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Stem Cell Therapy in Multiple Myeloma

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Abstract

Multiple myeloma is a haematogical malignancy caused by abnormality of plasma cells characterized by (a) hypercalcemia, (b) renal insufficiency or failure, (c)bone pain and abnormal bone radiographs, (d) anemia and (e) a monoclonal protein in urine or serum or both. It begins in the form known as monoclonal gammopathy of undetermined significance(MGUS) and progresses to asymptomatic myeloma and then lastly to symptomatic myeloma. The three main domains in the understanding of pathophysiology are cytokines and cell signaling, bone Marrow Microenvironment and cell Cycle. Bifunctional alkylating agents like Melphalan and cyclophosphamide are considered as standard therapy for multiple myeloma. Patients who are chosen for stem cell transplantation can be treated with Lenalidomide, an immunomodulatory agent and an aminosustituted variant of Thalidomide. It is given along with dexamethasone. In stem cell therapy, the patients receive stem cells intravenously similar to the blood transfusion and this phase takes 1-5 hours. After entering the blood stream through a process called engraftment, the stem cell produce new WBCs, RBCs and platelets. The immune rejection of donor cells by the host immune system is a major drawback of transplantation. Stem cell therapy in multiple myeloma is very effective and should be opted as one among the best for both older patients and patients younger than 65 years.

Index terms— autologous stem cell transplantation; multiple myeloma; stem cell therapy; transplant related mortality.

1 I. Introduction

ultiple myeloma is a haematogical malignancy caused by abnormality of plasma cells. It is made distinctive by mainly five features which includes (a) hypercalcemia, (b) renal insufficiency or failure, (c)bone pain and abnormal bone radiographs, (d) anemia and (e) a monoclonal protein in urine or serum or both. **??** It also leads to osteolytic bone lesions and immunodeficiency. **??** Multiple myeloma is incurable and it effects mainly elderly persons. **??** It comes out to be the second most common hematologic neoplastic abnormality and it depicts 10% of all hematological cancers and 1% of all other malignancies. **??** It diminishes the gross health related quality of life in patients especially pertaining to physical functioning. **??** Clinical manifestations of multiple myeloma includes bone pain, lytic bone lesions, thrombocytopenia, pathologic bone fracture, bleeding, fatigue, haste and easy bruis ability, recurrent infections, spinal cord compression, hyperviscosity and hypogamaglobulinemia. **??**, **??**, **??** Hyperviscosity which is one of the major presentation here is Author ? ? : Department of Pharmacy Practice, College of Pharmaceutical Sciences, Government Medical College, Calicut, Kerala, India, 673008. e-mail: roshnapp22@gmail.com caused by the presence of monoclonal Ig in the sera. **??** Etiological factors of multiple myeloma include radiation exposures, workplace exposures, lifestyle factors, precursor medical conditions etc. 1 Prolongation of the survival is the major treatment goal for multiple myeloma. The development and introduction of chemotherapy conjunct with the autologous stem cell transplantation (ASCT) elevated the life

endurance rate further. Allogenic stem cell transplantation is the only existing curative treatment because of the antitumor immunity mediated by donor lymphocytes. **??** II.

2 Path Physiology

In multiple myeloma, the bone healing is diminished because of the decreased osteoblastic activity and increased osteoclastic activity. The bone embedded growth factors enhances progression of tumor as bone is resorbed. It begins in the form known as monoclonal gammopathy of undetermined significance(MGUS) and progresses to asymptomatic myeloma and then lastly to symptomatic myeloma which results into osteolytic lesions and bone marrow infiltration. **??** Several intracellular and intercellular signaling stream, including RANK/RANKL/OPG, Notch, Wnt, and chemokines and interleukins are associated in the complex pathophysiological process. 8 A single molecular inadequacy cannot be accounted for explaining the pathogenesis of multiple myeloma. Defects of four main domains have been identified which are abnormalities of apoptotic mechanisms, signaling pathways, bone marrow micro environment and cell cycle. 1 a) Cytokines and cell signaling Interleukin (IL)-6 is one of the most significant survival and proliferation factors in myeloma is which is produced by the bone marrow stromal cellsmacrophages, fibroblasts, osteoclasts, osteoblasts and monocytes. In almost cases myeloma cells and their cell lines are capable of producing IL-6 and its receptor, IL-6 receptor results in the stimulation of autocrine system. Messages are transmitted by IL-6 intracellularly through the signal-transducing protein gp130. This activates 2 pathways: the Ras-MAP kinase pathway (Hallek et al. 1998) and the JAK-STAT pathway. Through the latter pathway (JAK-2 and STAT3), the antiapoptotic proteins Mcl-1 and Bcl-XL are up-regulated and through the former pathway, transcription factors such as ELK-1, AP-1, and NF-IL-6 are up-regulated. 1 Notch signaling pathway resulting from four transmembrane receptors (Notch 1-4) is actively involved in multiple myeloma M -induced osteoclastogenesis by the production of osteoclastogenic factor RANKL by multiple myeloma cells. 8

