Autologous Bone Marrow Transplant in Multiple Myeloma Patient With Bone Marrow Hematopoietic Stem Cell

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ABSTRAK

Multiple myeloma (MM) adalah keganasan dengan berbagai komplikasi seperti infeksi bakteri berulang, anemia, lesi osteolitik, kegagalan sumsum tulang, dan penurunan fungsi ginjal. Di pusat transplantasi yang sudah berkembang, prosedur transplantasi sumsum tulang dilakukan oleh sumber sel induk darah tepi. Mesin aferesis yang tidak selalu tersedia di semua Pusat Hematologi dan Onkologi di Indonesia diperlukan untuk pengambilan sel punca dari PBSC (peripheral blood stem cell). Laporan transplantasi stem cell sumsum tulang belakang dari BM dengan waktu 24 jam masih sedikit. penyimpanan dalam beberapa kasus myeloma. Kami melaporkan dua kasus dengan myeloma non-sekretorik stadium III dan IgG myeloma stadium II (Sistem Pementasan Internasional). Kedua pasien dirawat dengan regimen induksi CyBord sampai sembuh total. Setelah remisi tercapai, prosedur transplantasi sumsum tulang autologus dilakukan. Sumber sel punca hematopietik (HSCs) dipanen dari Sumsum tulang dan disimpan selama 24 jam pada suhu 4◦ C. Komplikasi yang terjadi adalah neutropenia, anemia, trombositopenia, mukositis, diare, rambut rontok, kegelapan kulit. HSC tumbuh baik pada hari ke 12 dan ke 23. Setelah perawatan di ruang isolasi, kondisi pasien membaik dan dipulangkan.

Kata kunci: *mieloma, sel punca hematopoetik, sumsum tulang, transplantasi autologus.*

ABSTRACT

Multiple myeloma (MM) is a malignancy with multiple complications such as recurrent bacterial infections, anemia, osteolytic lesions, bone marrow failure and decreased kidney function. In developed transplant center, the bone marrow transplant procedure is performed by the source of peripheral blood stem cells. Apheresis machine which is not always available in all Haematology and Oncology Centre in Indonesia, is required for harvesting stem cell from PBSC (peripheral blood stem cell). There are only a few reports on marrow-derived stem cells transplant from BM with a 24-hour storage in multiple myeloma cases. We report two cases with non-secretory myeloma stage III and IgG myeloma stage II (International Staging System). Both patients were treated with induction regimens CyBord until a complete remission. Once remission was achieved, an autologous bone marrow transplant procedures were performed. The source of haematopietic stem cells (HSCs) were harvested from bone marrow and stored for 24 hours at a temperature of 4◦ C. The complications were neutropenia, anemia, thrombocytopenia, mucositis, diarrhea, hair loss, and skin darkness. The HSCs grew well on day 12 and 23. After treatment in the isolation room, the patient's condition improved and the patients were discharged.

Keywords: *myeloma, haematopoetic stem cells, bone marrow, autologous transplants.*

INTRODUCTION

Multiple myeloma (MM) is a malignancy derived from lymphocytes-B, characterized by the accumulation of plasma cells clonal in bone marrow, increased production of immunoglobulin monoclonal (Ig) or often called M protein in serum or urine.[1] Complications of MM are recurrent bacterial infections, anemia, osteolytic lesions, bone marrow failure and decreased kidney function.[2-4]

Data Globocan indicates a diagnosis of MM as many as 114 251 new cases every year, where 229 468 people are living with MM in the worldwide.[5] Over 26,000 newly diagnosed case is expected to occur in US, with more than 11,000 of them would be ended up in mortality.[6] The incidence of MM increases 30% between the years 1975-2010.[7] The median age for MM case is 65 year, with the 5-year survival of 44.9%.[8] Incidence of MM in Asia is lower than western countries, but in Taiwan has risen dramatically in recent years.[9,10]

MM management is necessary to distinguish whether a patient eligible to bone marrow transplant or not. Standard therapy for patients who are not qualified for transplant is melphalan and prednisone (MP) or dexamethasone. Vincristine adriamycin doxorubicin (VAD) regimen is used as induction therapy in patients who eligible for the bone marrow transplant. 10CyBord (cyclophosphamide, bortezomib, dexamethasone) is a new regimen and show good results with mild toxicity, especially with sub cutan bortezomib administration.[11,12]

