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Autologous stem cell transplantation with moderate dose of Idarubicin and Busulphan as conditioning regimen in acute myelogenous leukemia

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Abstract:

Background: Over 50% of patients with AML still relapse after autologous stem cell transplantation. We investigated the efficacy and feasibility of a new conditioning regimen consisting of a moderate dose of Idarubicin plus conventional dose of oral Busulfan in patients undergoing autologous transplantation without favorable cytogenetic state and high dose therapy with Cytarabine or other drugs.

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Methods: Ten Patients were given three days of bolus infusion of IDA followed by four days of oral Busulfan as conditioning regimen. Unpurged peripheral blood stem cells were used in all cases. All the cases were in first complete remission (CR1).

The reasons for the selection of these patients in the first remission were that they had not received high dose chemotherapy or did not have available cytogenetic state.

Results: The transplant related mortality occurred in one case (refractory thrombocytopenia, leading to CNS hemorrhage). The median CD34+ cell infused was $8 \times 10^6/\text{kg}$. The median days to neutrophil recovery $> (0.5 \pm 10^9)$ and platelet recovery $> (20 \pm 10^9/\text{kg})$ were +9 days (4-12 days); +16 (2-30 days) respectively. The patients needed transfusion of a median of 15 platelet units and 7 blood units, respectively. Six out of 10 patients (60%) had variable grades of mucositis (three cases had grade III, two grade II and one case grade I). After a median follow up of 48 months from ASCT, 8 patients out of 10 (80%) were alive in continuous complete remission. One case had relapse after 6 months of transplantation.

Conclusion: The findings of the study demonstrated the efficacy and feasibility of a conditioning regimen based on a moderate dose of IDA plus Busulphan in AML. The results concerning anti-leukemic efficacy are promising but need to be confirmed on larger series.

Keywords: Acute myeloid leukemia; Stem cell transplantation; Idarubicin; Busulphan

Manuscript Body:

Introduction

Acute myelogenous leukemia (AML) is one of the bone marrow malignancies, having the same clinical manifestation but different morphology, immunophenotype and cytogenetic state. The pathogenesis of AML is unknown, but most of the patients have one or more chromosomal abnormality. The cure rate with advances in therapeutic approach increased from 20% in 1960-1980 to 40-70% in 2000.¹ The cytogenetic abnormality is significantly effective in the pathogenesis of AML. The incidence of AML is more in patients with cytogenetic abnormality and chromosomal instability.²⁻⁴ The therapeutic approach to AML includes cytotoxic chemotherapy with or without bone marrow transplantation. Another active treatment is monoclonal antibodies which is effective on blastic series directly.^{5,6} Prescription of Cytozar and Anthracyclin was the basis of treatment in 30 past years. Treatment with bone marrow transplantation in selective patients is superior to cytotoxic chemotherapy alone. Although high dose chemotherapy is another effective approach, this question that what therapeutic approach would be the best protocol for AML patients has not been clearly answered.^{7,8} The cure rate with chemotherapy alone is 10-30% which is also dependent on certain factors including age, prior MDS, cytogenetic state, speed of complete remission. High dose chemotherapy and allogenic bone marrow transplantation led to better results and allogenic BMT was superior to high dose chemotherapy due to low relapse rate. Unlike the allogenic transplantation, there is no GVL effect in patients undergoing autologous transplantation. As a result, the risk of relapse is more in such patients. In a prospective study by EORTC (European Organization for Research and Treatment of Cancer) group and the GIMEMA Italian group in 1986, all the patients with AML in the treatment protocol had one course of intensified chemotherapy and intermediate dose of Cytarabine and Amsacrine. The patients with HLA matched sibling were candidates for allogenic bone marrow transplantation,^{9,10} and other randomly selected patients were candidates for high dose chemotherapy and autologous bone marrow transplantation. The patients with chronic myelogenous leukemia or other myeloproliferative disorders were excluded from the study. Other exclusion criteria were MDS (myelodysplastic syndrome) or secondary leukemia. The median age was 33 years.^{7,11} The result of this study revealed that the relapse rate in the intensified group was more than that in the other groups (57.1%). In Auto BMT it was 40.6% and in allogenic bone marrow transplantation it was 24.4%. The mortality rate in chemotherapy group was 7.1%, in autologous bone marrow transplantation 9.4% and in allogenic transplantation 17.3%. The mortality rate in patients treated in the first remission in chemotherapy group was 5.8%, in autologous transplantation it was 10.4% and in allogenic transplantation 20%. The conditioning regimens used in autologous transplantation were Busulfan and Cyclophosphamide. These drugs were specifically used for allogenic transplantation. The main effect of these drugs was immunosuppression and anti-leukemic effect was minimal. In autologous transplantation, the anti-leukemic effect is the mainstay of conditioning regimen, and for this reason alternative chemotherapeutic conditioning regimen was considered and used.^{12,13} The previous studies have shown that Idarubicin was more effective.¹⁴⁻¹⁶ Therefore, it is administered for conditioning regimen in autologous setting.

