Demiroglu Science University Florence Nightingale Journal of Transplantation 2021;6(1-2):52-65
doi: 10.5606/dsufnjt.2021.026

Bone marrow transplantation use on treatment solid tumors

İlayda Üzümcü[1], Oytun Erbaş[2]

[1]*Institute of Experimental Medicine, Gebze-Kocaeli, Turkey*
[2]*Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey*

ABSTRACT

Bone marrow transplantation (BMT) has been applied in the treatment of solid tumors such as breast cancer, brain tumor, multiple myeloma, testis/germ cell tumor, neuroblastoma, and lymphoma. High dose chemotherapy, radiation therapy, and preparative regimen is also used with BMT to improve disease-free survival, morbidity, mortality, remission, complications, relapse, and response to treatment. Post-transplant infection, toxicity, graft-versus-host disease, recurrence, and secondary malignant tumors can occur. Therefore, the patient should be monitored for an extended duration, and intensive medical care should be applied to the patient. The treatment methods used during the transplant are constantly adapted to prevent these side effects. The success of the transplant depends on the transplant type, patient age, and disease status. Bone marrow transplantation is becoming increasingly common since its efficacy has been proven in many diseases and has curative/mitigating potential. This review aimed to define BMT and solid tumors and discuss related studies.

Keywords: Bone marrow transplantation, cancer, solid tumors, stem cell.

The second leading cause of death worldwide is cancer. Solid tumors are abnormal tissues that can be malignant or benign, and they do not contain fluid and inflammation. Bone marrow transplantation (BMT) has also been added to the methods used in its treatment for years. Allogeneic and autologous BMT started in 1957 when the transplant antigens and immune responses against transplants were unknown.[1] Its use is currently under investigation in many types of diseases, including solid tumors. Autologous BMT has been widely used in breast cancer, neuroblastoma, and germ cell and brain tumors. There are also studies comparing transplant types for lymphoma and multiple myeloma. Although BMT has potential as a treatment method, it also has many complications. However, BMT shows more promise than traditional treatments in curing solid tumors.

SOLID TUMORS AND ITS TYPES

According to the National Cancer Institute (NCI), solid tumors are abnormal and heterotypic tissue masses that do not contain inflammation or cysts. These tumors that multiply and form a mass can be benign or malignant. They are named according to the type of cell that makes up the tumor. Leukemia generally does not cause solid tumors.[2] Localized solid tumors are divided into three as sarcomas, carcinoma, and lymphomas.[3] Sarcomas arise from supporting or connective tissues such as muscle, cartilage, fat, and bone (for example, rhabdomyosarcoma, liposarcoma, and Ewing sarcoma). Carcinomas originate from epithelial or glandular cells, or the tissues that make up the internal organs (for example, lung cancer and colorectal cancer). Lymphomas are lymphoid organ cancers, such as spleen, thymus,

Correspondence: İlayda Üzümcü. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.
e-mail: ilaydauzumcuu@gmail.com

Cite this article as:
Üzümcü İ, Erbaş O. Bone marrow transplantation use on treatment solid tumors. D J Tx Sci 2021;6(1-2):52-65.

and lymph nodes, that store and produce cells in the immune system (for example, Hodgkin's and non-Hodgkin's lymphoma).

According to the statistics of the American Cancer Society (ACS), in 2020, the most frequent localized solid malignant tumors are breast, lung, prostate, and colon tumors, melanoma, Non-Hodgkin's lymphoma, leukemia, and liver cancer, respectively. Bone, ovary, pancreas, brain, head, and neck cancers are among other examples.[4]

STEM CELLS

A stem cell is a cell that can differentiate into any cell type of organism, has the ability to renew itself, and can be found in both adult cells and embryonic cells.[5] Stem cells are classified into five categories according to their differentiation capacity: totipotent, pluripotent, multipotent, oligopotent, and unipotent.[6]

Totipotent stem cells have the highest differentiation capacity, that is, they can differentiate into any cell type. These cells are the zygote cells formed by the fertilization of an egg with a sperm. Four days after zygote formation, the inner cell mass of the blastocyst becomes pluripotent.[7]

While pluripotent stem cells can form three germ layer cells, they are stem cells that cannot form extraembryonic tissues such as the placenta and have limited differentiation capacity. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are pluripotent stem cells. In studies on ESCs, positive results were obtained in defects related to the retinal pigment[8] in addition to spinal cord injury and age-related macular degeneration treatment.[9] However, there are ethical restrictions in medical use of ESCs.[10] Nevertheless, iPSCs are a type of stem cell created artificially by reprogramming somatic cells and a promising alternative for regenerative medicine.[11]

Multipotent stem cells can differentiate not only into certain cell lines but also into unrelated cell types. Hematopoietic stem cells (HSCs), which can transform into all cell types found in the blood, can be given as an example.[12] Hematopoietic stem cells are an alternative treatment method in hematological malignancy, immune deficiencies, hemoglobinopathies, congenital metabolic diseases, and bone marrow (BM) failure. In addition, BMT is also called hematopoietic stem cell transplant.[13] Mesenchymal stem cells (MSCs), another multipotent stem cell type, can differentiate into mesodermal and non-mesodermal cell lines. The umbilical cord, BM, adipose tissue, and endometrial polyps are sources of MSCs.[14] Mesenchymal stem cells also have immunomodulatory effects such as inhibition of the function and proliferation of B cells, T cells, and natural killer cells. Therefore, they do not lead to tissue rejection in allogeneic transplants.[15] It has been used in clinical trials to treat cardiovascular diseases, cartilage lesions, bone defects, and spinal cord injuries. When transplanted, it does not create teratoma unlike ESCs.[16]

Oligopotent stem cells differ into only a few cell types. For example, myeloid stem cells can differentiate into white blood cells but not red blood cells. Tissue-resident stem cells are another example.

