Acute Lymphoblastic Leukemia With Pancytopenia at Presentation: Clinical Correlates, Prognostic Impact, and Association With Survival

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Summary: Acute lymphoblastic leukemia has a wide variety of presentations. There is paucity of any data addressing pancytopenia at presentation in acute lymphoblastic leukemia. In this study we assessed 84 patients with pancytopenia at presentation. They had a significantly lower incidence of bulky disease at presentation. A significantly higher fraction of these patients (n = 66, 78.57%) opted for therapy ($P = 0.005$) as compared with the rest. The estimated mean survival in patients presenting with pancytopenia (67.2 ± 17.2 mo) was significantly higher ($P = 0.031$, log-rank test) as compared with that of other patients (47.2 ± 7.4 mo). Pancytopenia was an independent predictor of better survival ($P = 0.043$) in multivariate analysis.

Key Words: acute lymphoblastic leukemia, aplastic, pancytopenia, prognostic impact, outcome, resource limited

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Acute lymphoblastic leukemia (ALL) has a myriad of presentations. Although aplastic and pancytopenic presentation of ALL is known, available literature is relatively old and mostly in the form of case reports and small series on aplastic presentation of ALL.[1–3] There is a stark paucity of larger studies assessing clinicodemographic correlates of pancytopenia in ALL and its influence on survival outcome, especially from developing nations.

Therapeutic advances in childhood ALL have diluted the importance of traditional prognostic factors such as hepatosplenomegaly, lymphadenopathy, disease bulk, mediastinal adenopathy, symptom diagnosis interval, and several laboratory parameters including hemoglobin, platelet count, and white cell count, especially in the developed nations.[4] Furthermore, higher rates of mortality, therapy abandonment, relapse, as well as several socioeconomic and cultural factors influence the choice of therapy, adherence to therapy, therapy abandonment, and the ultimate survival outcome of childhood ALL in developing nations.[4–7] Specifically, data from India suggests that, despite gradual improvements, the survival outcome of ALL as such remains modest except in centers of excellence.[5]

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Thus to improve the outcome of ALL in all the treating centers, it is imperative to identify locally relevant prognostic factors and determinants of choice of therapy and of survival in developing nations along with holistic improvements in support services.[5] Several of these traditional prognostic parameters and other more easily available laboratory parameters might still be important and relevant in resource-limited nations as use of contemporary molecular and cytogenetic methods may not be feasible. Pancytopenia at presentation is one such laboratory parameter that can be easily assessed in most institutions. Previously, pancytopenia has been reported to be associated with lesser disease bulk and plausibly better outcome. However, there does not exist any conclusive data, especially from developing nations. Hence, this study was designed to assess the incidence, clinicodemographic correlates, outcome, and impact of pancytopenia at presentation in ALL in a large tertiary care setting. We also discuss the potential role of pancytopenia as a determinant of choice of therapy and survival outcome in ALL.

METHODS

Data of childhood ALL patients managed at PGIMER, Chandigarh between 1990 and 2006 (followed until 2009) was retrieved.[4] The overall survival outcome from the center has been previously published.[4] For the current study, data were updated and reanalyzed with primary focus on pancytopenia at presentation. Data on complete blood counts, liver function tests, renal function tests, bone marrow aspiration and biopsy, and cerebrospinal fluid were reviewed for the accrued patients. Further outcome data including overall survival, treatment abandonment, relapse, and mortality were reviewed in relation to pancytopenia at presentation. Appropriate ethics approval was obtained from the institution.

Therapy Protocol

The therapy protocols have been detailed previously. The treatment protocol used at our center was a modified version of UKALL X uniform therapy protocol. Remission induction chemotherapy consisted of vincristine, prednisolone, L-asparaginase, and intrathecal methotrexate. More recently (after 2000), patients with high-risk disease and/or those affording the drug were administered doxorubicin in addition to the above drugs during remission induction. All patients received either an early or an early and delayed intensification (vincristine, prednisolone or dexamethasone, daunomycin, and thioguanine) in the form of 5-day blocks. After 2007, several therapy advancements including further risk stratification, use of cytogenetic techniques, and high-dose methotrexate have been introduced; however, that cohort of patients does not form a part of the present

analysis, which was restricted to current population to ensure adequate follow-up period.

Definitions

There is variability on definitions of abandonment, default, refusal, and loss to follow-up, all of which are rampant in developing nations. Herein we used the definitions suggested by Arora et al,[8] where abandonment is defined as initiation but not completion of treatment.

In the current study, pancytopenia was defined as a combination of white cell count ($< 4.0 \times 10^9$/L) (or absolute neutrophil count $< 1.5 \times 10^9$/L), platelet count ($< 100 \times 10^9$/L), and hemoglobin (< 100 g/L) (due to high incidence of nutritional anemia in Indian children). Reticulocyte count was not used to enable better reproducibility in other resource-constraint settings.

