Case Report

Beginning of a Journey of Autologous Stem Cell Transplantation in Combined Military Hospital, Dhaka, Bangladesh

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Abstract

Haematopoietic stem cell transplantation (HSCT) involves the intravenous infusion of autologous or allogenic stem cells collected from bone marrow, peripheral blood or umbilical cord to re-establish haematopoietic function in patients whose bone marrow or immune system is damaged or defective. HSCT are mainly of two types –autologous stem cell transplantation (SCT) and allogenic SCT. Autologous SCT is mainly performed in multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma and less commonly in acute myeloid leukaemia. Haematopoietic stem cells are mobilized from bone marrow to the peripheral blood after the use of mobilizing agents, granulocyte colony stimulating factor (G-CSF) and plerixafor. Then the mobilized stem cells are collected from peripheral blood by apheresis and cryo-preserved. The patient is prepared by giving conditioning regimen (high dose melphelan). Stem cells, which are already collected, are re-infused into patient's circulation by a blood transfusion set. Engraftment happens 7-14 days after auto SCT. Common side effects of this procedure include nausea, vomiting, diarrhoea, mucositis, infections etc. The first case of SCT performed in Combined Military Hospital, Dhaka, Bangladesh is presented here.

Key words: *Bone marrow transplantation, multiple myeloma, stem cell transplantation.*

(BIRDEM Med J 2018; 8(2): 177-180)

Introduction

Haematopoietic stem cell transplantation (HSCT) has the potential to cure a variety of benign and malignant haematologic disease that may be incurable with conventional therapy. HSCT may be defined as a therapy in which defective haematopoietic stem cells are replaced with normal bone marrow stem cells after chemotherapy and/or radiotherapy.[1,2] HSCT may be indicated in acute myeloblastic leukaemia, myelodysplastic syndrome, lymphoma, acute lymphoblastic leukaemia, chronic granulocytic leukaemia, multiple myeloma, neuroblastoma, aplastic anaemia, thalassaemia, sickle cell anaemia, Fanconi's anaemia, severe combined immunodeficiency disorder (SCID).[3] There are three varieties of SCT: autologous SCT, allogenic SCT and umblical cord blood SCT. Auto stem cell transplantation (auto SCT) is commonly used for Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma and less commonly for acute myeloblastic leukaemia. The stem cell source in auto SCT can be either mobilized peripheral blood stem cells or bone marrow.[4] CMH Dhaka is a well reputed tertiary Hospital for Bangladesh Armed Forces as well as for nation.CMH Dhaka has the pride that it has started its journey in auto stem cell transplantation procedure since 2016 and it has performed bone marrow transplantation in a multiple myeloma patient as the first case.

Case Report

A 47-year-old male got admitted into CMH, Dhaka with the complaints of low back pain and generalized weakness for one month. On physical examination, he was found mildly anaemic and there was bony tenderness. The laboratory investigations showed Hb-10.5gm/dL, ESR-95mm in 1st hour, serum creatinine

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Received: November 22, 2017 **Accepted:** February 28, 2018

was 1.4mg/dL. Bone marrow examination revealed 85% atypical plasma cells. Serum protein electrophoresis showed monoclonal gammopathy and immunofixation electrophoresis (IFE) showed IgG Kappa monoclonal band. Serum ²2 micro globulin was 5.1 mg/dL. X-ray of thoracic spine showed fracture of 3rd and 4th thoracic vertebrae. Therefore, the patient was finally diagnosed as a case of multiple myeloma. He was treated with capsule thalidomide and tablet dexamethasone for six cycles, followed by injection bortezomib and tablet dexamethasone for another two cycles. After that he was evaluated thoroughly and found that his Hb was 10.7gm/dL, ESR-50 mm in 1st hour, serum creatinine was 1.5 mg/dL. Bone marrow aspiration showed 11 % plasma cells. Serum IFE showed a faint IgG Kappa band, serum ²2 micro globulin was 4.8 mg/dL.Immunoglobulin profile shows total IgA was <0.29gm/L, IgG 8.18 gm/L, IgM 0.18gm/L; Kappa: Lambda ratio was 78.79. So, the patient was in partial remission.

