INTRODUCTION

Current established regimens in adult acute lymphoblastic leukemia (ALL) result in a long-term overall survival (OS) rate of 40% to 50%. Over the years, improvement in OS has been attributed to more intensive combination therapies using high-dose methotrexate, cytarabine, monoclonal antibodies, and nelarabine, and, where appropriate, the optimal use of an allogeneic hematopoietic stem-cell transplantation (allo-SCT). Most of these results reflecting improvement in outcomes are from developed countries and were largely generated in the clinical trial setting. There has been a paucity of real-world data and even less data from developing nations, where good single-center registry or population-based registry data are usually not available. Available information from developing countries has been derived from small, retrospective, and often single-center studies, with the reported OS for ALL reaching up to 40% in a select few reports. Buyukasik et al retrospectively compared the commonly used regimen of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HCVAD) with the Cancer and Leukemia Group B 8811 regimens and reported an inferior OS rate (26.3% vs 44.2% at 5 years, respectively; \( P < .001 \)). Within the HR subgroup, there was no statistically significant difference in overall survival or event-free survival between patients who received the modified GMALL regimen (n = 59) and patients who received HCVAD (n = 53).

Purpose

Limited data exist on intensifying chemotherapy regimens in the treatment of adult acute lymphoblastic leukemia (ALL) outside the setting of a clinical trial.

Materials and Methods

Retrospectively, data from 507 consecutive adults (age ≥ 15 years) with a diagnosis of ALL treated at our center were analyzed. Standard-risk (SR) patients were offered treatment with a modified German Multicenter ALL (GMALL) regimen, whereas high-risk (HR) patients were offered intensification of therapy with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HCVAD). Because of resource constraints, a proportion of HR patients opted to receive the same treatment regimen as used for SR patients.

Results

There were 344 SR patients (67.8%) and 163 HR patients (32.2%) at diagnosis. Among the HR patients, 53 (32.5%) opted to receive intensification with the HCVAD regimen. The SR cohort showed a superior 5-year event-free survival rate compared with the HR cohort (47.3% vs 23.6%, respectively; \( P < .001 \)). Within the HR subgroup, there was no statistically significant difference in overall survival or event-free survival between patients who received the modified GMALL regimen (n = 59) and patients who received HCVAD (n = 53).

Conclusion

Intensified therapy in the HR subset was associated with a significant increase in early treatment-related mortality and cost of treatment. A modified GMALL regimen was found to be cost-effective with clinical outcomes comparable to those achieved with more intensive regimens.
subsequent infections leading to substantial morbidity and mortality.

Cancer care in India faces several economic challenges.\textsuperscript{18-20} As reported previously by us and others, challenges to administering intensive chemotherapy regimens include resource constraints, a predominantly self-paying system of medical care, and a high incidence of multidrug-resistant infections.\textsuperscript{18,19,21,22} Long interruptions and abandonment of therapy after successful initial induction remission also lead to more resistant disease, as a result of delays in cancer care.\textsuperscript{13,23} An earlier study from our center reporting on the outcomes of 202 adults (age $\geq$ 15 years) using a modified German Multicenter ALL (GMALL) regimen demonstrated a complete remission (CR) rate of 82.2% and a 5-year OS rate of 38%.\textsuperscript{15} To further improve results, we adopted a strategy of intensifying therapy for high-risk (HR) patients. The current analysis aimed to evaluate whether this strategy yielded improved results.

\textbf{MATERIALS AND METHODS}

\textbf{Study Population}

This was a retrospective, single-center study approved by our institutional review board (No. 7903, dated April 7, 2012). All consecutive adult patients (age $\geq$ 15 years) with a diagnosis of ALL from January 2004 to November 2014 were included in our study. Data for this analysis were frozen as of December 31, 2015. Diagnosis was made as per the WHO 2008 classification.\textsuperscript{24,25} Patients diagnosed before 2008 were reclassified to fit the WHO 2008 criteria.\textsuperscript{24,25} Prognostic risk stratification of cytogenetic abnormalities was performed based on the Medical Research Council UKALLXII/Eastern Cooperative Oncology Group 2993 trial and a population-based cytogenetic study of 349 adults (age $\geq$ 15 years) with ALL.\textsuperscript{26,27} Patients with t(8;14) were excluded from the current study. Molecular screening for BCR-ABL, TEL-AML, E2A-PBX, and MLL gene mutations was performed using conventional molecular techniques.\textsuperscript{28,29} CNS involvement at diagnosis was defined as reported previously.\textsuperscript{15,30,31}

