Outcome of FLAG and FLANG Regimens in the Treatment of Acute Leukemias Patients

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Abstract

Introduction: Despite all improvement in the treatment of acute myeloid leukemia (AML) patients, the management in relapsed or refractory disease is still controversial. The use of multiple chemotherapeutic agents will induce more toxicity and morbidity in patients. Fludarabin- containing therapy (FLAG and FLANG) mostly has been used in the treatment of relapsed or refractory AML patients.

Methods: In this retrospective study, we evaluated the response of treatment in 40 adult leukemia patients treated with these regimens from October 2007 to December 2011 in our center. They took FLAG (fludarabine, cytarabine, GCSF) and FLANG (fludarabine, cytarabine, mitoxantrone) according to the approved protocol. They were taken packed cells or platelets as needed and antibiotics in cases of established or highly suspicious infections. After these therapies, 12 patients with suitable donor made ready for allogeneic hematopoietic stem cell transplantation (HSCT) and one patient without donor underwent autologous HSCT.

Results: The median age of patients was 29.5 (range: 16- 50) years old. The male to female ratio was 30:10. The patients were diagnosed with ALL (15, 37.5%) and AML (25, 62.5%). The most common subtype of leukemia was ALL- L2 and AML- M4. The most common disease treated was AML-M4. Two patients had secondary leukemia (breast cancer and MDS). Except two patients which treated with FLAG regimen, others received FLANG. Most patients were primary refractory (18, 45%), first relapse (17, 42.5%) or second relapse (5, 12.5%) before this treatment. Thirteen patients underwent hematopoietic stem cell transplantation after FLANG. Four patients received FLANG as relapse treatment after transplantation. Pulmonary aspergillus infection occurred in 13 patients and aspergillus sinusitis in two after FLANG/ FLAG treatment. White blood cells and platelet recovery observed in 30 patients with a median time of 20 days after treatment. Treatment resulted in complete response (n=19), partial response (n=1) and no response (n=11) in patients. Early death (before 60 days) after treatment occurred in 9 (22.5%) patients. The most common causes of death were primary disease (relapse) (24, 60%) and infection (5, 12.5%). The one- year overall survival was 21.4% (SE: 7.1%). Among the survivors, only 5 patients received transplantation and 5 patients are alive without transplantation.

Conclusion: The study shows that refractory and relapsed leukemia patients can achieve complete remission with FLAG/ FLANG treatment. The side effects include serious fungal infections and sepsis. Moreover, high mortality during these treatments was observed

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Introduction

Introduction of anthracyclines and cytarabine containing chemotherapy regimens concluded to 55 to 85 % complete remission and prolonged disease- free survival in newly diagnosed cases of acute myeloid leukemia

(AML) patients (1-3). In spite of these treatment modalities, 15- 25 % of patients do not achieve complete remission (CR) and among patients who achieve CR, 40% will relapse within two years after treatment (4-9). Despite all improvements in the treatment of AML patients, the treatment strategy for patients with relapsed or refractory AML cases still remains controversial. The use of multiple chemotherapeutic agents will induce more toxicity and morbidity in some patients. Fludarabin as an inhibiting DNA repair agent mostly has been used in the treatment of many hematological malignancies like chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia. Then, the combination of fludarabine, Ara-C, and G-CSF (FLAG) has been used with idarubicin for the treatment of the AML and myelodysplastic syndromes (MDS) (10). This regimen showed good efficacy with acceptable toxicity in the treatment of refractory or relapsed AML and acute lymphoblastic leukemia (ALL) patients in previous studies (11-14). Some studies also emphasized the efficacy of this regimen with acceptable hematological and non-hematological toxicities in poor prognosis AML patients (15). FLAG regimen contains G-CSF 0.5 µu/kg intravenously, startingday 1 and continuing until remission (i.e., stop on the first day of neutrophils >1.0 $\times 10^9$/L). Twenty-four hours after the first G-CSF dose, fludarabine 25 mg/m^2 IV was given by 30- minute infusion (days 2–6), followed 4 hour later by cytarabine 2 gm/m^2 by a 4- hour infusion (days 2–6). FLANG regimen with a shorter duration (3 days) includes reduced Ara-C dosage (1 g/sqm) and administration of mitoxantrone (novantrone) (10 mg/sqm) at the end of Ara-C infusion (16). We assessed the efficacy and toxicity of these regimen therapies for 40 AML patients treated in two hematology- oncology wards in this center.