Unipotent stem cells are cells with the least differentiation capacity, able to form only one cell type. They can be a promising method for therapeutic use with their ability to be repeatedly divisible.[17]

In addition to ESCs, HSCs, MSCs, and iPSCs, there are also cancer stem cells. Cancer stem cells can regenerate to create new cells by cell division and can differentiate into various cell types. There are several approaches to how cancer stem cells are formed.[18]

A STEM CELL NICHE: BONE MARROW

Niche is the microenvironment that regulates the function of the stem cell and protects it, and the BM is a niche. Hematopoietic stem cells are a heterogeneous population because they contain many cell types such as MSCs, osteoblasts, adipocytes, and endothelial and neuronal cells.[19] Hematopoietic stem cells are abundant in the BM. Therefore, the BM, a place where various blood cells are produced (hematopoiesis), also regulates the mobilization, homing, self-renewal, and differentiation of stem cells. It also helps to alter the activities of HSCs for their varying

physiological needs.[20] In addition to the BM being the microenvironment of the progenitor and stem cells, it also contains some mature immune cells and is a hypoxic environment.[21] For example, B cells develop from HSCs in the BM and then migrate to peripheral lymphoid organs for further maturation.[22] The vascular niches of the BM are divided into two as endosteal and short-lived HSCs. These two niches are regulated by extravascular coagulation.[23]

The endosteal niche is rich in osteoblasts. The task of osteoblasts is to produce thrombopoietin and osteopontin, which deactivates HSCs. Osteopontin helps HSCs to combine with integrin a9β1 by preventing senescence.[24] Thus, it interacts with the purpose of promoting extravascular coagulation and reshaping bone, shaping the bone marrow matrix environment during mobilization, and homeostasis. Hematopoietic stem cells here are at resting state. It provides the HSC reserve with its self-renewal and asymmetric split features. It can proliferate rapidly with a stimulus from the environment and differentiate into damaged or aging blood cells.[25]

However, HSCs can also be found in the vascular niche rich in sinusoids. When hematopoiesis is needed or under stress, arterioles and sinusoidal vessels facilitate HSC mobilization in more permeable vascular niches. Thus, HSCs can be differentiated from their own niche.[26]

Hematopoietic stem cells are also found in the peripheral blood (PB), fetal liver, and umbilical cord. Hematopoietic stem cells are easier to collect from the PB, and the procedure is less invasive; however, the amount of HSCs in the blood is low. Therefore, granulocyte is treated with a stimulating factor and its number is increased.[20] In addition, stem cells collected from the PB showed a higher incidence of chronic graft-versus-host disease (GVHD) in some studies than those collected from the BM. This is because the tumor and graft effect are associated with T lymphocytes, and the number of T lymphocytes in the PB is higher than in the BM.[27] Nevertheless, studies have shown that when PB is used, the risk of relapse is lower, and thus disease-free survival rate is higher.[28]

Graft-versus-host disease is a complication that occurs when the immune system cells coming from the donor are identified as foreign by the recipient due to the human leukocyte antigen (HLA) difference in allogeneic transplants. There are acute and chronic forms of GVHD. Acute GVHD occurs 10 to 90 days after the transplant, can last about 25 days, and affects one-third to half of the recipients. Chronic GVHD can begin with a rash anywhere from 90 to 600 days after transplantation. As a result, most patients remain vulnerable to infections for months or years after treatment. Drugs that suppress the immune system, such as corticosteroids, are the primary treatment method.[29]

Hematopoietic stem cells kept in the G0 phase in the cord blood (CB) are more primitive than HSCs in the BM and PB. They are also characterized by a longer telomere length compared to others.[30] Consequently, it can be said that they have a higher proliferation capacity. In addition, the low amount of T lymphocytes in the CB poses a low risk for GVHD. The disadvantages of the CB are that the amount of stem cells is limited because it is collected from only one patient, the enrichment takes time, and it can cause infections during enrichment.[31] Moreover, the status of the donor and recipient is also considered in the selection of stem cells. Therefore, the HSC is the most preferred stem cell in the treatment of solid tumors.

BONE MARROW TRANSPLANTATION

Bone marrow transplantation is the infusion of the BM from a suitable donor into a conditioned recipient. The first successful human BMT in history was performed in identical twins with acute leukemia by E. Donall Thomas in 1957.[32] The first successful allogeneic BMT was performed by Robert Good in 1968 in a baby with immune deficiency syndrome using an HLA-compatible sibling donor.[1]

Donor selection

In allogeneic BMTs, donors with matching histocompatible antigens must be found. The major histocompatibility complex, called the HLA in humans, is located at the 6p21.3 position. The patient receives one class I antigen (A, B, C loci) and Class II antigens (DQ, DP, and DR) from each parent. The HLA-matched sibling donor will have the lowest GHVD rate, as they receive the same HLA haplotype from each parent. The probability of finding an HLA-compatible sibling is calculated

with the formula 1-(0.75)n (n=number of siblings). Since there will be an HLA difference in unrelated but matched donors, the GVHD rate will be higher than that of sibling donors. After determining the donor, the donor and recipient are evaluated in terms of appropriate organ function and infectious agents.[33]

Preparative regimen

The conditioning regimen can be done by a monoclonal antibody, chemotherapy, or radiation to the whole body. The preparative regimen includes reduced intensity conditioning, non-myeloablative and myeloablative conditioning. The method is chosen depending on the previous exposure to radiation, the disease to be treated, and the existing comorbidities. This step is necessary for reasons such as creating an immunosuppressor effect, creating a gap in the BM, eradicating the disease, and providing engraftment.[34]

As the HLA incompatibility increases, the need for immunosuppression is greater. It is mostly applied in allogeneic transplants. The risk of rejection increases if the patient has received too much blood transfusion before BMT or if T cell depletion is present in the transplant. However, the possibility of engraftment increases in cases with a high T cell dose and high stem cell count.

The purpose of creating a space in the BM is to empty the niche and make room for new stem cells. However, a study demonstrated that the engraftment rate of patients who were given myeloablative preparative regimens was lower than that of patients who were applied low intensity preparative regimen.[35] As a result of the eradication of the disease, the disease is taken under control for an extended period. It is particularly important in malignant solid tumors. Engraftment is created to ensure the attachment of the transplanted BM stem cells. Whether the transplant is successful or not is revealed at this stage.