Materials and Methods

Patients with AML treated with classic regimen 7-3 (Cytozar 100 mg/m² for 7 days and Daunorubicin 45 mg/m² for 3 days) and the consolidation therapy of 5-2 regimen (Cytozar 100 mg/m² for 5 days and Daunorubicin 45 mg/m² for 2 days) were all treated with this regimen. The reasons for the selection of these patients in the first remission were that they had not received high dose chemotherapy or did not have available cytogenetic state such as AML (M3), T (8:21), inv 16. The possibility of allogenic bone marrow transplantation was examined for all patients. If the patients did not have acceptable donors, they were candidates for autologous bone marrow transplantation. In this study, the patients with poor performance status, cytogenetic abnormality such as T (8:21), Inv:16 or T(15:17), and those treated with high dose chemotherapy were excluded. All patients were examined for cardiopulmonary problems and if they had cardiopulmonary contraindication for bone marrow transplantation, they were excluded from the study. Their laboratory profile was evaluated and if they had any abnormality as the cause of discontinuation of treatment, the autologous transplantation was stopped. At the end of these evaluations, legible patients were entered in this treatment protocol. The protocol started in day -18. On this day, the GCF began with a dose of 5-10 mgr/kg/day and continued for 5 days. On day -14, the patients were candidate for harvesting of stem cells. In the stem cell harvesting, the minimal acceptable nucleated cells were at least $4 \times 10^8/\text{kg}$, and if this number of nucleated cell could not be harvested on the other days, the procedure was repeated. At the end of harvesting, cryopreservation of nucleated cells in -76C was done, and thawing was done in day zero of stem cell transplantation. The conditioning regimen began in day -13 to -11 with Idarubicin in a dose of 12 mg/m²/day with bolus injection. Busulfan is another conditioning drug prescribed for 4 days with a dose of 4 mg/kg/day/PO. The thawing of stem cell was done in zero day of stem cell transplantation, and then infusion of stem cell was done in safe condition.

When the patient was admitted in bone marrow transplantation ward, he/she was in close follow up and if the patient needed any supportive care and transfusion of blood element, these requirements were replaced -18- -13 (GCSF 5-10 mgr/kg/day SC (-13 - - - 11) @ Idarubicin 12 mg/m² +200 ml N/S IV bolus for 3 days -5 - - 2 @ Busulfan 4mg/kg po daily for 4 days.

If the mucositis occurred, this side effect was confirmed with exact physical examination rated with WHO scoring system.¹⁻⁴ If the patient had fever during admission in BMT ward, the evaluation of fever was immediately done and empirical antibiotic therapy began. Then, the result of the culture was available the antibiotic therapy was exchanged. Other side effects such as cardiac, renal, and liver toxicity or skin lesion were documented and treated.

The complete blood count was examined every day. The bone marrow aspiration was done in day +13, followed by exact examination, and recovery of blood cells engraftment of the stem cells was evaluated. The mean of engraftment was platelet $>20000/\text{mm}^3$, and neutrophil count $>500/\text{microliter}$.

