Ajou Medical Journal
Vol. 1, No. 1, 1996

High Dose Chemotherapy Followed by Autologous Peripheral Blood Stem Cell Transplantation: Experience at Ajou University Hospital

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High-dose chemotherapy with autologous stem cell support is a new therapeutic modality for otherwise incurable malignancy. Peripheral blood stem cell(PBSC) is considered an excellent stem cell source alternative to bone marrow after myeloablative cytotoxic treatment.

We treated 7 patients with malignant disease (5 lymphomas, one gastric carcinoma and one undifferentiated cancer) with high-dose chemotherapy followed by autologous peripheral stem cell support at Ajou University Hospital.

All patients tolerated high-dose chemotherapy and reinfusion of PBSC well. Hematologic recovery was rapid and sustained. The response to high-dose chemotherapy was significantly improved as compared with that to prior conventional chemotherapy and /or radiotherapy, to which they had become refractory.

We confirm the feasibility and value of collection and reinfusion of PBSC in conjunction with the high-dose chemotherapy.

Key Words: High-dose chemotherapy, Peripheral blood stem cell transplantation

INTRODUCTION

High-dose chemotherapy with autologous stem cell support is increasingly utilized for treatment of lymphoma, leukemia, breast cancer and other solid tumors[1-4]. Studies in human with different neoplasia have shown that there is a dose-response curve for chemotherapy responsive malignancies[5,6]. Multiple cycles of high-dose combination chemotherapy are recommended for less chemo-sensitive tumors for long-term remission and cure[7]. However, bone marrow suppression associated with high-dose chemotherapy limits the full dose schedule. Chemotherapeutic agents which possess myelosuppression as their main dose-limiting toxicity would be excellent candidates for repeated administraion, if the risk of hemorrhage and infection could be limited by the concurrent use of hematopoietic growth factors. Blood derived hematopoietic stem cells is considered an alternative stem cell source for hematopoietic reconstitution following myeloablative treatment. Recent studies support the evidence that hematopoiesis reconstituted by autologous peripheral blood stem cells becomes complete and sustained[8,9]. In recent years a rapid progress has been made in the method of peripheral stem cell collection and cryopreservation and made it possible in clinical practice.

We report our initial experience of high-dose chemotherapy and autologous peripheral blood stem cell rescue at Ajou University Hospital in 7 patients with malignant disease. This report describes the feasibility and value of collection and reinfusion of PBSC following the high-dose chemotherapy.

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PATIENTS AND METHODS

Patients

Patients over the age of 18 years and under 60 years with the diagnosis of malignant disease who were consenting to

Table 1. Patients characteristics

Patient	Age	Sex	Diagnosis	Stage	Comment
1	26	f	HD	II	Bulky mediastinal disease
2	33	f	NHL	IV	bone marrow involvement primary refratory
3	41	f	NHL	III	intestinal lymphoma relapsed
4	44	m	NHL	II	primary refractory
5	39	f	NHL	II	CNS lymphoma
6	60	f	stomach cancer	IV	periaortic, left supraclavicular lymphnode involvement
7	56	f	undifferentiated		pericardial effusion, SVC syndrome

*HD, Hodgkin's Disease; NHL, Non-Hodgkin's Lymphoma

the treatment protocols were included for this treatment and were required to have normal liver, renal function test and cardiac ejection fraction and pulmonary function including diffusion capacity greater than 50% predicted. Patient characteristics are shown in Table 1.

Patient 1 had Hodgkin's disease with a huge anterior mediastinal mass and who were considered to be in a high risk of relapse. Patient 2 had a low grade follicular lymphoma with bone marrow metastasis and was refractory to initial induction chemotherapy. Patient 3 had a relapsed diffuse large cell lymphoma in the large intestine and tonsil. Patient 4 had a lymphoma which was refractory to the induction chemotherapy and radiotherapy. Consolidation high-dose chemotherapy for CNS lymphoma was recommended after surgical resection and post-operative adjuvant radiotherapy in patient 5. Neoadjuvant high-dose chemotherapy for gastric cancer with periaortic lymph node and left supraclavicular lymph node involvement was evaluated for effectiveness in patient 6. The last patient was refractory to chemo-radiotherapy and pathologically undifferentiated cancer.

