FLAG with Bortezomib in Childhood Relapsed Refractory Leukaemia- A Single Centre Experience

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Abstract

Relapsed refractory leukaemia 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 which determine the choice of salvage regimen. Here we present our experience with the combination of Fludrabine, Cytarabine, GCSF with Bortezomib. The morphological complete response rate was 58.% with 50% of the patients achieving complete remission. With only three patients requiring ICU admission during the period of care. 66.6% of the patients went on to undergo successful hematopoietic stem cell transplantation. Thus, proving to be a possible, safer alternative to other salvage regimens

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Abbreviations

G-CSF	granulocyte-colony stimulating factor
FLAG	Fludarabine, Ara-C, GCSF
HSCT	Hematopoeitic Stem Cell Transplant

Introduction

There has been a significant change in the survival rates of patients with childhood leukemias over the past few decades. The five-year survival rate for ALL has been documented to be over 95% while the same for childhood 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, 24-40% of patients relapse, with an approximately 30% chance of survival. Recent data points towards a five-year OS 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 CAR 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 FLAG (Fludrabine, Cytarabine and G CSF) has been studied in the setting of relapsed leukemia in several studies[4,5]. Fludrabine was found to have a synergistic effect with Cytarabine, by increasing the rate of production of its active metabolite 5'-triphosphate ara-CTP[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, makes this combination an attractive option in the relapsed setting, especially in the resource limited setting.

We are reporting our experience with this combination therapy.

Patients and Methods

We performed a retrospective analysis in the Department of Pediatric Hematology and Bone Marrow Transplant from January 2021 to June 2023. 12 patients of relapsed refractory AML/ALL (One patient had CML in blast crisis) were included in the analysis. All patients received at least one cycle of FLAG with Bortezomib. The toxicity profile analysed was the incidence of sepsis, the need for ICU admission or treatment related mortality. Morphological remission in the bone marrow and MRD status, performed at count recovery.

Chemotherapy Protocol

GCSF was given at 5 microgram/kg/day subcutaneously from Day 1 to Day 7, Fludrabine was given at a dose of 30mg/m2 as an infusion over 30 minutes from days two to six and Cytarabine (2gm/m2) was given daily as an intravenous infusion over 4 hours. Fludrabine 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 <5% blasts on bone marrow examination with evidence of normal haematopoiesis. 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± SD. Comparison of categorical variables were done by either $\chi 2$ test or Fisher exact test based on the number of observations. Comparison of continuous variables between the groups were done by independent sample "t" test. Data entry were done in MS Excel sheet. Data validation and analysis were carried out in SPSS version 25.0. All "P"-values <0.05 was 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, 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%), E 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 1 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 child. Among all patients, six children had achieved complete remission (50%). A total of eight patients (66.6%) went onto to undergo an allogenic 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]. Pre-clinical 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 was demonstrated in the therapeutic advances in leukemia and lymphoma study[8,10].Bertainia 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 was 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 favourable toxicity profile, can improve the accessibility of care in this difficult to treat population of patients.

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Table 1- Patient Characteristics of Children Receiving FLAG + Bortezomib as Remission Induction

S.NO	Age/Gender	Diagnosis	Sepsis	ICU Admission	Remission Status	Organism Isolate
1	14/M	ETP-ALL (Early Relapse)	Yes	No	Refractory	No

2	6/M	Refractory AML	Yes	Yes	Refractory	E COLI
3	3/M	Refractory AML	No	No	9% Blasts after 1 Cycle	No
4	5/M	ALL (Early Relapse)	No	No	Morphological Remission	No
5	4/M	ALL (Refractory)	No	No	Morphological Remission	No
6	4/F	AML (Refractory)	No	No	Morphological Remission	No
7	10/M	AML(Relapsed)	Yes	No	Morphological Remission	E.COLI, Klebsiel
8	5/M	B-ALL (Relapsed)	Yes	Yes	Morphological Remission	Klebsiella pneum
9	17/F	AML-CR1	Yes	No	Refractory	Acenitobacter
10	8/M	ALL- CR1	Yes	Yes	Morphological Remission	Klebsiella pneum
11	16/F	CML-Myeloid Blast Crisis	Yes	No	Morphological Remission	Klebsiella pneum
12	6/F	AML- Refractory	Yes	No	Refractory Disease	E COLI

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