\textbf{Clinical Risk Stratification}

Patients were stratified at diagnosis into either the standard-risk (SR) subgroup or HR subgroup (HR) to aid in the treatment regimen decision. HR disease was defined as presence of at least one of the following four criteria: poor prednisolone response (peripheral blood blast count $\geq$ 1,000/$\mu$L on day 8 of initiating corticosteroids);\textsuperscript{13} HR cytogenetics, including t(9;22) or t(4;11);\textsuperscript{24,32} (complex cytogenetics $\geq$ five chromosomal abnormalities) and low hypodiploidy or near triploidy (chromosomes 30 to 39 and 60 to 78) were not considered as high risk for the purpose of deciding initial therapy after diagnosis; residual disease at end of induction (> 5% blasts on bone marrow [BM] or persistent extramedullary disease); and early precursor T-cell ALL immunophenotype.\textsuperscript{33} Early precursor T-cell ALL was included in the HR category beginning in October 2012.\textsuperscript{33} Patients with none of these risk factors were stratified as being SR for the purpose of this analysis.

\textbf{Treatment Strategy}

Patients stratified as SR received the modified GMALL protocol, as reported previously by us\textsuperscript{15} (Data Supplement). Given the available financial resources, patients in the HR subgroup were offered the following treatment options: patients with financial limitations received our modified GMALL regimen, similar to our SR patients, whereas patients without financial limitations received the standard HCVAD-based therapy.\textsuperscript{34} A myeloablative allo-SCT (conventional cyclophosphamide and total-body irradiation) was offered to all HR patients in the first CR provided they had an HLA-matched donor\textsuperscript{35,36} and after they had received three to four cycles of HCVAD. Patients who did not have a donor or opted not to have an allo-SCT were scheduled to receive six to eight cycles of HCVAD followed by maintenance therapy for 2 years.\textsuperscript{34} Patients with CNS disease at diagnosis received six doses of triple intrathecal therapy (methotrexate 12.5 mg, cytarabine 40 mg, and hydrocortisone 50 mg) during the initial induction, in addition to assigned treatment protocol.\textsuperscript{31,37}

\textbf{Definitions}

CR was defined as the absence of blasts in the peripheral blood and CNS, an absolute neutrophil count $> 1.5 \times 10^9$/L, an unsupported platelet count of $> 100 \times 10^9$/L, and < 5% blasts in the BM at the end of phase I induction.\textsuperscript{38} Relapse
was defined as the reappearance of lymphoblasts at any site after achieving remission. The time points for relapse were defined as follows: very early relapse, < 18 months from initiation of therapy; early relapse, > 18 months from initiation of treatment but < 6 months after completion of final maintenance therapy; and late relapse, > 6 months after completion of final maintenance therapy. OS was defined as time from beginning of treatment to either death or the last follow-up date if alive. Event-free survival (EFS) was defined as time from beginning of treatment until the first event (relapse or death).

### Statistical Methods

A comparison between the quantitative parameters was performed using a Mann-Whitney U test or a t test as appropriate, whereas differences in the qualitative parameters were evaluated using the χ² statistics or the Fisher’s exact test. OS and EFS survival probabilities were estimated using the Kaplan-Meier method. A log-rank (Mantel-Cox) comparison was used to assess any statistically significant difference in the OS or EFS between the different subgroups. The prognostic significance of clinical and biologic factors in all of the patients was tested first using a univariate Cox regression analysis and then a subsequent multivariate Cox regression analysis as required. For all of the tests, a two-sided P ≤ .05 indicated statistical significance. All analysis was done using SPSS version 16.0 (SPSS, Chicago, IL).

### RESULTS

#### Patient Accrual and Baseline Characteristics

Over the study period, 507 adults (age ≥ 15 years) were diagnosed and treated for ALL at our institution. The median age was 26 years (range, 15 to 67 years), with 334 patients (65.8%) ≤ 35 years old. Three hundred fifty-one patients (69.2%) were male. A total of 117 patients (23.0%) presented with WBC counts ≥ 50 × 10⁹/L. A total of 344 patients (67.8%) were identified as SR, and 163 patients (32.2%) were identified as HR. The baseline demographic characteristics of the entire cohort are listed in Table 1.

