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A RETROSPECTIVE EVALUATION OF ADOLESCENT AND YOUNG ADULT ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS TREATED WITH COG0232 REGIMEN.

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Abstract

Purpose: Considering the young age and good tolerability to chemotherapies, adolescents and young adults (AYA) patients with acute lymphoblastic leukemia (ALL) are nowadays treated with more intensive pediatric protocols and consequently demonstrated improved outcomes in several studies. The purpose of this study was to evaluate the efficacy of COG0232 regimen on AYA ALL patients.

Methods: Medical records of newly diagnosed ALL patients registered between 2012- 2016 were screened. We analyzed data of 115 patients retrospectively for their post- induction remission, mortality and survival rates.

Results: Out of 115 patients, complete remission (CR) was achieved in 90 patients post induction chemotherapy. Additionally, after receiving salvage induction 02 patients achieved CR. Therefore, we observed an overall CR rate of 80%. MRD was found positive in 34.2% and negative in 65.8% patients at the end of induction. Majority of the 16 MRD positives (77%) were observed in B-ALL group. The event-free survival (EFS) and overall survival (OS) reported were 51.3% and 54% respectively, with more than 4 years of follow-up. EFS and OS were found significantly associated with post-induction remission (p-value = <0.0001, <0.0001 respectively) and post-induction MRD (p-value = <0.0075, <0.0275 respectively).

Conclusion: In conclusion, using a pediatric regimen for AYAs with ALL up to the age of 40 years is a feasible and beneficial treatment option, resulting in better survival rates.

Keywords: COG regimen, adolescent and young adults, acute lymphoblastic leukemia, event-free survival, overall survival

INTRODUCTION

Acute Lymphoblastic leukaemia (ALL) is the most frequent type of childhood cancer that has a wide range of genetic and clinical characteristics [1, 2] . Over the last five decades, survival rates in paediatric ALL have been improving to the range of 90% in current era, Reason being better risk stratification with availability of(MRD) and risk-stratified anti- Leukemic therapy with intensification of chemotherapy in those with high risk features While reducing intensity in those with good risk features and deep molecular remissions Early in the course of treatment [3, 4] . Adult patients with ALL are mostly treated on Protocols for the treatment of adults, which are designed to be less intense in view of poor Tolerance to chemotherapies in this age group. Also, more of adult ALL patients may have High-risk cytogenetic or molecular features. Thus, the outcomes of adult patients of ALL Have not improved that much and still are in range of 30-50% [5–7] .

ALL in adolescents and young adult (AYA) patients represent a diverse population that is Able to get care in both paediatric and adult cancer settings and have outcomes intermediate of paediatric and adult ALL [8] . A review of the Surveillance, Epidemiology, and End Results (SEER) database revealed that adult ALL survival has improved in recent years with the greatest improvement in the AYA group [9, 10] . Considering their young age and good tolerability to chemotherapies, AYA patients with ALL are nowadays treated with more intensive paediatric protocols and consequently demonstrated Improved outcomes [11] .

Even while >80-90% of children with ALL are cured of their illness, AYA outcomes traditionally have been significantly worse, with EFS ranging from 30 to 45% [12, 13] .

While outcomes for patients under the age of 15 have continued to improve, survival for AYAs with ALL appeared to stall in the 1990s [14].

The BFM (Berlin-Drnkfurt-Munich) baseline treatment regimen used in COG0232 is Remarkably similar to, but fundamentally different from, the Berlin-developed BFM Regimen created by Riehm and Colleagues in the early 1970s [15] . The fundamental Difference is that the COG0232 includes steroid/vincristine pulses during maintenance, which makes it a more intensive regimen.

Senger et al, in 2021 made an analysis based on data from a multi-centre retrospective database of nine centres in India on AYA ALL (aged 15-29, treated between 2012 and 2017). The data revealed that majority (80%) of the centers used “pediatric-type” protocols and reported two years disease/event free survival (EFS) and overall survival (OS) were 56% and 73% [16] . There is scarcity of prospective as well as retrospective data on use of pediatric protocols in adult population from India.

