Gender (M vs. F)	0.45	0.06–3.17	0.43	1.33	0.14–12.5	0.80
Socioeconomic status (low vs. nonlow)	1.04	0.23–4.77	0.96	0.75	0.11–5.26	0.77
Distance from home (>100 km vs. <100 km)	0.59	0.13–2.85	0.52	0.59	0.09–3.63	0.57
Folate level (<4 ng/ml vs. >4 ng/ml)	13.58	2.01–91.87	0.01*	16.16	1.2–223.5	0.03*
WAZ (<−2 vs. ≥ −2)	3.01	0.65–13.95	0.16	1.29	0.19–8.40	0.78
Albumin (<3.5 g/dl vs. >3.5 g/dl)	8.41	1.34–52.68	0.02*	2.93	0.34–25.2	0.33

HR, high risk; SR, standard risk; T, T-cell; B, B-cell; M, male; F, female; ng/ml, nanogram/milliliter; g/dl, gram/deciliter.
*Statistically significant association.

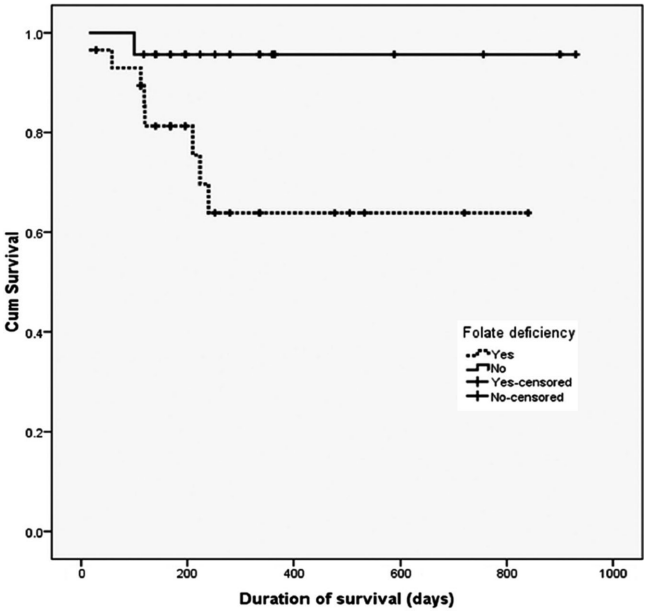

FIGURE 1 Difference in survival during maintenance based on folate status (n = 52); log-rank test (Mantel–Cox); $P = 0.028$

also not associated with any of the complications or adverse outcomes, including death, during maintenance chemotherapy.

4 | DISCUSSION

Despite the low intensity of treatment during maintenance chemotherapy for ALL, treatment-related toxicity and mortality is not uncommon during this phase, especially in children from LMICs (low- and middle-income countries).[2] The higher incidence of treatment-related toxicity and mortality in LMICs has been attributed to high rate of malnutrition, poor chemotherapy tolerance, high incidence of infections, lack of adequate supportive care, and poor compliance to therapy.[2,7]

We have previously shown the effect of malnutrition as well as micronutrient deficiencies on the complications during induction chemotherapy.[11] Additionally, the importance of folate deficiency has been highlighted by our previous studies both during induction and treatment with high-dose methotrexate.[7,12] Despite the fact that the antifolate agent methotrexate forms an integral constituent of maintenance chemotherapy, and that studies have shown enhanced chemotherapy toxicity during maintenance in children with mutations in the genes of the folic acid metabolism,[5,6] the effect of folate status on toxicities encountered during maintenance has not received much attention. However, based on experience from patients with rheumatological conditions on long-term methotrexate therapy, it can be derived that folate nutriture worsens with long-term antifolate therapy.[13]

Our study documents the high incidence of folate deficiency during the maintenance phase of chemotherapy. In contrast to a study from Denmark conducted in the 1980s reporting no folate deficiency among any of the children undergoing maintenance therapy for ALL,[14] more than half of the patients studied by us developed folate deficiency sometime during their follow-up while on maintenance. Probably, the children from developing countries such as India face stronger challenges in maintaining normal folate levels in the face of the high rate of preexisting folate deficiency in the population, predominant vegetarian diet, restriction of uncooked green leafy vegetables (apprehending infections during chemotherapy-induced immune suppression), reduced oral intake and unfortified cereals—all of which make falling folate levels a natural consequence of antifolate chemotherapy.[7] We were unable to find any similar study from a comparable setting, as the only studies we could identify were from European countries.[14,15]

A sizeable proportion of our patients (about one-third) were vegetarians predisposing them to such deficiency when on a diet largely free from raw green vegetables, the richest source of folic acid in vegetarian diet, which is further supported by the fact that the mean level of folate was lower in vegetarians, although this did not reach statistical significance in our study. In addition to documenting the burden of folate deficiency, we also explored the implications of folate deficiency and other nutritional parameters including WAZ scores and hypoalbuminemia on the course and complications during maintenance chemotherapy.