3 b) Bone Marrow Microenvironment

A synergistic relationship exists within the myeloma cells and the cells comprised in the bone marrow microenvironment which includes fibroblasts, osteoblasts, and osteoclasts. The IL-6 produced in large amount will result in the production of IL-1?, VEGF, and macrophage inflammatory protein-1? (MIP-1?) and activate osteoclasts. A cell adhesion molecule, CD56 (N-CAM) is expressed in most plasma cells and accounts for myeloma homing and cell adhesion to the marrow. Cell-cell liaison between marrow stromal cells and myeloma cells happens by the help of VCAM-1 and ? 4 ? 1 -integrin and increases the osteoclaststimulating action. 1 Enhanced expression of receptor activator of nuclear factor-kappa B and low level of its decoy receptor by osteoblast causes bone resorption and results in bone lesions. 7

4 c) Cell Cycle

There are four regulatory signals mechanizing in the escalation of myeloma cells which are enhanced expression of cyclin D1, hypermethylation of the cyclindependent kinase (CDK) pathway, the ras oncogene mutations, and loss of p53 (Hallek et al. 1998). Majority of the data suggests hypermethylation of p15 or p16 is associated with disease progression. K-and N-ras mutations have been described in 25% to 100% of newly diagnosed patients and in one third of the patients causes cyclin D1 expression. **??** Cytogenetics reveal the patients with hyperdiploid multiple myeloma tend to have better forecast than hypodiploid patients. 7

5 III. Conventional Treatment

The main treatment goal is to improve the quality of life of the patients and to prolong the duration of non progressive disease. 9 Patients should be refrained from the treatment until they reach the final stage that is symptomatic multiple myeloma. The diagnosis can be done on the bais of manifestation of monoclonal protein in serum or urine and an affirmation of end-organ damagewhich can be identified by assessing abnormalities like hypercalcemia, renal insufficiency, anemia, bone lesions with pathologic fractures. Patients with active multiple myeloma can be classified in two which is high-risk or standard-risk ailment and then subject to the appropriate treatment. Bifunctional alkylating agents like Melphalan and cyclophosphamide are considered as standard therapy for multiple myeloma. 1 Patients who are chosen for stem cell transplantation can be treated with Lenalidomide, an immunomodulatory agent and an aminosustituted variant of Thalidomide. It is given along with dexamethasone. 10 The next option for induction chemotherapy is Bortezomib which is a proteasome inhibitor Velcade. It is combined along with dexamethasone cyclophosphamide or Adriamycin to improve efficacy. 11 Patients are evaluated for response after every treatment cycle. At the time of relapse the autologous stem cell transplantation eligible patients who did not received it with first phase of the treatment should be treated with high dose chemotherapy and then only it should be followed by autologous stem cell transplantation. 12

6 IV. Stem Cell Therapy

Stem cells are produced from bone marrow which contains several types of cells like t-cells, B-cells, interferons etc. Mechanism underlying in working of tcells is that they adhere to cancerous cell surface bind to the cell membrane and effectively damage the cancerous cells through the process like apoptosis and phagocytosis.