The stem cell can be obtained from bone marrow (BM), peripheral blood stem cell (PBSC) or umbilical cord. Harvesting of stem cell from bone marrow is a simple method, with multiple aspirations under general anesthesia.[13,14] Harvesting of stem cell from PBSC requires apheresis machine that may not be available at all Hematology Medical Oncology center in Indonesia. There are only a few reports on marrow-derived stem cells transplant from BM with a 24-hour storage in multiple myeloma cases.[15]

CASE ILLUSTRATION

Case 1

A 50-year-old male came with the complaint of low back pain, weakness of lower extremity.

Table 1. Clinical Data of the Case.

Patients characteristics	Case 1	Case 2
Age	50	57
Sex	Male	Male
Symptoms at admission	Low back pain, lower extremity weakness	pain in the bones, stiffness in the fingers and toes of the both lower extremities
Type	IgG Myeloma	Nonsecretory myeloma
Staging ISS	II	III
HSCT source	Bone marrow	Bone marrow
TNC	3.3 x 10^8/ kgBW	1.3 x 10^8/ kgBW
Medium for preservation	RPMI, free preservative heparin as anticoagulant, Procaine Penicillin, Gentamicin	RPMI, free preservative heparin as anticoagulant, Procaine Penicillin, Gentamicin
Storage	4◦ C, 24 ours	4◦ C, 24 ours
Conditioning	Melphalan 200mg/m^2	Melphalan 200mg/m^2
Platelet support	Multiple donor collection, filtered, irradiated	Single donor with apheresis, filtered, irradiated
Packed red cell support	Filtered, irradiated	Filtered, irradiated
Nutrition	Partial parenteral nutrition	Partial parenteral nutrition
Engraftment	Day 21	Day 12
Hospitalization	26 days	39 days
Maintenance	Thalidomide	-
Supportive care	Zolendronic acid 4mg/month (1 year)	Zolendronic acid 4mg/month (1 year)

The bone survey showed multiple lytic lesion of calvaria, humerus, tibia, fibula, compression fracture of vertebra lumbalis, in accordance with the diagnosis of multiple myeloma. The serum protein electrophoresis showed monoclonal gammopathy. The immunofixation increased IgG as IgG myeloma. The bone marrow aspiration showed an increase in the plasma cell above 10%. The diagnosis of this patient was IgG myeloma, stage II (ISS, the International Staging System).

Case 2

A male, 57 years old, came with complaints of pain in the bones, stiffness in the fingers and toes of both lower extremities. The bone survey examination revealed multiple lytic lesions of calvaria and humerus, in accordance with the diagnosis of multiple myeloma. The results of a bone marrow biopsy was hypocellular according to age, suggesting indolent myeloma. Serum protein electrophoresis did not show a monoclonal gammopathy. Immunofixation examination obtained an increase in Free Light Chain (FLC) Kappa. Based on these data the patients diagnosed as non-secretory multiple myeloma stage III (ISS, the International Staging System).

Both patients were given a chemotherapy with CyBord protocol (cyclophosphamide iv, bortezomib SC, dexamethasone PO). After 4 cycles of chemotherapy, a complete remission was achieved and patients prepare for a bone marrow transplant.

Bone Marrow Transplant Program

Preparation of a bone marrow transplant program included; dental, mouth, nose, throat, lung function, and echocardiographic examination. Screening of virology and communicable disease infection were conducted before the transplant program. Culture from perineum, blood, urine, sore throat was performed for detection of possible bacterial infection.

The haematopoietic stem cells harvested from bone marrow, obtained under general anesthesia with multiple aspiration. The BM product filtered with 200 microns and preserved with RPMI, free preservative heparin. Procaine penicillin and gentamicin were added to protect bacterial contamination. The minimal target of total nucleated cells (TNC) was $2x10^8$/kgBB. The BM product was cultured before storage 4◦ C for 24 hours. Patient transported to Positive Pressure Room and prepared to conditioning chemotherapy. After conditioning with melphalan 200mg/m^2, the stem cell were infused with 200 microns filter.

