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Case Series

Oncology Section

FLAG Regimen and Bortezomib: A Study of Eight Cases with Relapsed Leukaemia

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ABSTRACT

Historically, relapsed and refractory Acute Lymphoblastic Leukaemia (ALL) and Acute Myeloid Leukaemia (AML) have been associated with a dismal prognosis. Relapse-refractory ALL is associated with cure rates of <10% in adults and 30% in the paediatric population. Similarly, the five-year survival rates for relapsed and refractory AML are only 10%. This case series describes eight patients with relapsed/refractory leukaemia (6 with ALL and 2 with AML) who received the FLAG-Bortezomib protocol from January 2021 to August 2022. In this case series, the authors investigated the remission rate and toxicity of the regimen, including Intensive Care Unit (ICU) admissions and the incidence of neutropenic sepsis. In the present study, the rates of culture-positive sepsis and High Dependency Unit (HDU) admission were 50% (4/8) and 37.5% (3/8), respectively, with no post-chemotherapy mortality in this cohort. Morphologic remission was documented in 87.5% (7/8) of cases, and negative minimal residual disease was achieved in 62.5% (5/8), with 100% (2/2) remission in those with AML. One patient with ALL experienced disease progression during treatment. The FLAG with Bortezomib protocol induces remission in relapsed and refractory ALL and AML patients with an acceptable toxicity profile. This protocol requires rigorous blood product support in the form of packed red blood cells, platelet-rich plasma, and single-donor platelet apheresis. It serves as a bridge to stem cell transplant.

Keywords: Acute myeloid leukaemia, Acute lymphoblastic leukaemia, Fludarabine+Ara-C+G-CSF

INTRODUCTION

Despite advancements in AML therapy, relapse remains the most difficult aspect of the disease. While 10-40% of younger AML patients are primarily resistant to AML induction therapy, the number is significantly higher (40-60%) in patients over 60 years old [1]. After achieving Complete Remission (CR), most fit patients will undergo Hematopoietic Stem Cell Transplantation (HSCT). However, 40% of these patients experience relapse following HSCT. Relapse-refractory ALL has had a poor prognosis, with a cure rate of 10% in adults and 30% in children [2]. With standard chemotherapy, the CR rate in adult ALL is 30% to 40% in the first relapse and 20% to 25% in the second relapse [2]. In this group of patients, inducing remission is critical before consolidating with HSCT. The persistence of Minimal Residual Disease (MRD) after re-induction and/or consolidation therapy has been shown to have a significant impact on the risk of post-HSCT relapse in patients with relapsed ALL and AML.

Fludarabine is a fluorinated purine analogue that synergizes well with cytarabine in-vivo. Fludarabine triphosphate is the active metabolite of fludarabine, which inhibits ribonucleotide reductase, resulting in an increased intracellular level of the active metabolite of cytarabine [3,4]. The addition of Granulocyte Colony-Stimulating Factor (G-CSF) has been shown to improve the combination's efficacy by increasing the fraction of leukemic cells in the "S" phase [3,4]. Bortezomib was the first proteasome inhibitor to be approved for use, and its efficacy in relapsed/refractory acute leukemia has been studied in recent years [5,6]. FLAG in combination with Bortezomib was studied with the goal of limiting anthracycline and gut-toxic chemotherapy exposure in these heavily pre-treated patients with relapsed/refractory leukaemia. The aim of the study is to highlight the toxicity profile, culture-positive sepsis, rate of high dependency unit admission, morphologic remission rate, minimal residual disease status, and cost-effectiveness in comparison with conventional anthracycline-based chemotherapy.