The agents used in the preparative regimen include total body irradiation, busulfan/cyclophosphamide, busulfan, and anti-thymocyte globulin. For example, the BEAM preparative regimen, which contains carmustine, etoposide, cytarabine, and melphalan, is mostly used in the treatment of Hodgkin's and non-Hodgkin's lymphoma where autologous BMT is preferred. Nevertheless, allogeneic transplants with low-intensity preparative regimens used to reduce toxicity have also been found to be successful.[36]

Stem cell reinfusion

The BM is collected from the posterior iliac crest under general anesthesia or epidural. In cases where more BM is required, the sternum or anterior iliac crest can be used. After the BM is collected with large-hole needles and heparinized syringes, it is preserved in the culture medium. It can be infused directly after harvest, but it can also be stored at 4°C for 24 h so that it does not lose its vitality. In addition, the BM must be drained after being harvested to remove clots and unwanted small particles before intravenous transfusion into the recipient. If the recipient has minor or major ABO incompatibilities and high anti-B or anti-A antibody titers, plasma and red blood cells may be depleted.[37] Afterward, the stem cells collected are administered to the patient. In one study, administration of high-dose therapy with growth factors at this stage increased the efficacy of some chemotherapeutic drugs in solid tumors by 10 times.[38]

Transplantation: Autologous or allogeneic

Bone marrow transplantation can be allogeneic or autologous. Autologous transplant is a transplant performed using the patient's own stem cells. Allogeneic transplantation is the use of stem cells from a suitable donor. The choice of transplantation method depends on the age of the recipient, the availability of a compatible donor, the type of malignancy, the stage of the tumor, and the risk of GVHD. Since the patient's own cells are used in autologous transplantation, it is not necessary to have an HLA-compatible donor. There is no risk of GVHD, and thus there is no need for immunosuppressive therapy to prevent GVHD. It is also unlikely to cause complications after transplantation, and it takes less time to restore the immune system. In most studies, the death rate due to treatment is less than 5%, and elderly patients can tolerate the treatment better than others.[39] However, it does have some disadvantages. Most malignant solid tumors have a higher recurrence rate in autologous transplantation than in allogeneic transplants, but this is offset by lower mortality. Patients receiving their first treatment may develop secondary

acute leukemia and myelodysplasia.[40] Although the risk of recurrence of the disease is lower in allogeneic transplantation, the immune system is slower to restructure, and thus the patient is open to infections. Supportive care, control of infections, and nonablative preparative regimens should be developed specifically to treat patients over the age of 65. To prevent graft rejection in allogeneic BMT, patients are generally subjected to a preparative regimen with cyclophosphamide. Finally, allogeneic transplantation has generally been used in the treatment of myelodysplastic syndromes and leukemias. In addition, successful results have been obtained from solid tumors to certain types of non-Hodgkin's lymphoma and patients with recurrence of Hodgkin's lymphoma. Autologous transplantation is preferred in the treatment of myeloma, lymphoma, and other solid tumors.[41]

Neutropenic

At this stage, which lasts for two to four weeks, the immune system of the patient is inhibited. In other words, in this immunosuppression period, the patient is at risk for infections such as viral hemorrhagic cystic, fungal infections, and herpes zoster. Prophylactic antibiotics are used to prevent these infections. Allogeneic recipients are at risk of infection during the entire period of treatment, while autologous transplant recipients are at risk only during pre- and post-vaccination periods.[42]

Engraftment

Engraftment is the sequence of events in which the administered stem cells are first taken up by the BM vasculature, and then they migrate to the transendothelial extravascular space. Regulation of HSC differentiation and proliferation takes place through adhesion molecules, growth factors, and some signaling pathways. Thus, the stem cell settles in a suitable niche environment, and the BM regains its immunological function. Studies have shown that E-selectin, P-selectin, chemokine (CXC) receptor type 4 (CXCR4), stromal cell-derived factor-1 (SDF-1), and very late antigen (VLA)-4 are essential in directing HSCs to the BM. Therefore the stem cells must first interact with P-and E-selectin expressed from the BM vascular cells for orientation.[43] Integrin-dependent stem cells, such as lymphocyte function-associated antigen 1 and VLA-4,5, and their vascular ligands, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, adhere to the vessel wall. Afterward, they extravasate the hematopoietic department. These steps take place with the support of SDF-1. In addition, it has been observed that the regulation of the actions of VLA-4,5 and FMS-like tyrosine kinase 3 (FLT3) ligands is important in the proliferation of HSCs.[44] Furthermore, it has been shown that the transmembrane isoform of the stem cell factor plays an important role in the emplacement of HSCs in their niche. In the study of Möhle et al.,[45] it has been proven that other non-peptide mediators such as the cysteinyl-leukotriene receptor 1 (stimulate HSC migration. In another study, the effects of proteoglycans such as dermatan sulfate and heparin on SDF-1 were revealed, and it was found that this played a role in HSC homing.[46] It has also been demonstrated that hyaluronic acid can be synthesized by HSCs, and this molecule is also important for HSC migration and engraftment. However, the CXCR4/SDF-1 pathway must be inactivated for the mobilization (leaving the BM and entering the bloodstream) of stem cells.[47]

Complications after BM transplant

After engraftment, donor cells restructure the recipient's immune system. This process is faster in autologous transplants, slower in allogeneic transplants, and even slower in transplants that require immunosuppression due to the development of GVHD. In the early stage of stem cell infusion, neutropenic patients are at risk of fungal infection, bacterial infection, respiratory viruses, while after engraftment, allogeneic recipients are at risk of the reactivation of herpes and cytomegaloviruses.[48] In addition, side effects that may occur immediately after BMT include mouth-throat pain, nausea, vomiting, bleeding, lung problems such as interstitial pneumonia, and hepatic veno-occlusive disease. Depending on the patient's general health, pre-transplant chemotherapy or radiation therapy, post-transplant problems, and age of the patient, infertility, organ damage, hormone changes, cataracts, secondary cancers, and lymphoproliferative may develop after an allogeneic transplant.