#### Cytogenetic and Molecular Genetics

BM karyotype results were available in 442 patients (87.1%). Three hundred forty-five patients (78%) had SR cytogenetics (normal karyotype and other non-HR chromosomal abnormalities), and 97 patients (21.9%) had HR cytogenetics (Table 1). Of these 97 patients with HR cytogenetics, 61 (62.8%) were Philadelphia chromosome positive [t(9;22)] and 36 (37.1%) were Philadelphia chromosome negative [complex cytogenetics, t(4;11), and low hypodiploidy or tetraploidy (chromosomes 30 to 39 and 60 to 78)].

### Table 1. Summary of Baseline Characteristics of the Entire Cohort at diagnosis

| Characteristic                          | Value (N = 507), No. (%) |
|----------------------------------------|--------------------------|
| Median age at presentation, years (range) | 26 (15-67)               |
| Male sex, No. (%)                      | 351 (69.2)               |
| Median WBC count, × 10⁹/L (range)      | 9.3 (0.3-821.4)          |
| CNS stage III, No. (%)                 | 63 (12.4)                |
| Testicular disease (n = 361), No. (%)  | 3 (0.8)                  |
| Immunophenotype (n = 497), No. (%)     |                          |
| B cell                                 | 371 (74.6)               |
| T cell                                 | 126 (25.4)               |
| RT-PCR (n = 394), No. (%)              |                          |
| BCR-ABL                                | 89 (22.6)                |
| TEL-AML                                | 8 (2.1)                  |
| MLL-AF4                                | 8 (2.1)                  |
| E2A-PBX                                | 12 (3.1)                 |
| Cytogenetic risk stratification (n = 442), No. (%) |
| SR                                     | 345 (78.0)               |
| HR                                     | 97 (22)                  |
| t(9;22), Ph positive                   | 61 (62.8)                |
| Ph negative                            | 36 (37.1)                |
| Protocol (n = 507), No. (%)            |                          |
| Modified GMALL (342 SR + 110 HR patients) | 452 (67.9)             |
| HCVAD (53 HR + 2 SR patients)          | 55 (32.1)                |
| Allo-SCT CR1 (only HCVAD HR patients)  | 18 (33.9)                |

Abbreviations: allo-SCT, allogeneic stem-cell transplantation; GMALL, German Multicenter Acute Lymphoblastic Leukemia; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; HR, high risk; Ph, Philadelphia chromosome; RT-PCR, reverse transcriptase polymerase chain reaction; SR, standard risk.

*CNS disease: stage I, total count < 5 cells and absence of blasts; stage II, total count > 5 cells and absence of blasts or a traumatic tap; stage III, presence of blasts irrespective of the total count.

†Cytogenetic risk: standard-risk cytogenetics include normal karyotype and other non-HR abnormalities; t(9;22) and Ph-negative high-risk cytogenetics such as t(4;11), complex cytogenetics, and low hypodiploidy or tetraploidy (chromosomes 30 to 39 and 60 to 78). Eighteen patients had < 10 metaphases but a normal karyotype in the available metaphases. For purpose of this analysis, these patients were classified as having SR cytogenetics because of the absence of an HR marker.
Table 2. Summary of the Baseline Characteristics of the Different Risk Cohorts

