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Original Article

FLAG with Bortezomib Salvage Therapy in Relapsed/Refractory Childhood Leukemia—A Reliable Bridge to Transplantation with Limited Toxicity

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Abstract

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Relapsed refractory leukemia represents a difficult-to-treat population of patients. The balance between perceived benefit and potential side effects along with the significant financial burden of managing multidrug-resistant sepsis are factors that determine the choice of salvage regimen. Here, we present our experience with the combination of fludarabine, cytarabine, granulocyte-colony stimulating factor with bortezomib. The morphological complete response rate was 58% with 50% of the patients achieving complete remission. With only three patients requiring intensive care unit admission during remission induction, 66.6% of the patients went on to undergo successful hematopoietic stem cell transplantation. Thus, it proved to be a possible, safer alternative to other salvage regimens, while enabling a significant percentage of patients to achieve remission and proceed to allogenic stem cell transplantation.

Keywords

- childhood leukemia
- FLAG
- neutropenia
- relapsed leukemia
- salvage chemotherapy

Introduction

There has been a significant change in the survival rates of patients with childhood leukemias over the past few decades. The 5-year survival rate for acute lymphoblastic leukemia (ALL) has been documented to be over 95%, while the same for childhood acute myeloid leukemia (AML); long-term survival is currently 70% or higher.[1,2] The state of the relapsed disease is still guarded. In case of childhood AML, 24 to 40% of patients relapse, with an approximately 30% chance of survival. Recent

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data points toward a 5-year overall survival of 50% in childhood ALL at first relapse.[3] The armamentarium of therapeutic options for relapsed acute leukemias have expanded to include several therapeutic options, including newer monoclonal antibodies and chimeric antigen receptor T cell therapy, but salvage chemotherapy followed by hematopoietic stem cell transplantation remains the mainstay of treatment in resource limited settings.

The choice of salvage regimens is influenced by several factors, including the dose of anthracyclines received previously and the balance between the perceived benefit and potential toxicity. One of the most significant challenges posed during salvage chemotherapy is the translocation of gut bacteria and neutropenic sepsis secondary to it. Hence, there is a need for a chemotherapeutic regimen that limits exposure to anthracyclines while at the same time reducing the gut toxicity.[1]

The combination chemotherapy regimen fludarabine, cytarabine, and GCSF (FLAG) has been studied in the setting of relapsed leukemia in several studies.[4,5] Fludarabine was found to have a synergistic effect with cytarabine, by increasing the rate of production of its active metabolite 5′-triphosphate ara-cytidine-5'-triphosphate.[6] GCSF used in this combination further sensitizes the leukemic cells to the cytotoxic effects of cytarabine, by recruiting the leukemic cells into the S phase and potentiating the incorporation of ara C metabolites into the cell and the subsequent ara C-induced apoptosis.[7] Historically Idarubicin has been used in combination with the FLAG regimen, but there has been evidence supporting the use of the proteosome inhibitor bortezomib in its place. The use of bortezomib has shown to have complete remission rates of more than 70% in several studies,[8] reducing the exposure to anthracyclines and potentially reducing gut toxicity, making this combination an attractive option in the relapsed setting, especially in the resource limited setting.

We are reporting our experience with this combination therapy.

Materials and Methods

We performed a retrospective analysis in the Department of Pediatric Hematology and Bone Marrow Transplant from January 2021 to June 2023. Twelve patients of relapsed refractory AML/ALL (one patient had chronic myelogenous leukemia [CML] in blast crisis) were included in the analysis. All patients received at least one cycle of FLAG with bortezomib. The toxicity profile analyzed was the incidence of sepsis, the need for intensive care unit (ICU) admission or treatment-related mortality. Morphological remission in the bone marrow and minimal residual disease (MRD) status evaluation was performed at count recovery.

Chemotherapy Protocol

GCSF was given at 5 µg/kg/day subcutaneously from day 1 to day 7; fludarabine was given at a dose of 30mg/m2 as an infusion over 30 minutes from days 2 to 6 and cytarabine (2gm/m2) was given daily as an intravenous infusion over 4 hours. Fludarabine was given 4 hours preceding the cytarabine infusion. Bortezomib at a dose of 1.3mg/m2 was given on days 1, 4, 8, and 11 as an intravenous bolus push.

All patients received prophylactic antifungals and antivirals. Prophylaxis for pneumocystis jirovecii was also initiated for all patients.

Assessment of Response

Bone marrow examination was performed at the onset of neutrophil recovery (absolute neutrophil count of >1000 cells/mm3). Morphological remission was defined as less than 5% blasts on bone marrow examination with evidence of normal hematopoiesis. Complete remission was defined as morphological remission with a negative MRD study by flow cytometry.

The primary end-point was remission status after the FLAG–bortezomib regimen, and the requirement of ICU admission, presence of neutropenic sepsis, and treatment-related mortality were secondary end points.