In a study, secondary solid tumors with late complications were observed in five of 387 patients 2 to 13 years after BMT.[49] This means that 9% of solid tumors can occur in 15 years. These tumors can be thyroid gland carcinoma, endometrial carcinoma, small intestine sarcoma, ovarian carcinoma, tibial osteosarcoma, and cervical carcinoma. At the last follow-up, 213 of 387 patients (55%) were alive.[49] In addition, the probability of survival in 15 years was 38%. In the study, 128 patients developed a second solid tumor five years after the transplant, 72 patients after 10 years, and 125 patients after 15 years.

SOLID TUMOR EXPERIENCES

Although some solid tumors respond positively to chemotherapy, they are not fully treated with it only. Therefore, allogeneic and autologous BMT has been focused on as an alternative treatment method. Transplantation studies for some tumors are mentioned below.

Breast cancer

In a high-dose autologous BMT study, the event-free survival rate improved in women in the high-dose group at the three-year follow-up after treatment, while no significant evidence was seen in the other dose groups.[50] There was no significant difference between the groups during the follow-up period. In addition, treatment-related deaths and adverse events were observed in the high-dose group in later periods.

In another study, eight males received stem cells from the blood, three from the BM, and two received hematopoietic support.[51] All patients recovered hematopoietically, and no toxicity was observed due to the regimen. In a mean follow-up period of 23 months (6-50 months), seven of 10 individuals were disease-free. In one out of three treated males, a progressive and recurrent disease occurred in the 6^{th}, 7^{th}, and 16^{th} months after the transplant. Similar results were obtained with the autotransplant treatment of females.

In a third study, in which the preparative regimen was combination chemotherapy or autologous BMT containing high doses of a single agent, before transplantation, 37 females were in first partial or complete remission, eight were in second partial or complete remission, five were in untreated relapse, and four had stable disease, while 14 had progressive disease.[52] After the treatment, 29 (43%) females were in complete remission and 12 (18%) females were disease-free for 2 to 73 months and onward. Those in initial or partial remission before transplantation had an 86% higher response rate, 62% higher complete response, and 27% were disease-free. There were nine (13%) deaths due to treatment. Recurrences occurred within 22 months after transplantation and 47 (69%) patients died. Relapses occurred in these patients. As a result, a disease-free survival rate of 27% was observed in complete or partial remission.

In a fourth study, autologous BMT was performed in 27 of 172 patients who received radiation, single or multiple drug chemotherapy, or both.[53] Response rate to treatment was found to be 58%. Response rates were higher than studies involving previously untreated patients or alkylating agents. All of these suggest that BM autotransplants and high-dose therapy can lead to remission in patients with advanced breast cancer that do not give positive results with conventional therapy.

In a fifth study, autologous BMT was performed with alkylating agents (high-dose cyclophosphamide, cisplatin, carmustine, and melphalan).[54] In this high-dose therapy, women with Stage 4 breast cancer had a higher rate of remission than standard-dose chemotherapy, and the overall and disease-free survival rates did not increase. However, faster and more complete responses were produced than with conventional chemotherapy.

Lymphoma

In a study, 133 patients with 133 non-Hodgkin's and 20 patients with Hodgkin's lymphoma were treated with total body irradiation, cyclophosphamide, etoposide, and infusion.[55] It was observed that patients treated with peripheral blood stem cell transplantation (PBSCT) or autologous BMT had less transfusion, faster vaccination, and shorter hospital stay than patients who received BMT alone. No statistically significant difference was found between the two groups regarding recurrence, survival, event-free survival, and death for reasons other than recurrence.

In another study, 100 individuals with malignant lymphoma were treated with BMT and chemoradiotherapy.[56] Twenty-eight of the patients survived, and the probability of disease-free survival for five years after transplant was 22%. The primary reason for the failure of the treatment is the actuarial probability of 60% of the disease recurrence. The recurrence rate in patients treated with allogeneic BMT was higher than in patients treated with autologous BMT. However, non-relapse mortality risk was higher in patients receiving autologous transplantation. The type of disease (moderate/high-grade lymphoma or Hodgkin's lymphoma) or the mode of administration of the BM did not significantly affect the likelihood of relapse and disease-free survival. Nonetheless, it was thought that this method shows promise for the long-term survival of young patients. The most successful results with BMT were obtained in patients who had not received prior chest radiotherapy and were administered at second remission or early relapse.

Another study used myeloablative therapy and BMT for 127 Hodgkin's lymphoma patients who were resistant to treatment or relapsed.[57] The five-year probability of survival, event-free survival, relapse, and relapse-related death was 21%, 18%, 65%, and 49%, respectively. It was observed that autologous BMT recipients have a lower recurrence rate but no difference in survival and event-free survival.

Neuroblastoma

In a study, 56 children older than one year with Stage 4 neuroblastoma entered a protocol that included radiation therapy, chemotherapy, and autologous BMT.[58] Immunomagnetic procedure was applied in 32 of 35 cases and chemical procedure was applied in three of these cases. Forty-five of the 56 patients were evaluated, and it was determined that 14 patients were in complete remission and 23 were in remission. No significant progression-free survival difference was found between these remission groups. The recurrence rate was 32%, the progressive disease rate was 19%, and the acute toxic death rate was 19%. These results are higher than traditional chemotherapy results.

In another study performed on children with Stage 4 neuroblastoma, the effect of autologous BMT and high dose chemotherapy was investigated.[59] Eight of 30 patients survived. There patients died one month after treatment. The other 19 patients had a mean survival of 15 months. Two-year disease-free survival was 26.6% during a mean follow-up period of 118.5 (range, 29-150) months.

In a third study, 12 children with advanced neuroblastoma, selected according to their response to chemotherapy with cyclophosphamide/adriamycin/vincristine, received consolidation therapy with high-dose melphalan.[60] After the subsequent autologous BMT, seven patients had a decrease in tumor diameter and six patients had a complete response. In three of these six patients, the disease was not observed at the 18th, 33rd, and 35th months after the treatment. Although there was no death due to treatment in 12 patients who received autograft, the survival of all patients (23 months) was longer than the survival of 28 children who received conventional chemotherapy (14 months). However, there was no statistically significant difference.