Hence stem cell therapy becomes crucial in future. 16 The patients receive stem cells intravenously similar to the blood transfusion and this phase takes 1-5 hours. After entering the blood stream through a process called engraftment, the stem cell produces new WBCs, RBCs and platelets. After transplantation engraftment occurs within 2-4 weeks. 18 The procedure of stem cell transplantation includes conditioning, infusion and monitoring the patient postinfusion. Antibiotics are given orally as a prophylaxis and the main antibiotics given are penicillin and levofloxacin. Acyclovir and fluconazole are also given for prophylaxis. The breakthrough fever should be managed and maintained >38ºC, with vancomycin or cefepime. The standard drug is melphalan (200mg/m 2) for competent patients and melphalan (140mg/m 2) if the patient is weak or the serum creatinine is ?2.0mg/Dl. 22

7 a) Auotologous transplant

The treatment with high dose melphalan was complicated by prolonged myelosuppression, and bone marrow support was subsequently indulged. High-dose chemotherapy followed by autologous stem cell transplantation improves the overall response rate and survival. Autologous bone marrow transplantation is replaced by autologous peripheral blood stem cell transplantation because in latter, there is more rapidengraftment and less contamination with myeloma cells. The complete number of CD34+ cells/kg is the most practical and reliable method for identifying the adequacy in collection of stem cell. The mortality rate from autologous stem cell transplantation is currently less than 5%. 1 and it issafer and effective method for elderly and make the patients fit even in the time of novel agents. 14

8 b) Transplantation timing

The transplantation timing is very important to be considered in both salvage and consolidation therapy. **??** The best timing to undertake Autologous stem cell transplantation is when the patients are having least residual disease and in patients who have not received numerous preliminary chemotherapy treatments. 21 The main advantage of early transplantation is that it circumvents inconvenience and the high cost of chemotherapeutic agents. 1

9 c) Donor lymphocyte infusions

After the administration of donor peripheral blood mononuclear cells for relapse after allogeneic transplantation,a graft-versus-myeloma reaction has been found. 1 Donor lymphocyte infusions were used as treatment for multiple myeloma relapse and also as for relapse in multiple myeloma patients who are currently abiding allogenic hematopoietic stem cell transplantation. This strategy induces response rates of 40-52%.Its side effects include bone marrow aplasia, infectious complications, immune escape of plasmocytoma in extramedullary tissues. 17

10 d) Non myeloablative Allogeneic Transplant

Allografts have been implicated with lowsurvival despite a significant decrease in the relapse rate and graft-versus-myeloma effects, in nearly all comparisons because of high peritransplantation mortality, late complications of chronic graft-versus-host disease (GVHD), and late infections. Promising approaches include non myeloablative conditioning ("mini") regimens for chosen patients with myeloma, either at the

11 Drawbacks

Donating involves the use of anesthesia and risk underlying it and in some individuals it causes feeling of stiffness or sore in the part from where bone marrow is taken. Different individuals take variable time to get back to the full strength after the donation. Graftversus host disease can develop sometimes and it involves formation of skin rash, abdominal pain, hepatitis, jaundice etc. 18 Sometimesthe immune rejection of donor cells by the host immune system is also a major drawback of transplantation. 25 VI.

12 Conclusion

Stem cell therapy in multiple myeloma is very effective and should be opted as one among the best for both older patients and patients younger than 65 years. Novel drugs can be indulged along with stem cell transplantation in order to improve overall outcome including health related quality of life. 19 the cellular heterogenecity both functional and phenotypical in multiple if rapidly emerging and this can be more promising in the future. 20 In future purging will become a routine practice in order to make sure that no contamination takes place. The culturing of stem cells and their expansion in the laboratories can lead to an increase in the number of transplantations and subsequently increase the rate of cure in patients. 24 References Références Referencias i. Aspect of Purging Tumor purging is the process of treating the residual ailments in the patients after they have been undergone with chemotherapy or transplantation. Immunocy to chemical assays and molecular techniques are used in detection and characterisation of tumor contamination. 23 Derivatives of cyclophosphamide or monoclonal antibodies can be used to purging with marrow and it has found to be reliable method. It has a disadvantage that it causes long lasting my elosuppression following after the transplantation. **??** ii. Allogenic transplant Allogenic transplantation abolishes the defect of contamination with the tumor cell in the stem

cells that is inevitable with autologous stem cell transplantation. In those patients with a molecular complete remission, the relapse rate was only 16% in the allogeneic group and 41% in the autologous group. This shows that molecular complete responses are related with a longer relapsefree survival. 1 Reduced intensity allogenic transplantation strategy has been employed to reduce the transplant related mortality (TRM) while retaining the graft versus myeloma effects. 13 Survival status is very low in this case, so it is not deemed as a criterion for both newly diagnosed and relapsed multiple myeloma patients. 15 [1]

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