| Characteristic                          | SR (n = 344) | HR (n = 163) | P     |
|----------------------------------------|-------------|-------------|-------|
| Age, years                             | 25 (15-67)  | 32 (15-67)  | < .001|
| Male                                   | 252 (73.3)  | 99 (60.7)   | .005  |
| WBC, × 10⁹/L                           | 7.5 (0.3-21.4) | 8.0 (0.4-531) | < .001|
| CNS stage III                          | 44 (12.7)   | 19 (11.6)   | .714  |
| Testicular disease                     | 252 (71.8)  | 99 (28.2)   | 1.000 |
| Immunophenotype                        | 336 (97.6)  | 161 (98.7)  | .036  |
| B cell                                 | 241 (71.8)  | 130 (80.8)  |       |
| T cell                                 | 95 (28.3)   | 31 (19.3)   |       |
| RT-PCR                                 | 258 (75.0)  | 136 (83.4)  |       |
| BCR-ABL                                | —           | 89 (65.4)   | < .001|
| TEL-AML                                | 6 (2.3)     | 2 (1.6)     | 1.000 |
| MLL-AF4                                | —           | 8 (6.3)     | < .001|
| E2A-PBX                                | 11 (4.3)    | 47 (34.6)   | .114  |
| Cyto genetic stratification⁹          | 295 (85.7)  | 147 (90.1)  | < .001|
| SR                                     | 275 (93.2)  | 70 (47.6)   |       |
| t(9;22)                                | —           | 61 (41.4)   |       |
| Ph-negative HR¹                        | 20 (6.7)    | 16 (10.8)   |       |
| Protocol                               | 344 (100.0) | 163 (100.0) | < .001|
| Modified GMALL                         | 342 (99.4)  | 110 (67.5)  |       |
| HCVAD ± allo-SCT                       | 2 (0.6)     | 53 (32.5)   |       |

Abbreviations: allo-SCT, allogeneic stem-cell transplantation; GMALL, German Multicenter Acute Lymphoblastic Leukemia; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; HR, high risk; Ph, Philadelphia chromosome; RT-PCR, reverse transcriptase polymerase chain reaction; SR, standard risk.

*Values are medians, with ranges in parentheses.
†Complex cytogenetics, t(4;11), and low hypodiploidy or near triploidy (chromosomes 30 to 39 and 60 to 78).

BCR-ABL, TEL-AML, MLL-AF4, and E2A-PBX transcripts, respectively (Table 1).

Risk Stratification and Distribution of Patients

Of the 344 SR patients (67.8%), two had received one cycle of HCVAD-based therapy before coming to our center and hence were continued on the same regimen. The modified GMALL regimen was offered to the remaining 342 SR patients (99.4%). None of these SR patients opted for palliation.

Of the 163 patients (32.2%) who were stratified at diagnosis as being HR, 53 (32.5%) opted to receive the intensified HCVAD-based regimen and an allo-SCT was performed in 18 of these patients (33.9%). Of the remaining 110 HR patients (67.5%), 59 (53.6%) opted to receive a modified GMALL regimen, whereas 51 (46.3%) opted for chemotherapy with palliative intent (individualized at treating physician’s discretion). The baseline characteristics of the two different risk cohorts (SR and HR) and the two HR subsets treated with two different regimens are listed in Tables 2 and 3, respectively.

Induction Outcomes

Forty-nine patients (9.6%) did not have an assessment at the end of induction chemotherapy. Ten patients (1.9%) were lost to follow-up before their end-of-induction assessment, two patients (0.3%) refused a BM assessment, and a further 37 patients (7.2%) suffered induction deaths (Data Supplement and Table 4). A total of 433 patients (85.4%) achieved a CR, and 25 patients (4.9%) remained refractory at the end of induction (Table 4).

Outcomes of Patients Refractory to the Initial Induction

Of the 25 refractory patients (4.9%), five (20.0%) opted for palliation at a local place. Eleven patients (44%) continued therapy with the same
Of these patients, four (36.6%) achieved transient remission but died later as a result of relapse and seven (63.6%) remained refractory and died later as a result of progressive disease (PD). Nine (36%) of the 25 refractory patients opted for intensified therapy with the HCVAD regimen. Of these nine patients, three (33.3%) achieved remission but experienced relapse later and died. Five patients (55.5%) remained refractory to therapy and died as a result of PD. One patient (11.1%) was lost to follow-up.

Profile of Disease Relapse
A total of 150 patients (29.5%) experienced relapse, with a median time to relapse of 14 months (range, 2 to 81 months; Table 4). Isolated medullary and extramedullary relapse was seen in 120 patients (80.0%) and 19 patients (12.6%), respectively. CNS was the most frequently involved extramedullary site (n = 14; 9.3%). Combined medullary and extramedullary disease was seen in 11 patients (7.3%). Of the 150 patients who experienced relapse, six patients (4.0%) continue to remain in second or third CR, and 144 patients (96.0%) have died as a result of PD after opting for palliation.