Patients and methods

Patients

From October 2007 to December 2011, forty leukemia (AML and ALL) patients were treated in this center. The median age of patients was 29.5 (range: 16- 50) years old. The male to female ratio was 30:10. The patients were diagnosed with ALL (15, 37.5%) and AML (25, 62.5%). The most common subtype of leukemia was ALL- L2 and AML- M4. The study included patients with secondary leukemia (n=2), previous breast cancer (n=1) and history of myelodysplastic syndrome (n=1). There were 22 cases of relapsed and 18 refractory AML and ALL patients. The most common disease treated was AML-M4.

Treatment protocols applied to patients as follows

FLAG regimen

G-CSF: at a dose of 300 µg/day subcutaneously on days 1 to 5, given 12 hours before fludarabine, continued for 5 days and then one week after the end of regimen until remission (stop on the first day of neutrophils >1.0 $\times 10^9$/L); Fludarabine: at a dose of 30 mg/m^2/day IV by 30- minute infusion (days 1–5); Cytarabine: at a dose of 2 gm/m^2 by a 4-hour infusion (days 2–6) followed in 4 hours after fludarabine infusion.

FLANG regimen

G-CSF: at a dose of 300 µg/day subcutaneously on days 1 to 3, given 12 hours before fludarabine, continued for 3 days and then one week after the end of regimen until remission (stop on the first day of neutrophils >1.0 $\times 10^9$/L); Fludarabine: at a dose of 30 mg/m^2/day IV by 30- minute infusion (days 1–3); Cytarabine at a dose of 1g/m^2 from on days 1 to 3 by a 2- hour infusion, followed in 4 hours after fludarabine infusion; Mitoxantrone (novantrone) at a dose of 10 mg/ m^2 /day in 30-minute infusion at the end of Ara-C infusion.

Among forty patients, thirty- eight were treated with FLANG and two received FLAG regimen according to the center- approved protocol (as mentioned earlier) in the Hematology-Oncology and Stem Cell Transplantation Research Center.

Four patients received FLANG as relapse therapy after transplantation (group C). Of whom, 3 were affected by AML and 1 was diagnosed as having ALL.

Thirty-six patients received FLANG/FLAG as second or more line therapy for refractory or relapsed leukemia. Among them, thirteen underwent stem cell transplantation after FLAG/FLANG regimen therapy (group B); 12 patients with suitable donor made ready for

allogeneic hematopoietic stem cell transplantation and one patient underwent autologous HSCT. Furthermore, one patient retransplanted (allogeneic transplantation after failure of autologous transplantation). There were 9 AML and 3 ALL patients among those transplanted. Twenty-three patients just received FLAG/FLANG without any transplantation (group A).

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation was performed under the series of protocols approved by the center. The transplantation process was described earlier (17). The patients were followed- up from the start date of FLAG/ FLANG treatment until March 2012.

Supportive care

The patients received packed cells or platelets for supportive care as needed and antibiotics in the cases of established or highly suspicious infections.

Statistics

Categorical data were presented with frequencies and percentages, while continuous variables were described using median and range. Survival data were estimated using Kaplan-Meier estimator.

Results

Patients

The demographic and laboratory characteristics of patients are summarized in table 1. Six (6/40: 15%) patients had pancytopenia at the time of diagnosis and 10 (10/40: 25%) presented with leukocytosis (WBC> 50,000/ μl). The study included patients with primary refractory (18, 45%), first relapse (17, 42.5%) or second relapse (5, 12.5%) before the treatment. The WBC, Hb and Platelet count of patients before FLAG/ FLANG treatment are summarized in table 2. Eleven (27.5%) of patients were pancytopenic before onset of treatment.

Recovery and Side effects

White blood cells and platelet recovery were observed in 30 (75%) patients with a median time of 20 days (range: 10-35) in both groups after treatment. Totally, among side effects of treatment, pulmonary aspergillus infection and aspergillus sinusitis were seen in 13 (32.5%) and 2 (5%) patients, respectively. Notably, one patient affected by typhlitis, one with pseudomonas cellulitis of leg and one with shingles.