Statistical Analysis

Statistical analysis was conducted using SPSS software version 18. Descriptive statistics with means and percentages were used as appropriate to describe the data. Univariate analysis was done to identify significant clinical and laboratory variables associated with survival outcome. On the basis of the univariate analysis, multivariate regression modeling was done to identify significant predictors of outcome. The corresponding odds ratio and their confidence intervals are depicted. Survival outcome (overall survival) was estimated by the Kaplan-Meyer method. Log-rank test was used for comparison of survival outcome in ≥ 2 groups. A P value of < 0.05 was considered significant. Details of multivariate analysis are outlined in Appendix I.

RESULTS

Of the 762 patients assessed in this study, 84 (11.02%) patients presented with pancytopenia. In these 84 patients, male:female ratio was 3.5:1. Only 11 patients had severe pancytopenia. Seven patients (0.92%) had pancytopenia without hepatosplenomegaly or lymphadenopathy (aplastic presentation).

The mean hemoglobin at presentation was 6.12 ± 1.8 g/dL, the mean TLC at presentation in the cohort was $3.105 \pm 0.611 \times 10^9$/L, and the mean platelet count at presentation in these patients was $27.84 \pm 2.84 \times 10^9$/L.

A comparative analysis was done between patients with (n = 84) and without pancytopenic ALL (n = 678) (Table 1). The distribution of L1 and L2 FAB-subtype of leukemia was similar in the 2 groups. A significantly lower fraction of patients with pancytopenia had splenomegaly (n = 56) ($P = 0.008$), renal failure ($P = 0.02$), vena cava obstruction ($P = 0.024$), and mediastinal adenopathy ($P = 0.001$) at presentation. These observations indicate lower disease bulk in these patients.

Table 2 depicts comparison between patients with and without pancytopenia excluding those who abandoned therapy. Despite exclusion of patients who abandoned therapy, patients presenting with pancytopenia had significantly lower incidence of splenomegaly (>5 cm; $P = 0.006$), lymphadenopathy (>2 cm; $P = 0.017$), renal failure at presentation ($P = 0.057$), and mediastinal adenopathy ($P = 0.001$). None of the patients with pancytopenia who opted for therapy had vena cava obstruction at presentation.

TABLE 1. Comparative Analysis of the Clinical and Laboratory Characteristics in Patients With and Without Pancytopenia at Presentation

Characteristics	Patients With Pancytopenia (n = 84)	Patients Without Pancytopenia (n = 678)	*P*
Age (y)	5.53	5.69	0.636
Sex			
Male	65	510	0.375
Female	19	168	
Symptom diagnosis interval			
< 8 wk	43	405	0.387
8 wk-6 mo	39	260	
> 6 mo	2	14	
Hepatomegaly > 5 cm	27 (32.4)	240 (35.2)	0.279
Splenomegaly > 5 cm	15 (17.8)	202 (30.0)	0.008
Lymphadenopathy > 2 cm	14 (16.6)	238 (35.2)	0.001
Renal failure at presentation	1 (1.1)	11 (1.6)	0.02
Mediastinal adenopathy	1 (1.1)	98 (14.5)	0.001
Superior vena cava obstruction	0	24 (3.5)	0.001
Juvenile rheumatoid arthritis-like presentation	6 (7.1)	54 (7.9)	0.339

Therapy and Outcome

A significantly higher fraction of these patients (n = 66, 78.57%) opted for therapy ($P = 0.005$) as compared with the rest of the patients among whom 466 (68.7%) opted for therapy. Financial constraints were the

TABLE 2. Comparative Analysis of the Clinical and Laboratory Characteristics in Patients With and Without Pancytopenia at Presentation (Patients Who Defaulted Therapy Excluded)

Characteristics	Patients With Pancytopenia (n = 66)	Patients Without Pancytopenia (n = 466)	*P*
Age (y)	5.59 ± 3.02	5.54 ± 3.1	0.856
Sex			
Male	50	340	0.532
Female	16	126	
Symptom diagnosis interval			
< 8 wk	32	327	0.499
8 wk-6 mo	30	130	
> 6 mo	2	9	
Hepatomegaly > 5 cm	20 (30.3)	163 (35.1)	0.216
Splenomegaly > 5 cm	11 (16.6)	140 (30.0)	0.006
Lymphadenopathy > 2 cm	10 (15.2)	137 (34)	0.017
Renal failure at presentation	0	7 (1.5)	0.057
Mediastinal adenopathy	1 (1.5)	64 (13.7)	0.001
superior vena cava obstruction	0	15 (3.2)	0.001
Juvenile rheumatoid arthritis-like presentation	5 (7.5)	39 (7.6)	0.516

main cause (cited by parents of over 85% of the patients) of therapy default followed by low socioeconomic status and illiteracy.