Results

Regarding inclusion and exclusion criteria, ten patients were enrolled in this study as candidates for autologous bone marrow transplantation with Idarubicin & Busulfan as the conditioning regimen. The patients' characteristics were shown in Table 1. The median age was 24 years (9-40 years). The median time of diagnosis to transplantation was 10 months (4-20 years). The regimen of induction therapy was 7-3 (Cytarabine for 7 days and Daunorubicin for 3 days). All patients had not received high dose chemotherapy. Consolidation therapy was 5-2 regimen (5 days Cytarabine and 2 days Daunorubicine). The patients had been referred from several centers and for this reason cytogenetic study was done in four patients. In the cytogenetic transplantation, 3 cases had normal karyotype and one patient had hyperdiploidy. Ten patients were admitted in BMT ward and received only GCSF for stem cell harvesting. The median MNC was $5.8 \times 10^8/\text{kg}$ (3.6-6.1) and median CD34 $8 \times 10^6/\text{kg}$ (2.5-20). During the admission, the complete cell count was checked daily, and if the patients had cytopenia requiring correction red blood cell or platelet was transfused. The median number of platelet transfusion was 12 units (3-23) and that of red blood cell transfusion 7 units (1-15). In BMT ward, all patients experienced a period of fever and neutropenia. Eight had fever and positive culture and two had fever of unknown origin. *Staphylococcus aureus* was the most common pathogen in those patients. The fever and the neutropenia were controlled with antibiotic therapy. Antibiotic therapy in 8 patients was only anti-bacterial therapy and in 2 cases treatment was anti-bacterial and anti-fungal. During the admission, the patients were closely examined and hematologic recovery was carefully evaluated, and on days +13-+17 of transplantation, bone marrow aspiration was done for all patients. The hematologic recovery was defined with neutrophil and platelet count (Table 2).

No of patients	10
Age (median age)	24
Sex M/F	1.1
FAB classification	5 cases
M2	5cases
M4	3cases
M5	1cases
M6	1case
Cytogenetic	3 cases @ Normal Cytogenetic 1 case @ Hyper diploidy Others @ Not available
Courses of chemotherapy to CR1	Courseof One 7-3 Regimen and 2 courses of 5-2 Without High dose therapy (all of patients)
Patients transplant in CR	10 cases
Interval CR/to ASCT(month)	10 months
Number of CD 34+	8×10^6 (2.5 –20)

	Median	Range
Days to leukocytes recovery	+9	(4–12)
Days to platelet recovery	+16	(2–30)
No of PLT transfusion	12	(3-23)
No of erythrocyte transfusion	7	(1–15)

The hematologic recovery was observed in 9 cases and refractory thrombocytopenia in one case which was resistant to treatment and so the patient died due to CNS hemorrhage.

One of the common toxicities was mucositis. The mucositis was mild, tolerable and completely resolved with supportive care. Three patients did not have any evidence of mucositis. Two cases had mucositis grade 1, one grade 2, and three cases had grade 3 mucositis. Grade 4 mucositis was not observed. Other treatment related toxicity was fever. This toxicity was culture positive in 8 cases and with fever of unknown origin in 2.

All patients who received autologous transplantation tolerated this new conditioning regimen well, and also had hematologic recovery except one patient that had refractory thrombocytopenia and died due to this problem. Nine patients were discharged with good status, among them, one case had evidence of relapse after 8 months of transplantation. In this study, the transplant related mortality occurred in one case.

Discussion

The new chemotherapeutic regimen used for treatment of acute myelogenous leukemia had complete response in 60-80 % of patients, but the majority of them had relapse without other intensive treatments. Autologous stem cell transplantation after initial complete response was commonly used in an additive way. There are many studies indicating the superiority of autologous transplantation to intensive chemotherapy.¹⁷⁻²⁰ Although this modality was a good therapeutic approach, about 30-50% of these patients had relapse after this modality of treatment.²¹ For this reason, other approaches such as in vivo purging, ex vivo purging, use of peripheral stem cell and immunotherapy were considered.²¹ The early conditioning regimen was Busulfan-Cyclophosphamide used by Baltimore and his coworker and then modified by Columbus. This was the most common regimen used for autologous and allogenic transplantation. The major