Current Status
At the time of study closure, 166 patients (32.7%) were in continuous CR and 61 patients (12%) were in CR on active treatment. Fifty-seven patients (11.2%) were identified as being lost to follow-up. Of a total of 217 deaths (42.8%), 163 deaths (75.1%) occurred as a result of PD and 54 deaths (24.8%) were secondary to infection and sepsis. Six patients achieved a second or third CR and were alive at the last documented follow-up (Table 4).

Univariable and Multivariable Analysis
On univariable analysis, older age at diagnosis was associated with an inferior EFS (age > 20
but ≤ 40 years: hazard ratio \( [HR] \), 1.4; 95% CI, 1.04 to 1.97; \( P = .028 \); and age > 40 years: HR, 1.8; 95% CI, 1.26 to 2.64; \( P = .001 \). In addition, the following parameters were also identified as indicators of an inferior EFS: presence of \( BCR-ABL1 \) fusion abnormality (HR, 1.8; 95% CI, 1.34 to 2.51; \( P < .001 \)), poor prednisolone response on day 8 (HR, 2.1; 95% CI, 1.53 to 2.99; \( P < .001 \)), and no achievement of CR at the end induction (HR, 7.4; 95% CI, 4.78 to 11.66; \( P < .001 \)). On multivariable analysis, only a higher age at diagnosis (age > 20 but ≤ 40 years: HR, 1.6; 95% CI, 1.0 to 2.7; \( P = .044 \); and age > 40 years: HR, 2.2; 95% CI, 1.2 to 3.9; \( P = .008 \)) and no achievement of CR at the end of induction (HR, 4.2; 95% CI, 2.2 to 7.9; \( P < .001 \)) were identified as independent prognostic factors.

Survival Statistics

The 5-year OS and EFS rates (± standard deviation) of the entire cohort were 50.0% ± 2.6% and 47.3% ± 2.7% (Figs 1A and 1B), respectively, at an actuarial median follow-up time of 59 months. The 5-year OS and EFS rates of the SR cohort were 61% ± 3.1% and 58.8% ± 3.2% (Figs 1C and 1D), respectively, whereas OS and EFS rates of the HR cohort were 27.2% ± 4.2% and 23.6% ± 4%, respectively (Figs 1C and 1D). The OS and EFS rates between these two groups were statistically significantly different (OS, \( P < .001 \); and EFS, \( P < .001 \)). Among the HR subsets, the group that received the modified GMALL protocol (n = 59) had 5-year OS and EFS rates of 40.4% ± 8.1% and 35.1% ± 7.6%, respectively, whereas the group that received HCVAD with or without an allo-SCT based on availability of donor (n = 18) had 5-year OS and EFS rates of 26.6% ± 7.2% and 22.0% ± 6.8%, respectively (Figs 1E and 1F). However, there was no statistically significant difference in survival between these two groups (OS, \( P = .217 \); and EFS, \( P = .263 \)). The survival analysis of the subset of patients who received only the modified GMALL regimen, which included SR and HR patients (n = 452) with different additional variables such as age, cytogenetic risk group, and immunophenotype, is shown Figure 2 and the Data Supplement.

Cost Analysis of Different Regimens

For cost analysis purposes, 15 HR patients were selected randomly from both subgroups (modified GMALL and HCVAD-based regimens). For the modified GMALL regimen subgroup (chemotherapy only; n = 15), the total cost incurred over 2.5 years from the date of first contact, which including all incurred outpatient and inpatient costs during initial induction, consolidation, and the subsequent 2 years of maintenance therapy, was included. For the group that received the HCVAD-based regimen (chemotherapy with or without maintenance [n = 8] or allo-SCT in first CR [n = 7]), the total cost incurred from the date of first contact, which included all incurred outpatient and inpatient costs during the initial induction, consolidation, and either 2 years of maintenance (n = 8) or up to 3 months after a successful allo-SCT (n = 7), was included. All cost-related data were the data captured comprehensively on the computerized hospital information and payment system. For the purpose of this analysis, only HR patients with an uneventful course and who had successfully completed their entire course of treatment were included. The average cost of treatment of patients in the modified GMALL subgroup and the HCVAD...
Fig 1. (A) Five-year Kaplan-Meier product-limit estimates of overall survival (OS) of the entire cohort (N = 507). (B) Event-free survival (EFS) of the entire cohort (N = 507). (C) OS and (D) EFS of the standard-risk group (n = 344) and the high-risk (HR) group (n = 163). (E) OS and (F) EFS of the two HR subsets that received either the German Multicenter Acute Lymphoblastic Leukemia protocol (n = 59) or the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen (n = 53).
Fig 2. Five-year Kaplan-Meier product-limit estimates in the cohort treated with the German Multicenter Acute Lymphoblastic Leukemia regimen (n = 452). (A) Overall survival (OS) and (B) event-free survival (EFS) in the different age groups (15 to 20 years, n = 141; > 20 to 40 years, n = 212; and > 40 years, n = 99). (C) OS and (D) EFS of the following three cytogenetic risk groups: standard-risk cytogenetics (n = 326) include normal karyotype and other non–high-risk abnormalities; Philadelphia chromosome–negative high-risk cytogenetics (n = 25) include t(4;11), complex cytogenetics, and low hypodiploidy or tetraploidy (chromosomes 30 to 39 and 60 to 78); and Philadelphia chromosome–positive high-risk cytogenetics (n = 40) include t(9;22). (E) OS and (F) EFS of the following two immunophenotypic subsets: B cell (n = 328) and T cell (n = 116).
DISCUSSION