CASE SERIES

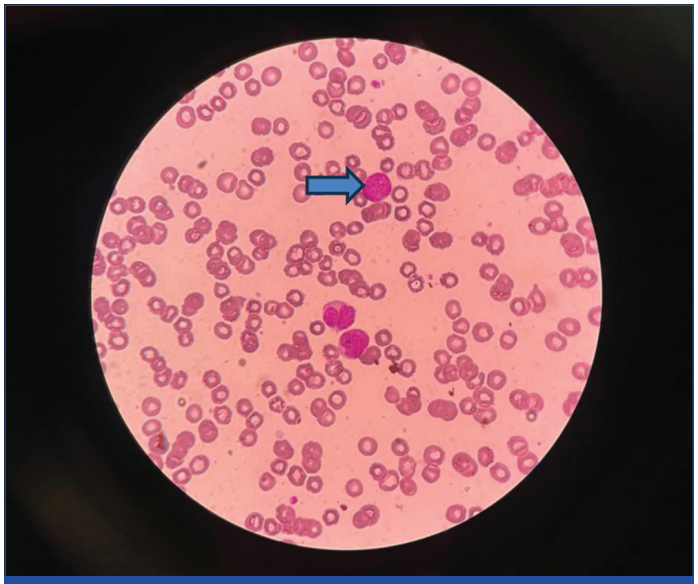
From January 2021 to August 2022, the authors conducted a retrospective study in the Department of Clinical Haematology, Blood, and Marrow Transplantation at Sher-I-Kashmir Institute of Medical Sciences, Srinagar. The authors enrolled eight patients with relapsed/refractory ALL and Acute Myeloid Leukemia (AML) [Table/Fig-1,2]. All AML patients received the 3+7 protocol, which includes daunorubicin, cytarabine, and high-dose cytarabine as a consolidation protocol before receiving FLAG-Bortezomib [Table/Fig-3]. ALL patients received the UK ALL-XII, BFM-95, BFM-85, and BFM-90 protocols before receiving the FLAG-Bortezomib protocol [Table/Fig-4].

Patient	Age/sex	Diagnosis	Molecular marker	Cytogenetics	Chemotherapy received previously before giving FLAG-Bortezomib protocol
Case 1	22/Male	ETP-ALL	No abnormal markers	XY	UK-ALL-XII Protocol
Case 2	12/Male	ALL-pre-B cell	No abnormal markers	XY	BFM-95 (Medium Risk), BFM-85
Case 3	6/Female	ALL-pre-B cell	No abnormal markers	XX	BFM-95 (Medium Risk), BFM-85
Case 4	22/Male	ALL-pre-B cell	No abnormal markers	XY	BFM-95 (Medium Risk)
Case 5	28/Female	ALL-pre-B cell	BCR-ABL	XX	BFM-95 (Medium Risk), hyper-CVAD protocol
Case 6	42/Male	AML	No abnormal markers	XY	3+7 protocol (Daunorubicin+cytarabine)
Case 7	32/Female	ALL-pre-B cell	No abnormal markers	XX	BFM-90, hyper-CVAD protocol
Case 8	30/Male	AML	No abnormal markers	XY	3+7 protocol (Daunorubicin+cytarabine)

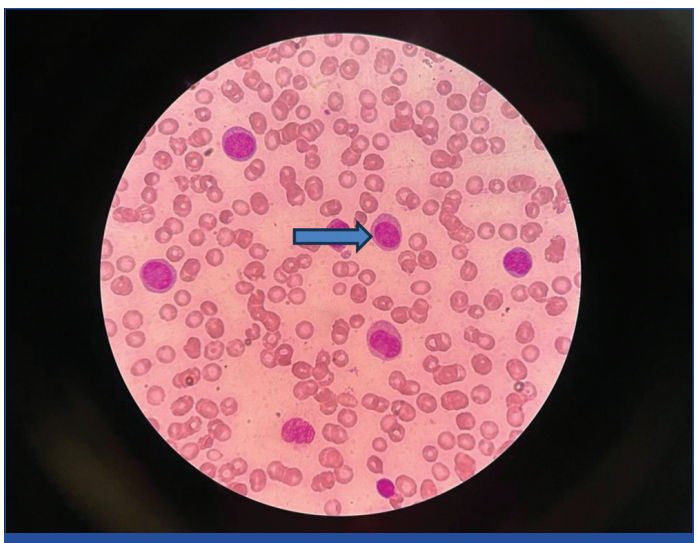
[Table/Fig-1]: Base line characteristics of patients at the time of diagnosis.
ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; Hyper-CVAD, (A: cyclophosphamide+vincristine+Doxorubicin+Dexamethasone; Bplan:Methotrexate+Cytarabine); Berlin-frankfurt-Munster (BFM);United Kingdom XII acute lymphoblastic leukaemia.(UK ALL-XII)