Multiple myeloma

Multiple myeloma is a malignant and yet incurable disease that affects plasma cells. Median survival for symptomatic patients is about one year. Therefore, alternative treatment methods have been used. For example, in a study, some of the 200 myeloma patients under the age of 65 who were not previously treated received high-dose therapy followed by autologous BMT, and some also received conventional chemotherapy.[61] The five-year probability of survival of the patients who received traditional chemotherapy was 10%, while five-year probability of survival of patients who received high doses and BMT was 28%. The response rate of these patients was 81% (22% complete response and 16% very good partial response), while the response rate of those treated with traditional chemotherapy was 57% (5% complete response, 9% very good partial response). Treatment-related mortality was similar in both groups. In summary, autologous stem cell transplantation with high dose chemotherapy prolongs the median overall survival for another five years.

In another study, 20 patients underwent a conditioning regimen with busulfan and cyclophosphamide, followed by allogeneic BMT.[62] Two patients died from recurrent or progressive multiple myeloma, and 10 patients died from complications related to the transplant. Eight patients survived and seven (35%) patients were in remission for 190 to 1,271 days after transplantation. Most importantly, the disease-free survival of the patients was improved.

It is correct to apply allogeneic BMT to patients under 50 years of age since transplant-associated mortality is expected to be 30% at maximum.[63] The three-year survival probability is 40% and the complete remission rate is 70% for allogeneic BMT, and mortality is less than 10% in autologous BMT.[63] Complete remission rate is higher than 30% and three-year overall survival is higher than 80% for autologous BMT.[63] However, these results can be achieved in cases where the tumor has a small volume and standard treatment doses are still effective.[63]

Glioma

Glioma, a type of brain tumor, can be treated with autologous BMT. Since patients are generally younger, glioma does not usually metastasize to the BM, and BM suppression is a dose-limiting factor in nitrosourea chemotherapy and can suppress BM glioma cells.[64]

In a study, high-dose chemotherapy followed by autologous BMT treatment was administered to eight patients (four females and four males).[65] After transplantation, patients recovered from the inhibition of the BM. Platelets and granulocytes in the blood started to increase 10 to 14 days after transplantation and normalized after three weeks. Autologous BMT has allowed high-dose chemotherapy. However, this treatment should be done considering the blood-brain barrier.

In another study, three patients with malignant glioma tumors were treated with high-dose chemotherapy and autologous BMT.[66] Platelets and granulocytes increased 10 days after transplant and normalized within the next three weeks. Tumors were reduced by 89% on the computed tomography scan performed six days later. It was concluded that autologous BMT enables the application of high-dose chemotherapy.

In a third study, 11 patients with recurrent glioma were given high doses of 1-3-bis(2-chloroethyl)-1-nitrosourea, and a subsequent autologous BMT was performed to prevent myelosuppression.[67] Thrombocyte and polymorphonuclear leukocytes were reconstituted within 30 days after treatment in eight patients receiving 600 and 1200 mg/m^2 medication. During the 19-month follow-up period, three patients stabilized, four patients recovered, and three died. The median survival time was seven months. Mass effect decreased in eight patients.

In a fourth study, none of the seven patients who underwent high-dose lomustine and autologous BMT gave a definite response to the treatment.[68] Blood toxicity occurred early and severely in three patients. Although the severity and duration of blood toxicity were altered by BM transfusion, the treatment was not successful.

Testis or germ cell tumor

Germ cell tumor is the most common solid organ tumor that can be treated and is generally seen in men between the ages of 15 and 35. Standard dose chemotherapy is effective in the treatment of this type of cancer; however, treatment with traditional regimens fails in 30 to 40% of patients. In a study, high-dose chemotherapy was administered to 40 patients with etoposide, carboplatin, and ifosfamide, and then autologous BMT was performed.[69] Twenty-six patients (65%) responded to the treatment; 12 of these patients (30%) gave a complete response, while the remaining 14 (35%) partially responded to treatment. Of the 12 patients who gave a complete response, five relapsed without evidence of germ cell cancer 27.5 months after the transplant and one died of acute leukemia resulting from the treatment. Six (15%) patients, three of whom were cisplatin-refractory, were in complete remission after 24 months of follow-up. In summary, this treatment resulted in a two-year disease-free survival rate of approximately 20%.

Autologous BMT was performed with high-dose carboplatin and etoposide treatment in patients with refractory or recurrent germ cell tumors in another study.[70] A response was achieved in 17 (45%) of 38 patients, eight of whom were in partial remission and nine were in complete

remission. Five of these patients remained in complete remission during the one-year follow-up. Five (13%) patients died due to the primary hematological toxicity complication.

In another study in which autologous BMT was performed with high-dose carboplatin and etoposide treatment, seven (21%) of 33 patients died due to treatment. These deaths were experienced at the lowest level of the granulocyte, and five of them were associated with sepsis. Fourteen (44%) of 32 patients could be evaluated for response, and eight of them reached complete remission. Three patients remained disease free for more than a year, and eight had a complete remission response.[71]

In a third study, seven out of 11 patients responded to the treatment of autologous BMT following etoposide and cyclophosphamide treatment (two complete responses of >66 and 46 weeks, five partial responses with a 12-week response time).[72] Therefore, it was concluded that this method is not successful for testicular nonseminomatous germ cell tumors.

OTHER TREATMENT STRATEGIES

Other treatment strategies include surgery, tumor excision, chemotherapy, and radiation therapy. These strategies cannot be applied in patients with concomitant diseases such as diabetes, chronic obstructive pulmonary disease, and cardiovascular diseases. Radiation therapy is the method used in the presence of inoperable localized solid tumors, and it has several forms. However, lung damage, suppression of BM function, induction of secondary tumors, such as thyroid cancer and leukemia, can lead to conditions such as myelopathy and intestinal necrosis. Another method is chemotherapy; it interferes with cell division and damages DNA by inducing apoptosis. In addition, it prevents the use of nucleotides necessary for DNA synthesis by replicating tumor cells, interfering with mitosis. It also has some limitations: tumors may be resistant to the drug or may avoid the drug, causing toxicity by damaging normal tissues. Combinations of these three methods can also be used. Antihormonal therapy is used in cancers that are dependent on hormones. Antiestrogens are recommended for breast cancer, antiandrogenic drugs for metastatic prostate cancer, and corticosteroids for lymphoma.[73] Although positive results are obtained from these methods in the treatment of some solid tumors, they are not effective for many. For this reason, stronger and superior results are obtained by combining with BMT.