This single-center retrospective study over 10 years broadly illustrates the challenges and long-term outcomes of treating adult ALL (patients age ≥ 15 years) in India, although we do recognize that only a prospective multicenter study can definitively address the issue of dose intensification and improved clinical outcomes. With 5-year OS and EFS rates of 50.0% and 47%, respectively, the overall outcomes from our study cohort are comparable to several published studies.2,40,41 Our induction mortality rate of 7.2% is similar to that from previously published studies.2,42,43 Long distances of travel leading to delays before initiating treatment, environmental factors, and an increased risk of bacterial and fungal infections during the initial induction could partly explain our high induction mortality rate, as reported in this analysis and previously by us.15,22,44

In this study, 11.2% of patients were lost to follow-up after an initial remission. In another study from India, Malhotra et al13 had reported an abandonment rate of 14.9%. Although several reasons have been attributed to the discontinuation of the therapy, limited finances often remain the most significant factor leading to abandonment of treatment, as has been previously reported from our center in the context of treatment of acute myeloid leukemia.22 The cost of intensified chemotherapy in HR subsets, which has been reported to be successful in developed countries, is often not feasible because of the high cost of such therapy, as illustrated in this study (10-fold more expensive than GMALL regimen in this study). In a predominantly self-pay system such as exists in India, only 32.5% of the HR patients could afford and opted for the HCVAD regimen. The relatively low-cost modified GMALL protocol used at our center offers an acceptable long-term survival rate, which has been previously reported by us and further validated in this analysis.7 An interesting observation in our study was that we did not find a significant difference in outcomes between the two HR patient subgroups treated with either the low-cost modified GMALL regimen or the HCVAD-based regimen (with or without maintenance therapy or allo-SCT). Although not statistically significant, the lower incidence of PD in the HCVAD subgroup was offset by its higher nonrelapse mortality rate. It is important to note that this comparison was limited by its small numbers and the retrospective nature of the study.

This study illustrates the caution required in implementing dose-intensive regimens in resource-constrained environments or where additional challenges exist in their implementation. One cannot assume that the excellent results with these regimens, often in the context of a clinical trial, will be duplicated in different economic and social settings. Attention also needs to be given to the additional cost required to administer such regimens, and the cost-effectiveness of such approaches needs to be carefully addressed.

DOI: https://doi.org/10.1200/JGO.17.00014
Published online on jgo.org on February 8, 2018.
Punit Jain
No relationship to disclose

Anu Korula
No relationship to disclose

Prashant Deshpande
No relationship to disclose

Nisham PN
No relationship to disclose

Ansu Abu Alex
No relationship to disclose

Aby Abraham
Travel, Accommodations, Expenses: Novoseven

Alok Srivastava
Consulting or Advisory Role: Bayer
Research Funding: Bayer (Inst), Alnylam (Inst)
Travel, Accommodations, Expenses: Merck, Novo Nordisk

Nancy Beryl Janet
No relationship to disclose

Kavitha M. Lakshmi
No relationship to disclose

Poonkuzhali Balasubramanian
No relationship to disclose

Biju George
No relationship to disclose

Vikram Mathews
No relationship to disclose

Affiliation
All authors: Christian Medical College, Vellore, India.