In the current study, we sought to assess COG0232’s effectiveness in treating AYA ALL patients. We also aimed to analyze remission rate, mortality and survival rates of Indian AYA patients with ALL treated on COG0232 regimen.

MATERIALS AND METHODS

This retrospective study was carried out at an Indian comprehensive cancer care center. ALL patients of 10 to 40 years of age group, who were started on COG0232 regimen from 1st January 2012 till 31s December 2016 were analyzed for post induction remission rate, mortality and survival. The patients were identified from the hospital database.

Patients not completing induction chemotherapy were censored though were included in calculating early deaths. The Institutional Ethics Committee gave its approval to the current study. Treatment and response criteria of ALL Patients received treatment with COG0232 based regimen for high risk ALL. Post induction response was recorded as complete remission (CR) in absence of identifiable blasts in peripheral blood and less than 5% marrow blasts along with absence of any palpable lymphadenopathy and organomegaly and disappearance of any mass or testicular enlargement by clinical or radiological examination. Patients not achieving a CR by above definition were considered to be refractory disease. Those who had undergone chemotherapy but had no available results from a bone marrow examination were referred to as having an ‘undefined’ response. From the first day of induction chemotherapy to the time of death or the final follow-up, OS (overall survival) was

calculated. ALL-cause death within 42 days after the start of the induction chemotherapy or until the next cycle of chemotherapy was referred to as induction mortality. Event free or disease free survival (EFS) was calculated from the first day of treatment to relapse or disease refractoriness, death from any cause, or the last follow-up in the absence of an event. Risk assessment The standard risk(SR) subset was determined by white blood cell (WBC) count, lack of
BCR-ABL 1 rearrangement in B-ALL, and WBC count 100 plus the cortyical CD1a+ phenotype in T-ALL. At the conclusion of CR induction and during consolidation Therapy, MRD in the bone marrow was assessed. Patients who did not fall within the category of very high risk or standard risk made up the high-risk group. Regardless of MRD, patients at very high risk had early or mature T-ALL, a WBC count greater than 100, and unfavourable cytogenetics/genetics.

Statistical Analysis

Kaplan-Meier method was used to estimate the survival rates of EFS and OS.The log-rank Statistic was used to compare the patterns of event-free and overall survival. To account for the probable modifying effect of other factors on the comparison of interest, stratified log-rank tests were performed.
The relationship between the factors and a number of survival outcome measures, including overall survival (OS) and event-free survival (EFS) was examined using Cox models.

RESULTS

Baseline data

A total of 115 newly diagnosed cases of AYA ALL were found who were started on COG0232 regime in the study period. The cohort's median age was 22 years (10-40 years) with male to female ratio of 4:1.Table 1 summaries the baseline features of all AYA ALL patients.

Response to chemotherapy

Post-induction, 90 patients were eligible for further consolidation therapy and were evaluable for survival rate. After consolidation therapy, 50 (55.5%) patients remained in Remission, 4 (4.4%) patients either abandoned the treatment or lost to follow-up, 28 (31%) Patients relapsed and 08 (9%) patients died in complete remission. Out of 28 patients who got relapsed 25 died due to prognosis of disease and 03 survived the treatment (figure 1).
Out of 115, for only 38 patients MRD assessment was available. At the conclusion of induction, MRD was discovered to be positive in 13 patients (34.2%) and negative in 25 patients (65.8%). Majority of the MRD positives were seen in B-ALL (77%) than T-ALL (23%) patients.

Survival rate

Four -year EFS and OS were observed to be 51.3% and 54%, respectively, during a median follow-up of 51 months (Table-2). The median EFS was 49.2 months with [95% confidence interval (CI) 14.2-68] of the whole cohort. Median OS was not reached.
On univariant analysis, EFS and OS were found associated with post-induction remission (p-value = <0.0001, <0.0001), post induction MRD (p-value = 0.0075, 0.275) and age (p- value = <0.0189, 0.0389) as shown in figure 2.