Standard chemotherapy and other methods are not sufficient in the treatment of some solid tumors. In this context, stem cells have been used as an alternative method. Hematopoietic stem cells are promising not only in cancer treatment but also in diseases with metabolic and immune deficiency. Stem cells can be found in the PB, CB, BM, embryo, and fetal liver.

Although the bone marrow is a heterogeneous niche, it is divided into two microenvironments, vascular and endosteal. Before the BM is transplanted, the method of transplantation, be it allogeneic or autologous, should be decided. Transplant steps are then followed. When it comes to the post-transplant period, some early and late complications have been observed, such as vomiting, bleeding, infection, relapse, and secondary solid tumors.

Alkylating agents, high-dose chemotherapy, and radiation therapy are also applied in addition to BMT. For example, in breast cancer, autologous BMT is usually performed with some alkylating agents or with high-dose chemotherapy. This treatment is more successful than standard dose chemotherapy in terms of patient response.

No difference was found between PBSCT and BMT in lymphoma treatment. In studies comparing autologous and allogeneic BMT, no significant difference was observed between the two administration methods in terms of survival and event-free survival. In general, the disease-free survival rate is between 21 and 22%, and the mortality rate is in the range of 49 to 72%.

There are studies with both autologous and allogeneic BMT in multiple myeloma. Patients receiving autologous BMT have a higher probability of survival than patients receiving conventional chemotherapy, and more patients respond to the treatment. Survival is extended by five years in these patients. Autologous BMT has a 81% response and 28% disease-free survival rate, while allogeneic BMT has a 60% death and 35% remission rate. As a result, higher mortality and

lower remission and survival rates are detected in allogeneic BMT than autologous BMT.

Autologous BMT has been used in neuroblastoma and no significant results have been found with conventional chemotherapy. Generally, the mortality rate is between 19 and 36%, and approximately 50% of the patients respond to the treatment.

The rate of testicular cancer patients in complete remission after autologous BMT is 15 to 30%, and mortality is between 8 and 21%. Forty-four to 65% of the patients respond to the treatment. In one study, the recurrence rate was found as high as 42%. The studies discussed show that autologous BMT therapy is generally used in the treatment of solid tumors.

Bone marrow transplantation has given a chance to treat many solid tumors. However, how the BM is infused is crucial. Since there is a difference in HLA in allogeneic transplants, the risk of developing GVHD is high. An extra treatment should be applied for immunosuppression to prevent this issue, which negatively affects the patient since the patient is vulnerable to infections due to immunosuppression. However, the method of marrow delivery should be chosen according to some criteria, such as the type and stage of the tumor. However, allogeneic transplantation has yielded positive results in some types of lymphoma and leukemia. The reasons for using BM instead of PB is that it contains more stem cells than PB, and the risk of GVHD formation is low because it contains less T lymphocytes. However, PB is more easily obtained, and less recurrence is seen when used. The reason for using BM instead of CB is that the number of stem cells in the CB is limited, the vaccination takes an extended duration, and the patient is susceptible to infections. Nevertheless, with CB having higher reproductive capacity, the risk of GVHD is also low. For these reasons, PBSCT and cord blood stem cell transplantation can also be tried in solid tumors. Since BMT also creates some complications, it should be performed with comprehensive consideration.

The studies conducted demonstrate that BMT is applied as a supportive treatment in addition to high-dose chemotherapy or radiation methods since BMT allows high-dose drugs and chemotherapies to be performed. For example, in breast cancer, alkylating agents, drug chemotherapy, and combination chemotherapy have also been used in addition to autologous BMT. A study on breast cancer found no difference between PBSCT and BMT. This may be due to the ingredients included in the regimen. Although the results obtained are superior to standard-dose chemotherapy, it is necessary to determine whether patients with complete response are fully treated and whether the conventional dose is higher than that of chemotherapy. Therefore, patients should be followed for an extended period.

Recurrence is an important problem in studies conducted in lymphoma, and an HLA-compatible sibling donor may be preferred since the recurrence rate is lower in autologous BMT. However, there is no difference in disease-free survival. In addition, BMT can provide successful results in the treatment of lymphoma when the tumor chemosensitivity is high, the disease burden is low (for example, when it is performed early after relapse), or when applied to young patients with advanced malignant lymphoma after the first combination chemotherapy.

The treatment of multiple myeloma with autologous BMT showed higher response and event-free survival rates. Since the treatment was administered in tolerable doses, the results were improved, which is a promising development. Nonetheless, the results should be investigated in the advanced stages of the disease and in a more aggressive treatment method. Autologous BMT can be preferred since it is more advantageous than allogene in terms of mortality, complete remission, and overall survival. Although autologous BMTs performed following high-dose chemotherapy in neuroblastoma are more tolerable and safer than conventional chemotherapy, there are deficiencies in the effect of patients at an advanced stage. Some of the studies on testicular/germ cell tumors have shown it to be curative for resistant/recurrent tumors and ineffective in others. The reason for this may be the difference in the substances used in high-dose treatments with autologous BMT. Commonly used substances are carboplatin, etoposide, cyclophosphamide, cisplatin, carmustine, melphalan, and ifosfamide.

Autologous BMT has generally been used in the treatment of solid tumors. The reasons

for this may be the lower risk of GVHD, complications, and mortality and rapid immune system restructuring. Many preclinical studies, clinical trials, and research protocols have been published. Some have encouraged the development of new treatment methods with better results than conventional dose chemotherapy. However, there are still some obstacles and risks: the incidence of GVHD, the long duration of prospective studies, the low number of cases, and the absence of BMT, resulting in advanced stages of some tumors.