Support
Supported by senior fellowship programs of Wellcome DBT India Alliance, New Delhi, India (IA/S/11/2500267 [V.M.] and IA/S/15/1/501842 [P.B.]) and Fluid Research Grant No. FG/7903/07/2012 (IRB Min No. 7903; P.J.).

REFERENCES

1. Kantarjian H, Thomas D, O’Brien S, et al: Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 101:2788-2801, 2004

2. Gökbuget N, Hoelzer D: Treatment of adult acute lymphoblastic leukemia. Semin Hematol 46:64-75, 2009

3. Annino L, Vegna ML, Camera A, et al: Treatment of adult acute lymphoblastic leukemia (ALL): Long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood 99:863-871, 2002

4. Fielding AK: The treatment of adults with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 381-389, 2008

5. Huguet F, Leguay T, Raffoux E, et al: Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: The GRAALL-2003 study. J Clin Oncol 27:911-918, 2009

6. Kantarjian H, Thomas D, Wayne AS, et al: Monoclonal antibody-based therapies: A new dawn in the treatment of acute lymphoblastic leukemia. J Clin Oncol 30:3876-3883, 2012

7. Yeoh AE, Tan D, Li CK, et al: Management of adult and paediatric acute lymphoblastic leukaemia in Asia: Resource-stratified guidelines from the Asian Oncology Summit 2013. Lancet Oncol 14:e508-e523, 2013

8. Pulte D, Gondos A, Brenner H: Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. Blood 113:1408-1411, 2009

9. Buyukasik Y, Acar K, Kelkitli E, et al: Hyper-CVAD regimen in routine management of adult acute lymphoblastic leukemia: A retrospective multicenter study. Acta Haematol 130:199-205, 2013

10. Xu W, Li JY, Qian SX, et al: Outcome of treatment with hyper-CVAD regimen in Chinese patients with acute lymphocytic leukemia. Leuk Res 32:930-935, 2008

11. Charafeddine KM, Hatoum HA, Otrock ZK, et al: Long-term outcome of adult acute lymphoblastic leukemia in Lebanon: A single institution experience from the American University of Beirut. Hematol Oncol Stem Cell Ther 2:333-339, 2009

12. Abbasi S, Maleha F, Shobaki M: Acute lymphoblastic leukemia experience: Epidemiology and outcome of two different regimens. Mediterr J Hematol Infect Dis 5:e2013024, 2013
13. Malhotra P, Varma S, Varma N, et al: Outcome of adult acute lymphoblastic leukemia with BFM protocol in a resource-constrained setting. Leuk Lymphoma 48:1173-1178, 2007

14. Alacacioglu I, Medeni SS, Ozsan GH, et al: Is the BFM regimen feasible for the treatment of adult acute lymphoblastic leukemia? A retrospective analysis of the outcomes of BFM and hyper-CVAD chemotherapy in two centers. Chemotherapy 60:219-223, 2014

15. Bajel A, George B, Mathews V, et al: Adult ALL: Treatment outcome and prognostic factors in an Indian population using a modified German ALL (GMALL) protocol. Leukemia 21:2230-2233, 2007

16. Fogliatto L, Bittencourt H, Nunes AS, et al: Outcome of treatment in adult acute lymphoblastic leukemia in southern Brazil using a modified German multicenter acute lymphoblastic leukemia protocol. Acta Haematol 107:203-207, 2002

17. Duer D: Adult acute lymphoblastic leukemia: A cancer with no standard of care. Acta Haematol 130:196-198, 2013

18. Balarajan Y, Selvaraj S, Subramanian SV: Health care and equity in India. Lancet 377:505-515, 2011

19. Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, et al: Challenges to effective cancer control in China, India, and Russia. Lancet Oncol 15:489-538, 2014

20. Magrath I, Shanta Y, Advani S, et al: Treatment of acute lymphoblastic leukaemia in countries with limited resources: Lessons from use of a single protocol in India over a twenty year period [corrected]. Eur J Cancer 41:1570-1583, 2005

21. Horton R, Das P: Indian health: The path from crisis to progress. Lancet 377:181-183, 2011

22. Philip C, George B, Ganapule A, et al: Acute myeloid leukaemia: Challenges and real world data from India. Br J Haematol 170:110-117, 2015