efficacy of these drugs and the possibility of engraftment. In the autologous transplantation setting, an alternative regimen with more antileukemic efficacy was considered.^{12,13} Some studies revealed better results with intensified Idarubicin drug in allogeneic setting.¹⁴⁻¹⁶ These good results led to Idarubicin usage for conditioning regimen in autologous transplantation setting. In the literature review, the best report is by Felicetto Ferrara in Italy.¹¹ 13 patients were enrolled in this protocol therapy. The diagnosis was based on FAB classification and the usage of morphology and cytochemistry. The immunophenotype was done for all patients. Two patients had karyotype evaluation. The patients with T (8:21), Inv16, and M3 were excluded from the study. Thirteen patients who had autologous transplantation in 1999-2000 were included. Eight patients were men and five women. The induction therapy was ICE regimen (Idarubicin 10 mg/m² {for 1-3 days}, Cytozar 100 mg/m²/1-7 days, Etoposide 100 mg/m²/1-4 days). When the patients had complete remission, consolidation therapy with NOVIA regimen began. This regimen was (Cytozar 500mg/m²/12h/1-6 days, and Mitoxanteron 10 mg/m² for 3 days {4-6 days}). In days 15 of NOVIA regimen, the GCSF with a dose of 450 microgram/m² for induction of the stem cells and CD34 cells mobilization was started. Two cases in complete remission with FLAG regimen underwent transplantation. The median time of complete remission in autologous transplantation was 3 months (2-8 months). The median CD34 cells infused was 6.2 * 10⁶/kg (2.6-16.1). The conditioning regimen was Idarubicin 20 mg/m² in days -13 to -11 with 24 h infusion, and then Busulfan 4 mg/kg/day for 4 days. In this study, the induction regimen therapy was only 7-3 (Cytozar 100 mg/m² for 7 days and Dounorubicin 45mg/m² for 3 days, and consolidation therapy was only 5-2 regimen (Cytozar and Dounorubicin with a similar dose of induction therapy for 5 and 2 days) without high dose therapy. In comparison with Felicetto Ferrara's study, many differences were observed including 1. No usage of Etoposide; 2. No usage of Idarubicin in induction therapy; 3. No usage of high dose Cytozar in consolidation therapy; 4. No usage of Mitoxanterone; 5. Consolidation therapy in our study was only cytozar and dounorubicin (5-2) regimen; 6. The Idarubicin in conditioning regimen was with a dose of 12mg/m² with bolus injection that was against the Italian protocol with a dose of 20mg/m² and 24h infusion; 7. In our study we did not use aggressive mobilization regimen except GCSF which was against the Felicetto Ferrara's protocol.

In the Felicetto Ferrara's study, transplant related mortality was not observed but we had one case due to refractory thrombocytopenia leading to CNS hemorrhage. The hematologic recovery in Felicetto Ferrara's study for Neutrophil was 10 days and in our study 9 days. The platelet recovery was 20 days and in our study it was 16 days.

The platelet and packed cell transfusion in Felicetto Ferrara's study were 2 and 3 units and in our study 12 and 7. In his study, documentation of infection was not observed but in ours all patients had a period of fever and neutropenia. This neutropenia and fever was observed in 8 cases with culture positive and in 2 cases with FUO presentation. In his study, mucositis was the common non-hematologic toxicity (92%). The mucositis was grade 2 in 2 cases, grade 3 in 5 cases, and grade 4 in 5 cases. The toxicity in our study had mild representation and 2 cases had grade 1, one case grade 2 and 3 cases grade 3. Grade 4 toxicity was not observed. In the Ferrara's study, after 16 months of follow up, 11 patients were alive and in complete remission and 2 cases had relapse 12 and 14 months after transplantation. The duration of follow up in our study was 48 months, during which there was one relapse after 6 months of transplantation. Other cases are in complete remission now (after 52 months).

Although we studied ten patients with Acute Myelogenic leukemia and we used medium dose of Idarubicin and Busulfan (a more effective anti-leukemic drug) for conditioning regimen, it was revealed that this protocol was effective, comparable with high dose and aggressive therapy.

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