Statistical Analysis

Categorical variables were represented by percentage. Continuous variables were expressed as mean ± standard deviation. Comparison of categorical variables were done by either $\chi 2$ test or Fisher's exact test based on the number of observations. Comparison of continuous variables between the groups was done by independent sample "t" test. Data entry was done in MS Excel sheet. Data validation and analysis were carried out in SPSS version 25.0. All "*p*"-values less than 0.05 were considered as statistically significant.

Results

Our study population included 12 patients, with a mean age of 8.3 years. The male-to-female ratio was 2:1 (8 male patients and 4 female patients). There were six patients with refractory AML, five patients with relapsed/refractory ALL, and one patient was a case of CML in myeloid blast crisis. Nine patients received one cycle each of FLAG with bortezomib, while two patients received a second cycle of induction; patient characteristics are shown in ►**Table 1**.

All children included in the study had episodes of febrile neutropenia. Seven of the children had positive blood cultures (58.3%). *Klebsiella pneumoniae* was the most common organism grown in four patients (∼33%); *Escherichia coli* was grown in two patients during first induction, while Acinetobacter species was grown in cultures obtained from one patient. Two patients received a second induction with FLAG-bortezomib, and one of the patients had culture positive sepsis with *E. coli* species grown in the culture. Despite the incidence of sepsis and febrile neutropenia, only three patients required ICU admission during induction.

Seven patients (58.3%) had a documented morphological remission after one cycle of salvage therapy. Two patients went on to receive a second course of induction regimen, in view of MRD positivity and persistent blasts, respectively. The child with persistent disease went on to achieve complete remission, and the MRD positivity was significantly reduced in the second

Table 1 Patient characteristics of children receiving FLAG + bortezomib as remission induction

Sl. no	Age/ gender	Diagnosis	Sepsis	ICU admission	Remission status	Organism isolated	Proceeded to HSCT
1	14/M	ETP-ALL (early relapse)	Yes	No	Refractory	No	No
2	6/M	Refractory AML	Yes	Yes	Refractory	*E. coli*	No
3	3/M	Refractory AML	No	No	9% blasts after 1 cycle	No	Yes
4	5/M	ALL (early relapse)	No	No	Morphological remission	No	Yes
5	4/M	ALL (refractory)	No	No	Morphological remission	No	Yes
6	4/F	AML (refractory)	No	No	Morphological remission	No	Yes
7	10/M	AML (relapsed)	Yes	No	Morphological remission	*E. coli*, *Klebsiella pneumoniae*, Enterococci	Yes
8	5/M	B-ALL (relapsed)	Yes	Yes	Morphological remission	*Klebsiella pneumoniae*	Yes
9	17/F	AML-CR1	Yes	No	Refractory	Acinetobacter	No
10	8/M	ALL-CR1	Yes	Yes	Morphological remission	*Klebsiella pneumoniae*	Yes
11	16/F	CML-myeloid blast crisis	Yes	No	Morphological remission	*Klebsiella pneumoniae*	Yes
12	6/F	AML-refractory	Yes	No	Refractory disease	*E. coli*	No

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; E. coli, *Escherichia coli*; ETP, early T-cell precursor; FLAG, fludarabine, cytarabine, and GCSF; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.

child. Among all patients, six children had achieved complete remission (50%). A total of eight patients (66.6%) went onto to undergo an allogenic hematopoietic stem cell transplant (HSCT). One patient succumbed to treatment related sepsis during induction with FLAG–bortezomib.

Discussion

Remission induction in the relapsed refractory setting poses several challenges, especially in the face of limited resources. Prolonged hospitalization and the additional costs of antibiotics during the treatment course are factors that have been shown to significantly impact the rates of treatment discontinuation in childhood cancers.[9] The rationale for use of bortezomib in combination with chemotherapy for remission induction was based on the premise that proteosome inhibition by bortezomib could potentially sensitize the malignant cells to chemotherapy induced apoptosis, by proteosome inhibition.[10] Preclinical studies have shown the efficacy of bortezomib in combination with chemotherapy in the treatment of childhood leukemia. Horton et al had reported on the increased efficacy of bortezomib in combination with chemotherapy, while an overall response rate of upto 73% was demonstrated in the therapeutic advances in leukemia and lymphoma study (TACL).[8,10] Bertaina et al had shown that the addition of bortezomib to the classical four drug induction therapy was associated with a complete response rate of 72.9% but was associated with the occurrence of neuropathy.[11] The omission of vincristine was associated with significantly less neuropathy as demonstrated in an Indian study, which showed response rates of 88% in second remission, with a combination of bortezomib and reduced dose cytarabine.[12] Ravindran et al had studied 12 patients treated with the combination of FLAG and bortezomib; 92% of their patients had attained morphological remission.[1] While the rates of morphological remission were lower in our population, a significant proportion of our patients went onto receive a successful HSCT, with minimal treatment-related mortality in the remission induction phase. In a resource-limited setting, an accessible regimen with a favorable toxicity profile can improve the accessibility of care in this difficult-to-treat population of patients.

Conflict of Interest

None declared.

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