Patient	Age/sex	Diagnosis/CR	Culture positive sepsis/Organism isolated	high dependency unit admission/ ICU admission	Bone marrow remission status	Blood product support	Duration of neutropenia	Time for myelorecovery	Proceeded to HSCT
1	22/Male	Refractory ETP-ALL-CR-1	No	NO	Remission, and MRD negative	PCV:3 PRP:22 SDAP:3	21 days	22 days	Yes
2	12/Male	Refractory-ALL/CR-1	YES/Klebsiella pneumoniae	NO	Remission, and MRD not done	PCV:2 PRP:27 SDAP:2	24 days	26 days	No, was in remission for 2 months
3	6/Female	Relapse-Cell ALL-CR-2	NO	NO	Morphological remission, and MRD not done	PCV:2 PRP:12 SDAP:3	15 days	18 days	No. was in remission for 7 months
4	22/Male	Relapse ALL-CR-2	Yes/staph epidermididis	High dependency unit	Not in remission	PCV:2 PRP:17 SDAP:1	Progressive disease	Progressive disease	No, Did not respond to chemotherapy
5	28/Female	Relapse BCR-ABL+ve ALL-CR2	No	No	In remission, MRD negative	PCV:5 PRP:16 SDAP:2	20 days	23 days	No, was in remission for 7 months
6	42/Male	Relapse AML-CR-2	Yes/Pseudomonas	High dependency unit	In remission, MRD negative	PCV:3 PRP:22 SDAP:4	24 days	28 days	No, was in remission for 6 months
7	32/Female	Relapse ALL-CR-2	Yes/Klebsiella pneumoniae	High dependency unit	In remission, MRD negative	PCV: 7 PRP: 42 SDAP: 5	36 days	38 days	No, was in remission for 4 months
8	30/Male	Refractory AML-CR-1	NO	NO	In remission, MRD negative	PCV: 4 PRP: 24 SDAP: 3	25 days	27 days	No, was in remission for 3 months

[Table/Fig-2]: Characteristics of patients receiving FLAG-Bortezomib.
ALL indicates Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; CR: Complete remission; F: Female; FLAG: Fludarabine, cytarabine, G-CSF: Granulocyte colony-stimulating factor; HSCT: Haematopoietic stem cell transplantation; ICU: Intensive care unit; M: male; PCV: Pack cell volume; PRP: Platelet rich plasma; SDAP: Single donor platelet apheresis; MRD: Minimal residual disease



[Table/Fig-3]: Photomicrograph showing blast cell (arrow) of ALL (X100).



[Table/Fig-4]: Showing blast cell (arrow) of AML (X100).

All patients received a single chemotherapy protocol, with Fludarabine administered as a 30-minute intravenous infusion at a dose of 30 mg/m^2 daily from days 1 to 5, totaling five doses. Cytosine arabinoside was administered intravenously at a dose of 2 g/m^2 daily for four hours, starting four hours after fludarabine on days 1 to 5, totaling five doses. G-CSF was administered subcutaneously at a dose of 5 micrograms/kg/dose for a total of six doses from days-1 to 6. Bortezomib was administered subcutaneously at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11. At count recovery, defined as an absolute neutrophil count of more than 1500 cells/mm^3, bone marrow was examined. Complete Remission (CR) was defined as 5% blasts in the bone marrow, normal hematopoiesis, negative minimal residual disease, and a normal Cerebrospinal Fluid (CSF) examination.

In the current study, all patients had medullary relapse, and all CSF examinations were negative. The baseline characteristics of the patients are shown in [Table/Fig-1]. The present study population consisted of six adults and two children, with an average age of 24 years and a male-to-female ratio of 5:3. In the cohort, there were six cases of relapsed/refractory ALL and two cases of relapsed/refractory AML. Before entering the study, the average cumulative anthracycline dose given in the previous chemo protocol was 342 mg/m^2.

The median duration of neutropenia, defined as an absolute neutrophil count of 1000, was 24 days, and complete recovery from myelosuppression took 26 days, with one adult needing 38 days for recovery.

Two ALL patients developed grade 2 mucositis and neutropenic enterocolitis, requiring three days of granulocyte infusion. All patients developed febrile neutropenia, with 4 out of 8 (50%) developing culture-positive sepsis, and 3 out of 8 (37.5%) requiring a stay in a high dependency unit for an average of five days. Gram negative bacilli and gram-positive cocci were among the organisms isolated. Two patients became infected with *Klebsiella pneumonia* and developed resistance to carbapenems. Two patients became infected with *Pseudomonas aerogenes* and *Staphylococcus epidermidis*, both of which were sensitive to all antibiotics.