A significantly lower fraction of these were non-survivors ($P = 0.009$). The percentage of relapse (14.8%, n = 13) was slightly lower than the remaining patients (16.7%). The distribution of types of relapse was similar in patients with and without pancytopenia at presentation. There were 16 (19%) deaths, mostly during induction and related to sepsis and toxicity, in patients with pancytopenia. In contrast there were 85 (11.06%) deaths in the remaining population. The difference in the proportion was statistically significant ($P = 0.02$).

The estimated mean survival in patients presenting with pancytopenia (67.2 ± 17.2 mo) was significantly higher ($P = 0.031$, log-rank test) as compared with that of other patients (47.2 ± 7.4 mo). Survival was also calculated after censoring those who did not opt for or abandoned therapy. The estimated mean survival for patients who had pancytopenia and opted for therapy was 82.5 ± 9.1 months as compared with 69.3 ± 5.2 months in the remaining patients. Adjusting for the different therapy default and abandonment rates in the 2 groups, the difference remained statistically significant ($P = 0.050$).

In multivariate analysis (Table 3), pancytopenia at presentation was found to be an independent predictor of survival ($P = 0.043$; odds ratio, 0.795; 95% confidence interval, 0.636-0.992) along with absence of bulky disease at presentation and symptom diagnosis interval. Thus pancytopenia was a marker of good prognosis.

TABLE 3. Multivariate Analysis for Predictors of Survival

			95% Confidence Interval for Odds Ratio	
	P	Odds Ratio	Lower	Upper
Sex	0.788	1.027	0.845	1.249
Age	0.959	0.997	0.888	1.119
Symptom diagnosis interval	0.001	1.272	1.097	1.476
Absence of bulky disease	0.001	0.726	0.611	0.863
Pancytopenia at presentation	0.043	0.795	0.636	0.992

DISCUSSION

This is the first study with a large sample size assessing the clinicodemographic features and survival outcome of ALL patients presenting with pancytopenia and demonstrates superior survival in these patients. In contrast, the previous studies addressing the issue are in the form of small case series or case reports.[1–3] Further, most of these studies focus on aplastic presentation of ALL and not pancytopenia at presentation making comparisons difficult and limited.

Percentage of aplastic presentation (0.92%) is similar to that in the published literature.[1–3,9] This observation may actually be a strength of our study as it supports the potential generalizability of our findings. Stark paucity of any data from developing nations makes it difficult to compare the present study data with that stemming from developing nations. However, the clinical presentation of patients with pancytopenia clearly differed from the ALL patients without pancytopenia at presentation. These clinical indicators may denote less aggressive nature of the ALL blasts and of the disease in these patients and may potentially point to a distinct biology of disease in them. Another important observation of the current study was that the death rate, especially during induction, was significantly higher in patients with pancytopenia at presentation. Moreover, sepsis was the most important contributor. Because of their low counts, pancytopenic patients are especially at a high risk of infection and sepsis. Induction chemotherapy further adds to this risk. Sepsis is a well-known cause of mortality in Indian ALL patients and contributes to inferior survival outcomes.[4,5] Our observation further underscores the need of excellent supportive care and use of preventive measures to reduce or potentially eliminate this preventable cause of mortality, especially in the pancytopenic cohort of patients who are likely to have a better survival outcome. The pattern of relapse in patients with pancytopenia was similar to that observed in the remaining patients. Our observation that patients presenting with pancytopenia had a better survival outcome corresponds with previous case reports indicating similar observations.[1–3] However, our study was adequately powered to assess the survival outcome and other risk predictors unlike previous studies. The association of pancytopenia with pattern of relapse, mortality, and survival has not been delineated before from developing nations. Our observations support that the pediatric oncologists in developing nations be aware of the clinical needs and excellent supportive care that ALL patients with pancytopenia are likely to need to ensure optimum survival.

Despite ongoing improvements, the overall survival outcome of childhood ALL has clearly not kept pace with that of the resource-plenty nations.[5] Several barriers including high rates of therapy abandonment, higher mortality and relapse rates, infrastructural inadequacies, and sociocultural and financial factors have been deemed to be contributory. In addition, difficultly in access to treating centers, distant locales (> 150 to 200 km) from treating centers, and misplaced faith in alternate systems of medicine (AYUSH: Ayurvedic, Yoga and Naturopathy, Unani, Siddha, and Homeopathy) are recognized hindrances. Lack of national population-based registry, robust epidemiological data, and financial and logistic difficulties in conduct of multicentric trials are additional barriers in therapy advancement.[4,5] Further, due to these challenges, a minority of the >10,000 children diagnosed with ALL in India annually are likely adequately treated. Thus conclusively determining definitive factors impacting choice of therapy and survival of ALL in India is challenging.