Relapse and Mortality

Fifty-three (46%) patients died out of the whole study population after a median follow-up of 51 months, which included 28 (31%) patients who experienced relapses (median time of relapse:11.5 months)[cause of death: progressive disease, induction death, infection, relapse of disease and progressive acute renal failure (ARF)].
Overall mortality was reported in 53 (46%) patients. There were 4 deaths reported during induction period (reason of death: fungal pneumonia, progressive ARF, sepsis, cardiac arrest). Eight patients died in CR [reason: infections (fungal, bacterial and others), secondary hemophagocytic

lymphohistiocytosis, progression of disease) post-induction period. Twenty-eight patients relapsed after remaining in CR for a mean duration of 590 days, out of which 25 patients died due to prognosis of disease.

DISCUSSION

The present study analyzed the real-world data of AYA ALL patients up to 40 years of age, treated withCOG0232 based regimen with more than 04 years of follow up. The complete remission rate of the present cohort after induction was found 80%. Most trials that have used a paediatric protocol have seen an increase in CR rated of >90% as a result. [17–21] .

We observed 4 induction deaths (3.5%) and 3-treatment discontinuation (2.6%) as a cause of low CR rate. A study from India has also reported 81.6% remission rate at the end of Induction following BFM90 protocol [4] .

With a median EFS of 49.2 months and [95% CI, 14.2-68 months],the 4-year EFS and OS were 51.3% and 54% respectively. Outcome of our study are in concurrence with a multi- center study of 9 centres in which 2 years EFS and OS of 56% and 73%, respectively [16] . Studies on AYA ALL patients of 15-30 years of age group has reported EFS and OS ranging from 61% to 86% and 66% to 88% respectively [9, 18–20, 22] .

In the present study, post-induction MRD was found to be positive in 34.2% and negative in 65.8%. Majority of the MRD positives were seen in B-ALL 77% than TALL 23%patients. Patients achieving MRD-negative status had a longer OS (84%), and fewer relapses (20%) during and after completion of treatment. Similarly, findings from a regional Cancer Centre in western India demonstrated that patients with negative MRDs had higher survival times than those with positive MRDs [4] .

There were 31% relapses in our study, which is consistent with other published series of MCP, BFM, UK ALL based protocols. Following an initial remission, 6% of the patients were lost to follow-up in this study. However, in another study conducted by Malhotra et al [21] reported 14.9% desertion rate in another study from India. Although a variety of factors have been identified as contributing to treatment termination, poor financial Resources are often the most critical one. In addition, the high expense of treatment is a Major factor that contributes to treatment discontinuation.

We demonstrate the potential challenges involved in administering a high-intensity regimen therapy to an Indian population. The lower outcomes, even utilizing intensive regimens, can be explained in part by the high proportion of patients at high risk.

However, we have identified modifiable factors that could be addressed to raise the survival rates of these people. These consist of the mortality rate during induction, treatment holdups, patient adherence, MRD assessment, and risk-adjusted therapy. /by modifying the treatment plan as necessary and raising patient awareness, all of he aforementioned problems can be resolved. Improved supportive care, such as a higher Doctor-to-patient ratio, improved infection control measures, and more intensive Monitoring, would almost certainly assist to reduce treatment-related mortality, although this may not always be possible in resource-constrained situations. In the actual world, Better supportive care and the implementation of risk-adapted therapy could potentially
Enhance results.

CONCLUSION

One of the study's main strengths was the uniform application of a single regimen to all of the patients. The fact that it is a single-center study is a key drawback. Uniform adoption of cytogenetic and molecular as well as MRD based risk stratification and risk-adapted therapy must be a focus of future research or studies in India. Using a paediatric regimen for AYAs with ALL up to the age of 40 years was feasible and beneficial, resulting in better survival rates.

STATEMENTS AND DECLARATIONS

Conflict of Interest

No potential conflict of interest was reported by the authors.

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Authorship statement

All authors contributed equally while preparing this manuscript.

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