For solid tumors, the severity of GVHD can be reduced or prevented to further improve BMT results. Studies on the inhibition of T cell subclasses in the BM of the donor are a good development for this purpose. In addition, the question of how to accelerate the chimerism of donor T cells without increasing the risk of GVHD can be answered. Lower relapse-free death rates or lower toxicity can be achieved by introducing reduced-intensity conditioning transplants. By creating disease heterogeneity, BMT can be performed in suitable solid tumors. By conducting studies with tumors in advanced stages, it can be learned at which stage BMT is more effective. Complications after BMT can be improved by making the transplant procedure reliable. Autografts can be cleaned *ex vivo*, and techniques can be developed to eliminate the underlying malignancy. High-dose therapy in the preparative regimen eliminates this malignancy but creates the risk of non-relapse death. Therefore, different preparative regimens can be tried.

In conclusion, BMT, which has been used as a supportive method in addition to the standard treatment methods for years, has provided more successful results in terms of mortality, morbidity, and disease-free survival compared to traditional therapies. Consequently, BMT transplants are becoming more common day by day. In the future, it is hoped that the problems described above will be resolved, and BMT will become a safer and more accessible method of treatment.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Simpson E, Dazzi F. Bone marrow transplantation 1957-2019. Front Immunol 2019;10:1246.
2. NCI Dictionary of Cancer Terms [Internet]. National Cancer Institute. 2021. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/solid-tumor [Accessed: January 23, 2021]
3. Zhuge Y, Cheung MC, Yang R, Eldick D, Koniaris LG, Sola JE. Pediatric intestinal foregut and small bowel solid tumors: A review of 105 cases. J Surg Res 2009;156:95-102.
4. American Cancer Society [Internet]. Cancer.org. 2021. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf [Accessed: January 23, 2021]
5. Kolios G, Moodley Y. Introduction to stem cells and regenerative medicine. Respiration 2013;85:3-10.
6. Smith A. A glossary for stem-cell biology. Nature 2006;441:1060.
7. Rossant J. Stem cells from the Mammalian blastocyst. Stem Cells 2001;19:477-82.
8. Schwartz SD, Regillo CD, Lam BL, Eliott D, Rosenfeld PJ, Gregori NZ, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: Follow-up of two open-label phase 1/2 studies. Lancet 2015;385:509-16.
9. Schwartz SD, Hubschman JP, Heilwell G, Franco-Cardenas V, Pan CK, Ostrick RM, et al. Embryonic stem cell trials for macular degeneration: A preliminary report. Lancet 2012;379:713-20.
10. Young RA. Control of the embryonic stem cell state. Cell 2011;144:940-54.
11. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663-76.
12. Ratajczak MZ, Zuba-Surma E, Kucia M, Poniewierska A, Suszynska M, Ratajczak J. Pluripotent and multipotent stem cells in adult tissues. Adv Med Sci 2012;57:1-17.
13. Yeşilipek MA. Hematopoetic stem cell transplantation in children. Turk Pediatri Ars 2014;49:91-8.
14. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. Cell Transplant 2011;20:5-14.
15. Beggs KJ, Lyubimov A, Borneman JN, Bartholomew A, Moseley A, Dodds R, et al. Immunologic consequences of multiple, high-dose administration of allogeneic mesenchymal stem cells to baboons. Cell Transplant 2006;15:711-21.

16. Hilfiker A, Kasper C, Hass R, Haverich A. Mesenchymal stem cells and progenitor cells in connective tissue engineering and regenerative medicine: Is there a future for transplantation? Langenbecks Arch Surg 2011;396:489-97.
17. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: Past, present, and future. Stem Cell Res Ther 2019;10:68.
18. Kreso A, Dick JE. Evolution of the cancer stem cell model. Cell Stem Cell 2014;14:275-91.
19. Uchida N, Fleming WH, Alpern EJ, Weissman IL. Heterogeneity of hematopoietic stem cells. Curr Opin Immunol 1993;5:177-84.
20. Yu VW, Scadden DT. Hematopoietic stem cell and its bone marrow niche. Curr Top Dev Biol 2016;118:21-44.
21. Zhang CC, Sadek HA. Hypoxia and metabolic properties of hematopoietic stem cells. Antioxid Redox Signal 2014;20:1891-901.
22. Wei Q, Frenette PS. Niches for hematopoietic stem cells and their progeny. Immunity 2018;48:632-48.
23. Zhang J, Niu C, Ye L, Huang H, He X, Tong WG, et al. Identification of the haematopoietic stem cell niche and control of the niche size. Nature 2003;425:836-41.
24. Guidi N, Sacma M, Ständker L, Soller K, Marka G, Eiwen K, et al. Osteopontin attenuates aging-associated phenotypes of hematopoietic stem cells. EMBO J 2017;36:840-53.
25. Kollet O, Dar A, Lapidot T. The multiple roles of osteoclasts in host defense: Bone remodeling and hematopoietic stem cell mobilization. Annu Rev Immunol 2007;25:51-69.
26. Itkin T, Gur-Cohen S, Spencer JA, Schajnovitz A, Ramasamy SK, Kusumbe AP, et al. Distinct bone marrow blood vessels differentially regulate haematopoiesis. Nature 2016;532:323-8.
27. Couban S, Simpson DR, Barnett MJ, Bredeson C, Hubesch L, Howson-Jan K, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Blood 2002;100:1525-31.
28. Cheuk DK. Optimal stem cell source for allogeneic stem cell transplantation for hematological malignancies. World J Transplant 2013;3:99-112.
29. Szyska M, Na IK. Bone marrow GvHD after allogeneic hematopoietic stem cell transplantation. Front Immunol 2016;7:118.
30. Hao S, Chen C, Cheng T. Cell cycle regulation of hematopoietic stem or progenitor cells. Int J Hematol 2016;103:487-97.
31. Smogorzewska EM, Barsky LW, Crooks GM, Wienberg KI. Purification of hematopoietic stem cells from human bone marrow and umbilical cord blood. Cent Eur J Immunol 1997;22:232-9.
32. Henig I, Zuckerman T. Hematopoietic stem cell transplantation-50 years of evolution and future perspectives. Rambam Maimonides Med J 2014;5:e0028.
33. Hellmann DM, Radojska S, Fimmers R, Gathof BS. Probability of success in the search for a related bone marrow donor in Cologne, Germany using HLA-A, -B and -DRB1 haplotype frequencies. HLA 2018;92:154-9.
34. Sorror ML, Sandmaier BM, Storer BE, Maris MB, Baron F, Maloney DG, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol 2007;25:4246-54.
35. Luger SM, Ringdén O, Zhang MJ, Pérez WS, Bishop MR, Bornhauser M, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. Bone Marrow Transplant 2012;47:203-11.
36. Ljungman P, Bregni M, Brune M, Cornelissen J, de Witte T, Dini G, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: Current practice in Europe 2009. Bone Marrow Transplant 2010;45:219-34.
37. Braine HG, Sensenbrenner LL, Wright SK, Tutschka PJ, Saral R, Santos GW. Bone marrow transplantation with major ABO blood group incompatibility using erythrocyte depletion of marrow prior to infusion. Blood 1982;60:420-5.
38. de Vries EG, de Graaf H, Boonstra A, van der Graaf WT, Mulder NH. High-dose chemotherapy with stem cell reinfusion and growth factor support for solid tumors. Stem Cells 1995;13:597-606.
39. Kusnierz-Glaz CR, Schlegel PG, Wong RM, Schriber JR, Chao NJ, Amylon MD, et al. Influence of age on the outcome of 500 autologous bone marrow transplant procedures for hematologic malignancies. J Clin Oncol 1997;15:18-25.
40. Friedberg JW, Neuberg D, Stone RM, Alyea E, Jallow H, LaCasce A, et al. Outcome in patients with myelodysplastic syndrome after autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol 1999;17:3128-35.
41. Champlin R, Khouri I, Komblau S, Molidrem J, Giralt S. Reinventing bone marrow transplantation. Nonmyeloablative preparative regimens and induction of graft-vs-malignancy effect. Oncology (Williston Park) 1999;13:621-8.
42. Cutler C, Giri S, Jeyapalan S, Paniagua D, Viswanathan A, Antin JH. Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: A meta-analysis. J Clin Oncol 2001;19:3685-91.
43. Xia L, McDaniel JM, Yago T, Doeden A, McEver RP. Surface fucosylation of human cord blood cells augments binding to P-selectin and E-selectin and enhances engraftment in bone marrow. Blood 2004;104:3091-6.