Then the patient was treated with injection bortezomib, capsule linalidomide and tablet dexamethasone for four cycles followed by capsule linalidomide (25 mg) daily for two months. After that he was evaluated clinically and by laboratory investigations. His Hb was 10.3 gm/dL, ESR 25 mm in 1st hour, serum creatinine was 1.4 mg/dL. Serum protein electrophoresis showed nonspecific finding and serum immunofixation electrophoresis identified a polyclonal band as IgG kappa and lambda. Bone marrow study showed 2% plasma cells, serum ²2 micro globulin was 3.0 mg/dL. Serum free light chain ratio was 2.66. So, the patient was finally labeled as multiple myeloma (kappa light chain) in very good partial remission (VGPR).

The patient was planned for autologous stem cell transplantation. He was counseled properly about the transplant procedure, the complications that might happened during transplant procedure and outcome of the transplantation in his particular case. After taking proper consent from patient, the patient was given mobilizing agent to mobilize stem cells from bone marrow to peripheral blood. The mobilizing agents, granulocyte colony stimulating factor (G-CSF) was given subcutaneously in a dose of 10 mg/Kg daily for 4 days and injection plerixafor (0.24 mg/Kg) on day four. When CD34 level (stem cell marker) in peripheral blood is >20 cells/¼l of blood, stem cells were collected from peripheral blood by apheresis. The CD34 cell dose (total) was 3.5 $X10^6$ cells/Kg and mononuclear cell (MNC) dose was 13.5$X10^8$ cells/Kg. The procedure was uneventful.

Then the patient was given conditioning regimen consisting of high dose melphelan (200 mg/m^2) I/V at day 1. The whole stem cells product was infused to the patient (day 0) 12 hours after injection melphelan and the infusion process were uneventful. The G-CSF was started on day +5 after stem cell infusion. Neutrophil engraftment (absolute neutrophil count >500/mm^3) was achieved on day +11. Platelet engraftment (unsupported platelet count) was achieved on day +12. The G-CSF was stopped after day +14, when patient achieved total leucocyte count >10000/mm^3. He received one unit of packed red blood cells and one unit of single donor platelet (SDP) transfusion during the peri-transplant procedure.

The patient developed loose motion and mucositis in gut during peri-transplant procedure, which was managed conservatively by metronidazole, hydration and total parenteral nutrition (TPN) infusion. He also developed several spikes of fever from day +6, so he was treated with injection piperacilline-tazobactam combination, injection teicoplanin, injection meropenem. After that the fever subsided. He was given antifungal and anti viral drugs for prophylaxis, as per protocol .He also developed mucositis (grade-1) on day +8, which was managed conservatively.Mucositis resolved gradually with recovering of the neutrophil counts.

Finally he was discharged from CMH on day +24 of stem cell transplantation. His laboratory investigations at the time of discharge was Hb 9.1 gm/dL, platelet count 22000/mm^3, WBC 4200/cmm, differential count: neutrophils 72%, lymphocytes 24%, monocytes 5%, eosinophils 01%, serum bilirubin 0.2mg/dL, alanine aminotransferase 44u/L, serum creatinine-1.3 mg/dL and serum electrolytes were normal. At the time of discharge, the patient was asymptomatic, clinically stable with a normal performance status and on a normal diet. He was advised to report on BMT centre, CMH Dhaka 2 weeks after for re-assessment. He was on regular follow up at 2 weeks interval for last 3 months and he is now clinically stable and asymptomatic.