Peripheral blood stem cell harvest and transplantation

Transient shift in the distribution of hematopoietic progenitor cells from the bone marrow to the peripheral blood, a process commonly referred to as mobilization, can be induced with the use of chemotherapy and growth factors, and can significantly increase the efficiency of PBSC collection. The mobilization method in our center is a combined method of intensive chemotherapy and cytokine administration during hematopoietic recovery. We administer granulocyte-colony stimulating factor(G-CSF) 5 μg/kg daily after leukocyte nadir following induction chemotherapy. Peripheral blood stem cells(PBSC) were collected in 2 or 3 consecufive days within 7 days of G-CSF administration. Apheresis procedures for PBSC collection were performed using continuous-flow cell seperator centrifuge machine, COBE Spectra(COBE, Boulder, CO) with standard citrate anticoagulation by peripheral vessels. During apheresis we calculated mononuclear cell count and hematocrit, and adjusted blood flow, duration and volume of collection. Dimethylsulfoxide(DMSO), cellular cryoprotectant, was added to result in a final concentraion of 7% in the bag of collected PBSC, and cell suspension was cryopreserved with rate-controlled freezer (KRYO10; Planars; TS Scientific, Perkasie, PA), and each bag was stored in a vapor phase of liquid nitrogen tank. A small aliquot, which was removed from the cell suspension before cryopreservation, was used for $CD34^+$ cell count by flow cytometry and CFU-GM assay.

Following high-dose chemotherapy, cryopreserved PBSC was removed from the liquid nitrogen tank, thawed in a 37℃ water bath at the bedside and immediately infused through a central venous catheter without filtration. The number of transplanted mononuclear cells, $CD34^+$ cells and CFU-GM count were shown in table 2.

High-dose chemotherapy

5 patients with lymphoma were given a high-dose chemotherapy consisting of BEAM (BCNU, Etoposide, Cytosine arabinoside, Melphalan) regimen. One patient with gastric carcinoma received EEP (Etoposide, Epirubicin, CDDP) regimen. The last patient with undifferentiated cancer received ICE (Ifosfamide, Carboplatin, Etoposide) regimen. Patients

Table 2. Cell dose of PBSCT and hematologic recovery

Patient	Transplantation			Days with ANC<500/ul	Days to ANC>500/ul	Days to Plt>50,000/ul
	MNC (×10e8/kg)	$CD34^+$ (×10e7/kg)	CFU-GM (×10e4/kg)			
1	6.2	1.8	31	5	9	12
2	1.7	0.4	ND	9	10	20
3	2.4	1.0	10	5	8	11
4	1.8	0.5	ND	11	15	20
5	2.8	0.5	ND	8	11	14
6	8.4	1.6	28	5	9	10
7	2.8	0.5	11	8	10	16
mean±SD	3.7±2.5	0.9±0.5	19.9±11.2	7.2±2.3	10.2±2.3	14.7±4.1

* ND, Not Done

were treated with high-dose chemotherapeutic regimen followed by the administration of G-CSF(5 μg/kg SC start day 1 after infusion of PBSC). All patients were cared in a single room with high efficiency particulate air(HEPA) filtration systems. An indwelling central venous catheter was placed in all patients and patients received total parenteral hyperalimentation. The patients received oral prophylactic antibiotics or selective gastrointestinal tract decontamination with quinolone.

To assess the response to high-dose chemotherapy, patients were reviewed clinically and radiologically. Toxicity and response were graded according to WHO toxicity and response criteria[10].

Table 3. Response to induction treatment and high-dose chemotherapy regimen

Patient	Prior treatment	Disease status	High-dose regimen	Response of high-dose
1	chemotherapy	CR	BEAM	CR
2	chemotherapy	PD	BEAM	PR
3	surgery	PR	BEAM	CR
4	chemotherapy, RT	PD	BEAM	PR
5	surgery and RT	CR	BEAM	CR
6	chemotherapy	SD	EEP	PR
7	chemotherapy, RT	PD	ICE	CR

*CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease.

RESULTS

Toxicity and hematologic recovery

All patients tolerated the procedure of stem cell pheresis without any complications. The high-dose chemotherapy protocol was, in general, well tolerated. No patient died of treatment-related toxicity. Grade 1 to 2 vomiting associated with high-dose chemotherapy was well controlled with the use of granisetron. Only one patient (patient 7) had mild elevation of hepatic enzyme. All patients became severely cytopenic after high-dose chemotherapy. Following the autologous PBSC infusion, median time to recovery to a neutrophil count of >0.5 × 10e9/L was 10 days (range 8 to 14), >50 × 10e9/L platelets was 14 days(range 11 to 25). Neutropenic period(<0.5 × 10e9/L) was 7 days(range 5 to 11)(Table 2). 4 patients developed febrile episode, but no Hickman line-related sepsis or cultured documented infection was seen. All patients well tolerated the prophylactic oral antibiotics.