Cytopenias (anemia, thrombocytopenia, or neutropenia) were noted in a sizeable portion of our patients during maintenance, of

which neutropenia and thrombocytopenia were observed more commonly in children with folate deficiency compared to children with low WAZ scores or hypoalbuminemia, highlighting the importance of folate status in bone marrow functioning during maintenance. We also observed that the complications related to bone marrow suppression commonly seen in the folate-deficient children translated into higher need for chemotherapy dose reduction and interruption of chemotherapy in these children.

Apart from the above findings, our study also revealed an association between folate deficiency, as well as hypoalbuminemia, with febrile neutropenia, one of the most commonly encountered but potentially serious complications of chemotherapy. In fact, febrile neutropenia encountered during nonintensive phases of treatment may have a poorer outcome due to delay in seeking medical care and longer distances to travel (as patients mostly go back to their native places during the maintenance phase of chemotherapy).[16]

Treatment-related deaths during maintenance were seen in 17% of our children. Interestingly, most of these were seen in folate-deficient children. The difference in survival was also significant between folate-deficient and folate-replete children, with the former having a lower survival compared to the latter. Though folate deficiency cannot be causally related to deaths during maintenance, our findings show that deficient children are more prone to development of febrile neutropenia, each episode of which can be potentially life-threatening. Unlike other studies,[16] we did not find a significant association of death during maintenance and distance from home, as almost half of the patients who died resided within 100 km of our hospital, but it was clearly evident that three of the six patients who died in hospital arrived in a state requiring upfront resuscitation. One-third of our patients who died, died at home and were not brought to hospital at the onset of their symptoms, which might potentially be due to lack of awareness among the caregivers.[16] Maintenance deaths account for 10–20% of all deaths during treatment for ALL in previously published series and are mostly related to infection-related complications similar to our study.[2]

Though a few studies in the 1980s have studied folate deficiency/supplementation during maintenance phase of ALL, none of them reported the clinical relevance of deficiency/supplementation.[14,15] One of these studies carried out on a small number of children documented folate deficiency in a subset of the study subjects and reported better tolerance of chemotherapy during phases of folate supplementation.[15] Similarly, the other study from Denmark documented higher leukocyte, neutrophil, and platelet counts in patients who were taking vitamins containing folic acid prior to maintenance in comparison to the nonsupplemented children. The authors, however, did not find folate deficiency among any of the 53 patients studied[14] and hence recommended against folate supplementation in children undergoing maintenance chemotherapy for ALL.[14] Though patients with rheumatological diseases are supplemented regularly with oral folic acid while on methotrexate,[13] no such guidelines exist for children on maintenance therapy for ALL. This apparent disparity in recommendations stems from the concern that folic acid supplementation during treatment of ALL may lead to the rescue of leukemic clones and relapse of ALL,[17] a concern not substantiated by human studies.[17,18] These observations when viewed in the light of the previous studies correlating higher folate levels to lesser chemotherapy efficacy[15] as well as the findings of the current study lead to the pertinent question about choosing between two evils: folate-replete children with purportedly less efficacious chemotherapy on one hand and folate-depleted children with higher number of days off chemotherapy or on less than optimum doses of chemotherapy experiencing more treatment-related toxicity on the other.[17]

The current study had some limitations: it was carried out on a small number of patients and was mostly limited to folate status in these children, whereas other micronutrient deficiencies may also have similar effects that should be studied. However, our findings call for more such studies from identical settings in LMICs in order to generate stronger evidence in this field. Additionally, randomized studies assessing the effect of folate supplementation during maintenance chemotherapy, especially in deficient children, would suggest whether supplementing folic acid can be an effective intervention in reducing treatment-related mortality, without compromising treatment efficacy, in children from similar backgrounds.[17,18]

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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