Morphologic remission was achieved in 87.5% (7 out of 8) of patients, and negative minimal residual disease was observed in 62.5% (5 out

of 8), with 100% (2 out of 2) remission in those with AML. However, one patient with ALL experienced disease progression while receiving treatment. Bortezomib caused peripheral neuropathy in two patients (2 out of 8), who were subsequently given B12 vitamins, B6, and gabapentin. The parameters of the patients treated with FLAG-Bortezomib are shown in [Table/Fig-2].

DISCUSSION

Hematologists have faced difficulties in treating relapsed or refractory Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) in both adult and paediatric populations for decades. Induction therapy can be challenging in patients with relapsed/refractory acute leukemia, especially when there are underlying co-morbidities and prior chemotherapy exposure. A unique method of treating this population is necessary, one that carefully balances efficacy versus toxicity. In preclinical trials, bortezomib was found to be synergistic with dexamethasone in-vitro and additive with asparaginase, vincristine, doxorubicin, and cytarabine [7,8].

Ravichandran N et al., from India, combined fludarabine, cytarabine, and G-CSF with bortezomib. They studied a total of 13 children with relapsed/refractory leukemia (9 with ALL and 4 with AML). The rates of culture-positive sepsis and intensive care unit admission were 38% and 30%, respectively, with no deaths in this group. Morphologic remission was reported in 92% of patients, with 61% having negative minimal residual disease, and those with AML achieving 100% remission. Three patients were found to have peripheral neuropathy. Nine individuals underwent stem cell transplantation [5].

Messinger Y et al., reported an overall response rate of 67% (6/9) in nine evaluable patients treated with bortezomib, vincristine, dexamethasone, pegaspargenase, and Adriamycin (B-VXLD) for relapsed/refractory ALL in 10 paediatric patients. During induction chemotherapy, one patient died. Haematological toxicity was the most common adverse event identified in all subjects. At a median follow-up of 21 months, four patients in their cohort survived, and six died [7]. Two patients (2/9) in their sample experienced grade 2 neuropathy, four (4/9) developed febrile neutropenia with sepsis, and one (1/9) developed neutropenic enterocolitis [7].

Bortezomib, vincristine, prednisone, pegaspargenase, and Adriamycin (B-VPLD) were administered to 135 paediatric patients with relapsed/refractory ALL/lymphoma [8]. The overall response rate in evaluable ALL cases was 68% (83/122), with hematological damage noted in over 55% of patients. Five (5/135) individuals experienced neuropathy, and eight (8/135) had neutropenic enterocolitis. In their trial, B-ALL had an 83% four-month overall survival rate, while T-ALL with low residual disease had a 67% three-year overall survival rate [8].

Similarly, Messinger Y et al., included 22 patients with relapsed/refractory B-ALL and T-ALL in their study. These patients were treated with B-VXLD. The study observed a response rate of 70%. Hematological damage was detected in all 22 patients, with a two-year overall survival rate of 41% [9]. Bertaina A et al., conducted another research study involving 37 patients with relapsed/refractory B-ALL and T-ALL who were given B-VXLD. They achieved an overall response rate of 72.9% (27/37). In terms of the toxicity profile, 81% of patients experienced hematological toxicity, 14.7% experienced infections, and 14.7% experienced neurotoxicity. In their cohort, the 2-year overall survival rate was 32% [10].

Yeo KK et al., included ten patients with relapsed/refractory B-ALL and T-ALL in their investigation. They administered a chemotherapeutic strategy that included Bortezomib, Dexamethasone, Mitoxantrone, and Vinorelbine (B-DMV) and observed an overall response rate of 70% (7/10) in patients. In terms of toxicity, 91% of patients experienced infection, while 45% experienced gastrointestinal and metabolic complications [11]. The one-year overall survival rate in their cohort was 40.9% [11].

Roy P et al., from India conducted a study that included 25 patients with relapsed/refractory B-ALL who were treated with Bortezomib, Vincristine, Dexamethasone, Pegaspargase, and Mitoxantrone (B-VXLMtz). The overall response rate was 88% (22/25). In terms of toxicity, 76% of patients had an infection, and 12% had a hypersensitive reaction. The one-year overall survival rate was close to 80% [12].