Response of treatment

Responses to treatment are listed in Table 3. All patients had a significant response for high-dose chemotherapy with PBSC transplantation. Also there was a significant response for patient who had refractory malignancy(patient 2,4,7) as compared with the prior conventional dose chemotherapy

and/or radiotherapy. 5 patients with lymphoma who were treated with BEAM regimen tolerated chemotherapy well and experienced no major organ toxicity. Patient 1 and 5 had no measurable disease before the high-dose chemotherapy and received high-dose chemotherapy for the purpose of reducing locoregional and systemic relapse. These 2 patients also developed less degree of non-hematologic toxicity as compared with other patients. Patients 6 had an advanced gastric cancer which were unresectable prior to high-dose chemotherapy. After the high-dose chemotherapy she underwent a radical subtotal gastrectomy. Staging showed a decrease from stage IV to stage IIIb on surgical pathology. She tolerated the high-dose chemotherapy and subsequent surgical resection well in spite of her old age. Patient 7 had an anterior mediastinal mass and SVC syndrome, which mass was refractory to chemo-radiotherapy. After high-dose chemotherapy, SVC syndrome disappeared and partial response was seen in CT scan.

DISCUSSION

The antitumor dose response curve for alkylating agents indicates that administration of higher doses of these agents results in a greater degree of tumor cell death[5,9]. But greater degree of toxicity to normal tissues associated with increased tumoricidal effect limits the usage of high-dose chemotherapy. If toxicities were decreased or rescued, the therapeutic benefits of these chemotherapeutic agents could be realized for the improved tumor control.

Recently, myelosuppression has been somewhat reduced with the use of the cytokines. However, despite the use of cytokines, intensive dose of myelosuppressive agents continue to result in profound and potentially life threatening cytopenia. Several recent reports indicate that the concurrent reinfusion of cytokine-stimulated autologous PBSC followed by daily G-CSF administration markedly reduces the degree and duration of cytopenia. There are potential advantages of PBSC over bone marrow transplantation that may account for its rapid acceptance, and include (1) easy, inexpensive cell collection without the need for operative procedure under general anesthesia, (2) applicability to patients with the bone marrow involvement by the tumor or prior pelvic irradiation, (3) reduced cytopenic period after myeloablation, (4) a lower incidence of infectious complications, (5) collection of large amount of stem cells for repeated cycles of rescue, and (6) feasibility of cell collection in an outpatient setting[11~13].

We treated 7 patients with malignant diseases using high-dose chemotherapy and PBSCT. All patients tolerated high-dose chemotherapy well unrelated to age or disease status. There were transient nausea and vomiting that was controlled with antiemetics. Only one patient had hepatic toxicity that was low grade(+1), also transient. Hematologic recovery was rapid and sustained. Although 4 patients had febrile episodes during the neutropenic period, there was no documented infection. Febrile episodes were easily controlled with systemic antibiotics and patients tolerated febrile episode well as their neutropenic periods were relatively short. There was a delayed recovery of thrombocytopenia in patient 3. She had low grade lymphoma with bone marrow involvement. She is planned to be treated with repeated cycles of high-dose chemotherapy for complete remission of low grade lymphoma. Patient 4 and 7 had refractory disease and partial remission to high-dose chemotherapy, and they are also planned to receive repeated cycles of high-dose chemotherapy and PBSCT.

In the present study, we confirmed that toxicity of high-dose chemotherapy was acceptable and hematologic recovery was fairly rapid reaching the absolute neutrophil count > 500/μl in 10 days. The possibility of application of the high-dose chemotherapy and PBSC rescue to induction therapy, consolidation and neoadjuvant aims was seen.

In conclusion, our result indicates the feasibility of PBSC collection and cryopreservation after disease oriented, conventional chemotherapy. Accelerated hematologic recovery in PBSCT would make it safer to perform high-dose chemotherapy for patients with otherwise incurable malignant neoplasm.

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