In case 1, the blood culture was sterile. In case 2, culture result from throat secretion on day 20 showed Klebsiella pneumoniae, sensitive to ciprofloxacin, while culture on day 21 samples taken from the central catheter and peripheral blood indicated Staphylococcus aureus. Clinically this infection resolved without severe complication.

During treatment, hemoglobin level decrease but the patient did not require transfusion. Thrombocytopenia improved with platelet supports. Neutropenia improves with G-CSF support. The engraftment occurred on day 21 and 12 cases respectively. However, case 2 have much longer hospitalization due to severe mucositis that impaired oral intake. The total lengths of stay of case 1 and case 2 during the bone marrow transplant program were 21 days and 39 days, respectively. Patients were allowed to discharge home after mucositis resolved, neutropenia improved and platelets level above 20,000 without transfusions.

Both patients have received immunization according to protocol during 1st year follow up. Serious complication experienced by case 1 was pneumonia that resolved with oral antibiotic. After 5 years post-transplantation, case 1 was still in remission with normal IgG level and good quality of life (QoL). After 3 years, case 2 was still in remission with normal FLC and good QoL. Both patients are still being evaluated annually.

DISCUSSION

Multiple myeloma (MM) is still an incurable disease, with 5-year survival rate of less than 40% 2, some patients can live within a few months to more than 10 years.[16,17] Median survival of patients with MM is approximately 33 months, similar to the rate suggested by a study conducted in China.[18] With bone marrow transplant program, some studies suggested an increase in median survival up to 10 years. Induction

with CyBord protocol I (cyclophosphamide, bortezomib, dexamethasone) provides 80% reduction in monoclonal protein in the second cycle and 88% partial remission. This new protocol provided fast response in case of new myeloma with controllable side effects.[19]

Stem cell can be isolated from bone marrow, peripheral blood and cord blood, bone marrow-derived stem cell can be harvested using general anaesthesia with multiple aspiration. Peripheral blood stem cells (PBSC) were obtained by using apheresis machine, after mobilization with G-CSF and chemotherapy. Umbilical cord blood (UCB, umbilical cord blood) were obtained at birth by taking the blood and stored in the Cord Blood Bank.[20] Stem cells can be stored in various ways as needed. Products used fresh (fresh infusion) can be stored at a temperature of 4° C for 24 hours prior to use. If it will be used more than 24 hours, the product needs to be frozen to preserve cellular viability. For this purpose, the products are frozen in liquid nitrogen vapor phase or deep freeze -80°; the product can be stored for more than 10 years, while there is no storage time limit. Long-term storage is generally carried out in liquid nitrogen phase.[16] We have performed autologous bone marrow transplant in patients with myeloma using BM as source of HSCT with 24 hours storage. PBSC harvest is simple and referred to the center that has apheresis machine. The results of this case report suggested that BMT using BM is a feasible option in the center with limited resource. The day engraftment of stem cell from BM is comparable with stem cells from peripheral blood.

Melphalan 200 is standard conditioning for the autologous bone marrow transplant in MM patient.[21-24] Complication due to conditioning regiment were nausea and vomiting, painful sore throat, mucositis, neutropenia, grade II diarrhea, fever related to catheter insertion, skin darkness, and hair loss. Blood cultures of peripheral and central venous access were performed to determine the type of bacteria and an appropriate antibiotic. Patients treated with GCSF 300 mcg/day intravenously until ANC (absolute neutrophil count) > 500. Antibiotic imipenem-cilastatin 500/500 mg/ 8 hours and amikacin 500 mg/ 12 hours were given while awaiting culture results. Antifungal Fluconazole 200 mg/ 24 h or Caspofungin 50 mg/ 24 hours for prophylaxis of systemic fungal infections. Oral hygiene education, rinses with mouthwash free alcohol applied to the patient for management of mucositis.

CONCLUSION

Autologous bone marrow transplantation in myeloma by using stem cells from bone marrow with 4◦ C temperature storage in 24 hours is a simple, feasible, and satisfactory procedure. Moreover, this particular procedure shows good results. Day engraftment is comparable with stem cells from peripheral blood. During follow up, all patients are still in remission and show no significant complication. This procedure can be applied at center without apheresis machine in developing countries.

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