Discussion

This is the first case report of autologous stem cell transplantation (Auto SCT) in CMH Dhaka. The case was multiple myeloma in VGPR. Multiple myeloma is a B-cell malignancy characterized by the accumulation of terminally differentiated clonal plasma cells in the bone marrow, the production of a monoclonal immunoglobulin detectable in the serum and /or urine and the presence of lytic bone lesions.[5] Currently newly diagnosed multiple myeloma patients are treated by four to six cycles of induction chemotherapy followed by autologous SCT,if the patients are eligible for stem cell transplantation.[6] In the broadest form, HSCT consist of three parts: a conditioning phase,stem cell infusion and for allogenic procedure, a method for prophylaxis of graft versus host disease (GVHD).[7] Stem cells are usually collected from peripheral blood by leukapheresis in auto SCT.[8]

After induction chemotherapy, when patient remain in complete remission, stem cells are mobilized from bone marrow to peripheral blood by use of the mobilizing agents. The commonly used mobilizing agents are G-CSF, which are used in a dose of 5mg/kg subcutaneously, twice in a day for 4 to 6 days.[9] Injection plerixafor can also be used for enhancing mobilization of stem cells. Plerixafor is a chemokine receptor-4(CXCR-4) antagonist that disrupts the interaction between stromal cell derived factor-1 (SDF-1) and CXCR-4, thereby enhancing the stem cell mobilization effect of G-CSF. The recommended dose is 0.24 mg/kg body weight per day 6 to 11 hours prior to apheresis initiation following four days of G-CSF pre-treatment.[10]Then the stem cells level in peripheral blood is counted by flow cytometry machine.Marker of stem cells is CD34;when CD34 level in peripheral blood is greater than 20 cells/¼l of blood, then stem cells are collected from peripheral blood by apheresis and cryo preserved. Then the patient receives high dose chemotherapy and possibly also radiotherapy. This treatment is referred to as the conditioning regimen. The conditioning regimen is given to kill any remaining myeloma cells and to make space within the bone marrow for the newly transplanted cells to grow.[11] High dose melphelan is usually used as standard conditioning regimen in multiple myeloma in a dose of 200 mg/m^2 (single dose).[12] High dose therapy (usually melphelan 200 mg/m^2),followed by autologous SCT prolonged overall survival compared with standard dose therapy in prospective randomized trials conducted by French (IFM)and English (MRC) groups and has provided evidence for more than 10 years survivorship in at least a subsets of patients.[13]

After 12-24 hrs of conditioning regimen (with high dose melphelan), the stored stems are re-infused into patients circulation through a catheter, like a blood transfusion. After infusion, the stem cells can find their way to the bone marrow (micro-environment) and replace the stem cells killed off by high dose therapy and then produce new, healthy immune cells. This process is called engraftment. It usually can take approximately 7-14 days for the new cells to begin to grow and produce functioning cells to support the patient's body. Engraftment is defined as an absolute neutrophil count greater than 500 cells/¼l and unsupported platelet count more than 20×10^9/L on three consecutive days with no subsequent decline.[14] Common side effects of high dose therapy and Auto SCT include nausea, vomiting, diarrhea, mucositis (involving oral cavities, digestive tract) and fatigue.[15] In addition, because of high dose therapy attacks healthy cells as well as cancerous cells, there is an increased risk of infection due to severe neutropenia. Other possible, but infrequent side effect may include organ damage, particularly to the lungs, liver and kidneys.

In conclusion, the conditioning regimen with high dose melphelan followed by auto SCT now-a-days remain the more effective therapeutic option in patients with newly diagnosed multiple myeloma and have improved both progressive free and overall survival. Advances have been made in autologous stem cell transplantation, novel anti multiple myeloma agents and immunotherapy for multiple myeloma. Combining these different strategies is to achieve a synergistic response in an exciting possibility. It is not unreasonable to hope that over the next decade, multiple myeloma will become a manageable chronic disease for many and perhaps a curable disease for some.

Conflict of interest: Nothing to declare.

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