To assess the relevance of all the above barriers in India, the authors initially assessed the local single center data for therapy abandonment, mortality, relapse pattern, and overall survival.[4,5,10] Thereafter, the authors attempted to assess the survival outcome of published studies and gray literature on ALL from India.[5] A clear need was felt to identify locally relevant and easily usable prognostic factors in addition to improvements in financial support and infrastructural facilities and personnel availability. In addition, a need was established to assess determinants of choice of therapy and those of therapy abandonment. The present study was specifically attempted to assess the relevance of pancytopenia at presentation in ALL.

During the accrual of patients assessed in the present retrospective study, pancytopenia was not used to risk stratify ALL patients. To the best of our knowledge, there

is no published study on ALL from developing countries that has risk-stratified patients based on pancytopenia. However, individually all of high total leukocyte count (TLC) (and not low TLC), low platelet counts, and hemoglobin have been identified as prognostic parameters from developing nations, especially India.[5] The role of pancytopenia at presentation in ALL and its association with prognosis needs to be prospectively assessed in well-designed clinical trials.

Furthermore, pancytopenia has not been previously studied in relation to therapy abandonment. Several factors have been linked to therapy abandonment in developing nations, one of which is higher risk and bulky disease. Previously Kulkarni et al[7] reported that none of the clinical and demographic parameters were significantly associated with therapy abandonment. In the present study we observed that a significantly higher proportion of patients with pancytopenia opted for therapy as compared with the remaining patients. Although the lower bulk of disease and lower incidence of high-risk disease may contribute to this observation, further studies assessing socioeconomic and clinical parameters are needed to delineate the association of pancytopenia with abandonment.

Furthermore, although several other factors including socioeconomic, cultural, and sex bias are likely contributory, financial constraints are often cited to be the most important reason contributing to therapy abandonment and choice of therapy in developing nations.[6,7] Some cancer treating centers from India have reported the use of lower intensity therapy in extremely financially challenged population who would otherwise abandon therapy.[5] On the contrary, in the present study, pancytopenia did not guide the choice of therapy protocol in any ALL patients.

Moreover, most major cancer treating centers in India till recently used uniform therapy protocols in ALL patients.[4,5] Hence if patients started therapy, they would get the same therapy regardless of the risk factors. Even in patients who abandon therapy, in general, efforts are made with attempts to provide financial support, to persuade patients and families to resume standard therapy protocol. More recently, several centers of excellence are attempting to risk stratify patients based on known risk factors to optimize survival and minimize toxicity. This recent positive change further emphasizes the need of locally relevant and usable prognostic parameters, similar to potentially pancytopenia at presentation, to risk stratify patients and guide choice of therapy. Despite its retrospective design, we believe that our observations will contribute to the body of literature on prognostic parameters in resource-constraint nations and sites where "state-of-the-art" therapy protocols using molecular techniques are currently clearly not feasible.

One of the limitations of this analysis was that treatment-related variables were not included in multivariate modeling due to data variability and heterogeneity as well as relatively limited sample size. Another limitation of the current study is noninclusion of molecular and cytogenetic data in analysis. This was done so due to patchy availability of that data especially from the patients treated before 2000. However, we believe that assessment and discussion of easily available, assessable, and usable clinical and laboratory parameters will help in better comparison of the present results and observations with similar studies from resource-constraint nations which will likely face similar problems.

In conclusion, in this large group of patients, we observed that patients with pancytopenia at presentation had a significantly better survival outcome as compared with other ALL patients and that pancytopenia was an independent prognostic marker. Further prospective studies are necessary to confirm this observation and establish its prognostic significance in developing nations. Identification of such locally relevant prognostic parameters and attempting to correlate them with determinants of therapy and survival of ALL will undoubtedly contribute to the improvement in the survival outcome of ALL in resource-poor nations.

APPENDIX I

Multivariate Analysis

In the current study, Cox multivariate regression analysis was used to identify significant predictors of survival in the entire cohort of patients. Age, sex, symptom diagnosis interval at presentation, presence of bulky disease (presence of ≥ 1 of enlarged lymph node [> 2 cm], hepatomegaly [> 5 cm], and splenomegaly [> 5 cm]), and presence of pancytopenia at presentation were entered in multivariate analysis. TLC and platelet count were not entered as separate variables as the variable "presence of pancytopenia" was a combined variable generated with values of hemoglobin, TLC, and platelet count at presentation. Further, in exploratory analysis, TLC and platelet count were significantly confounding the variable "pancytopenia at presentation." Because of significant differences in the distribution of survivors and nonsurvivors (death, relapse, and therapy defaulters), type of therapy administered and intensification regime were not entered in multivariate survival analysis.

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