Response to treatment and Survival

Totally, 47.5% (19/40) achieved complete response, 27.5% (11/40) of patients was refractory and did not response to regimen and 25% (1/40) had partial response. The median survival time was 6.7 months. The one-year overall survival was 21.4% (SE: 7.1%). (Figure.1) Now, ten patients are alive and seven of whom remain in continuous complete remission. The median follow- up time in survivors from the start of FLANG/FLAG until last contact was 4.6 months (range: 1- 12.3) in 5 patients included the group A. It was also 14.4 months (range: 5- 41.3) for 5 patients in group B. Early death (before 60 days) after treatment occurred in 9 (22.5%) patients (8 in group A and 1 in C group). The causes of death were primary disease (relapse) (24, 80%), infection (5, 16.7%) and severe gastrointestinal Graft- versus- Host Disease (GvHD) (1, 3.3%).

Among the 23 patients treated with FLANG without transplantation (group A), 18 (18/23: 78.3%) died. The cause of death was relapse in 15 (15/18: 83.3%) and infection in 3 (3/18: 16.7%) patients.

Of the 13 patients included in the group B, eight (6/13: 61.5%) died. Five (5/8: 62.5%) expired due to relapse after transplantation, two (2/8: 25%) due to infection and one (1/8: 12.5%) death occurred due to severe gastrointestinal GvHD 4 months after transplantation.

Four patients who received FLANG as relapse therapy after transplantation (group C), died due to relapse.

Discussion

Treatment of refractory and/ or recurrent leukemias is still debatable and needs to use new drugs and methods of chemotherapy. Fludarabine induces further accumulation of Ara- CTP in leukemic cells and inhibition of DNA repair mechanisms. It is used in combination with new drugs for the treatment of patients with high- risk and refractory AML (18-19). FLAG/FLANG regimen has been used in core- binding factor AML patients or in

combination with other drugs, too (20-21). In this retrospective study, we evaluated the effectiveness and safety of FLAG/FLANG regimen in the treatment of refractory / recurrent leukemias. The effectiveness of these regimens was evaluated with response to treatment, disease- free survival and overall survival. Like other studies myelosuppression and infection due to long period of neutropenia, were the most common side effects observed in these regimens (22). Although we observed 40% invasive aspergillus infection especially pulmonary, it was not the leading cause of death like other studies (23). The other side effects were tolerable. In small and mostly retrospective studies, such combination of fludarabine as FLANG or FLAG used as second-line therapy have resulted in complete response (CR) rates of 36-59% (24). Complete response occurred in 44% of our AML and 53.4% of ALL patients which is similar to IDA-FLAG regimen used in refractory leukemias (25). Twenty- seven and half percent of patients were resistant and did not response to treatment, while 25% achieved partial response. It seems that the regimen is feasible for salvage therapy in refractory and relapsed leukemias patients (25). Our complete response rate is the same as Lee et al. study in which FLAG without idarubicine was used on refractory/ relapsed leukemia cases (23). Although only 38.5% of patients treated with FLAG/FLANG relapsed after transplantation (group B), this regimen can be used as cytoreduction for patients who proceed to allogeneic stem cell transplantation when suitable donors are available (21, 25-26). One patient received autologous stem cell transplantation because of no suitable donor available. As mentioned earlier this therapy can be used as conditioning regimen for autologous transplantation safely without negative effects on stem cell mobilization (27). Age, sexuality, disease status (primary/ secondary leukemia), WBC count at diagnosis and leukemia subtypes did not have significant effect on response to treatment in Yavuz et al. study (25). We used FLAG/ FLANG regimen as second- line or relapse therapy, but it was used as front-line therapy in some other studies (20). Although most of our patients treated with this regimen were primary refractory and relapsed ones, our median survival time after one course of therapy without idarubicin was longer than median survival in refractory, relapsed adult leukemias and non- transplant children with poor prognosis leukemia treated with multiple cycles of IDA-FLAG (25-26, 28).

Conclusion

The study shows that refractory and relapsed leukemia patients can achieve complete remission with FLAG/ FLANG treatment. The side effects include serious fungal infections and sepsis. Moreover, high mortality during the treatment was observed. The duration of remission after these therapies is usually short.

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