23. Mostert S, Sitaresmi MN, Gundy CM, et al: Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. Pediatrics 118:e1600-e1606, 2006

24. Swerdlow SH, Campo E., Harris NL, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, International Agency for Research on Cancer, 2008

25. Campo E, Swerdlow SH, Harris NL, et al: The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood 117:5019-5032, 2011

26. Moorman AV, Chilton L, Wilkinson J, et al: A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Blood 115:206-214, 2010

27. Moorman AV, Harrison CJ, Buck GA, et al: Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): Analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood 109:3189-3197, 2007

28. van Dongen JJ, Macintyre EA, Gabert JA, et al: Standardized RT-PCR analysis of fusion gene transcripts from chromosome aberrations in acute leukemia for detection of minimal residual disease. Report of the BIOMED-1 Concerted Action: Investigation of minimal residual disease in acute leukemia. Leukemia 13:1901-1928, 1999

29. Mullighan CG: Molecular genetics of B-precursor acute lymphoblastic leukemia. J Clin Invest 122:3407-3415, 2012

30. Dutch Childhood Oncology Group, te Loo DM, Kamps WA, et al: Prognostic significance of blasts in the cerebrospinal fluid without pleiocytosis or a traumatic lumbar puncture in children with acute lymphoblastic leukemia: Experience of the Dutch Childhood Oncology Group. J Clin Oncol 24:2332-2336, 2006

31. Del Principe MI, Maurillo L, Buccisano F, et al: Central nervous system involvement in adult acute lymphoblastic leukemia: Diagnostic tools, prophylaxis, and therapy. Mediterr J Hematol Infect Dis 6:e2014075, 2014
32. Marks DI, Moorman AV, Chilton L, et al: The clinical characteristics, therapy and outcome of 85 adults with acute lymphoblastic leukemia and t(4;11)(q21;q23)/MLL-AFF1 prospectively treated in the UKALLXII/ECOG2993 trial. Haematologica 98:945-952, 2013

33. Coustan-Smith E, Mullighan CG, Onciu M, et al: Early T-cell precursor leukaemia: A subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol 10:147-156, 2009

34. Kantarjian HM, O’Brien S, Smith TL, et al: Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 18:547-561, 2000

35. Goldstone AH: Transplants in adult ALL--? Allo for everyone. Biol Blood Marrow Transplant 15:7-10, 2009 (suppl 1)

36. Weisdorf DJ, Woods WG, Nesbit ME Jr, et al: Allogeneic bone marrow transplantation for acute lymphoblastic leukaemia: Risk factors and clinical outcome. Br J Haematol 86:62-69, 1994

37. Thomas X, Le QH: Central nervous system involvement in adult acute lymphoblastic leukemia. Hematology 13:293-302, 2008

38. Rowe JM, Buck G, Burnett AK, et al: Induction therapy for adults with acute lymphoblastic leukemia: Results of more than 1500 patients from the international ALL trial—MRC UKALL XII/ECOG E2993. Blood 106:3760-3767, 2005

39. Tallen G, Ratei R, Mann G, et al: Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: Results of trial ALL-REZ BFM 90. J Clin Oncol 28:2339-2347, 2010

40. Thomas X, Boiron JM, Huguet F, et al: Outcome of treatment in adults with acute lymphoblastic leukemia: Analysis of the LALA-94 trial. J Clin Oncol 22:4075-4086, 2004

41. Stock W, Johnson JL, Stone RM, et al: Dose intensification of daunorubicin and cytarabine during treatment of adult acute lymphoblastic leukemia: Results of Cancer and Leukemia Group B Study 19802. Cancer 119:90-98, 2013

42. Ribera JM, Oriol A, Bethencourt C, et al: Comparison of intensive chemotherapy, allogeneic or autologous stem cell transplantation as post-remission treatment for adult patients with high-risk acute lymphoblastic leukemia: Results of the PETHEMA ALL-93 trial. Haematologica 90:1346-1356, 2005

43. Thiebaut A, Vernant JP, Degos L, et al: Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation: A follow-up report of the French protocol LALA 87. Hematol Oncol Clin North Am 14:1353-1366, 2000

44. Abraham A, George B, Ahmed R, et al: Outcome of treatment with a low cost protocol in adults with T cell acute lymphoblastic leukemia in a tertiary care center in India. Leuk Lymphoma 55:947-949, 2014