Kaspers GJ et al., included twenty-five patients with relapsed/refractory B-ALL and T-ALL in their study. They used a chemotherapy treatment that included Bortezomib, Dexamethasone, and Vincristine (B-VDex) and observed an overall response rate of 32% (8/25) in patients. In terms of toxicity, 90% of patients experienced hematological damage, 31% experienced neutropenic fever, and 17% experienced neuropathy. The five-month event-free survival was 29% in the early bortezomib group and 13% in the late bortezomib group [13].

Colunga-Pedraza JE et al., conducted a study in which 15 patients with relapsed/refractory B-ALL and T-ALL were given B-VXLD. The overall response rate was 60% (9/15). In terms of the toxicity profile, 33.3% of individuals had peripheral neuropathy, and 6.7% of the patients had gastroenteritis. The five-year survival rate in this cohort was 40% [14]. Similarly, August KJ et al., conducted a study that included ten patients with relapsed or refractory B-ALL or T-ALL who were treated with B-VXLMtz. The overall response rate was 80% (8/10) [15]. In terms of toxicity, infection was detected in 40% of the patients, and hematological toxicity was observed in 100% of the patients [12]. At the most recent follow-up, nine individuals had died, and one had survived [15].

Zhixiao Z et al., conducted a study that included eleven patients with relapsed/refractory B-ALL and T-ALL, who were treated with different chemotherapy protocols in combination with bortezomib, CODPL (cyclophosphamide + ChangchunNeobase + Prednisone + daunorubicin + asparaginase), VDLD (vincristine + Daunorubicin + asparaginase + Prednisone), CAM (cyclophosphamide + Cytarabine + Mercaptopurine), HyperCVAD (cyclophosphamide + vincristine + Epirubicin + Dexamethasone + methotrexate + Cytarabine), and HDMTX (high dose methotrexate). The overall response rate was 72.7%. In terms of toxicity, there were eleven cases (11/11) of hematological toxicity and seven cases (7/11) of neutropenic fever. Six patients (6/11) experienced transaminitis, and one patient acquired neuropathy during the induction treatment. Out of this group, nine individuals received stem cell transplants, while two patients underwent chemotherapy. The two-year overall survival rate is close to 64% [16].

Eight patients with relapsed/refractory leukemia (six with ALL and two with AML) were treated with Fludarabine, Cytarabine, G-CSF, and Bortezomib (FLAG-Bortezomib). The total response rate in this cohort was 87.5% (7/8). The current investigation reported a 50% (4/8) rate of culture-positive sepsis and a 37.5% (3/8) rate of high dependency unit admission, with no mortality during induction in this cohort. Two individuals in the study developed peripheral neuropathy and were treated with B12 vitamins, B6, and gabapentin. Two patients experienced neutropenic enterocolitis and grade 2 mucositis. Morphologic remission was achieved in 87.5% (7/8) of patients, with negative minimal residual disease in 62.5% (5/8), and 100% (2/2) remission in those with AML. Unfortunately, one patient with ALL died during treatment. The overall response rate to FLAG-bortezomib in this research is similar to that reported in previous investigations. In terms of toxicity, a similar complication rate was observed, which was managed with supportive care. Only one patient in the current cohort received a stem cell transplant, while the remaining patients in complete remission showed no interest in stem cell transplantation. The patients' outcomes are shown in [Table/Fig-2].

The FLAG plus Bortezomib treatment induces remission in relapsed and refractory ALL and AML patients with an acceptable toxicity profile. This approach requires the use of high-quality blood products

such as packed cell volume, platelet-rich plasma, and single-donor platelet apheresis. It serves as a gateway to stem cell transplantation.

CONCLUSION(S)

FLAG with Bortezomib protocol induces remission in relapsed and refractory ALL and AML patients with an acceptable toxicity profile. This protocol necessitates a high level of blood product support, including packed red blood cells, platelet-rich plasma, and single-donor platelet apheresis. The present protocol is cost-effective compared to conventional anthracycline-based chemotherapy, with fewer intensive care unit admissions in resource-limited settings, and acts as a gateway to stem cell transplantation.

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