44. Shibayama H, Anzai N, Ritchie A, Zhang S, Mantel C, Broxmeyer HE. Interleukin-3 and Flt3-ligand induce adhesion of Baf3/Flt3 precursor B-lymphoid cells to fibronectin via activation of VLA-4 and VLA-5. Cell Immunol 1998;187:27-33.
45. Mohle R, Boehmler AM, Denzlinger C, Kanz L. Nonpeptide mediators in the hematopoietic microenvironment. Ann N Y Acad Sci 2003;996:61-6.
46. Netelenbos T, van den Born J, Kessler FL, Zweegman S, Merle PA, van Oostveen JW, et al. Proteoglycans on bone marrow endothelial cells bind and present SDF-1 towards hematopoietic progenitor cells. Leukemia 2003;17:175-84.
47. Rettig MP, Ansstas G, DiPersio JF. Mobilization of hematopoietic stem and progenitor cells using inhibitors of CXCR4 and VLA-4. Leukemia 2012;26:34-53.
48. Helen E. Heslop. Chapter 103-overview and choice of donor of hematopoietic stem cell transplantation. In: Hoffman R, Benz EJ, Silberstein LE, Weitz JI, et al, editors. Hematology. 7th ed. Elsevier; 2018. p. 1591-5.
49. Favre-Schmuziger G, Hofer S, Passweg J, Tichelli A, Hoffmann T, Speck B, et al. Treatment of solid tumors following allogeneic bone marrow transplantation. Bone Marrow Transplant 2000;25:895-8.
50. Farquhar C, Marjoribanks J, Lethaby A, Azhar M. High-dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. Cochrane Database Syst Rev 2016;2016:CD003139.
51. McCarthy P, Hurd D, Rowlings P, Crump M, Gale R, Lazarus H, et al. Autotransplants in men with breast cancer. ABMTR Breast Cancer Working Committee. Autologous Blood and Marrow Transplant Registry. Bone Marrow Transplant 1999;24:365-8.
52. Saez RA, Selby GB, Slease RB, Epstein RB, Mandanas RA, Confer DL. Autologous bone marrow transplantation for metastatic breast cancer. J Okla State Med Assoc 1994;87:405-10.
53. Antman K, Gale RP. Advanced breast cancer: High-dose chemotherapy and bone marrow autotransplants. Ann Intern Med 1988;108:570-4.
54. Peters WP, Shpall EJ, Jones RB, Olsen GA, Bast RC, Gockerman JP, et al. High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. J Clin Oncol 1988;6:1368-76.
55. Brunvand MW, Bensinger WI, Soll E, Weaver CH, Rowley SD, Appelbaum FR, et al. High-dose fractionated total-body irradiation, etoposide and cyclophosphamide for treatment of malignant lymphoma: comparison of autologous bone marrow and peripheral blood stem cells. Bone Marrow Transplant 1996;18:131-41.
56. Appelbaum FR, Sullivan KM, Buckner CD, Clift RA, Deeg HJ, Fefer A, et al. Treatment of malignant lymphoma in 100 patients with chemotherapy, total body irradiation, and marrow transplantation. J Clin Oncol 1987;5:1340-7.
57. Anderson JE, Litzow MR, Appelbaum FR, Schoch G, Fisher LD, Buckner CD, et al. Allogeneic, syngeneic, and autologous marrow transplantation for Hodgkin's disease: The 21-year Seattle experience. J Clin Oncol 1993;11:2342-50.
58. Philip T, Bernard JL, Zucker JM, Pinkerton R, Lutz P, Bordigoni P, et al. High-dose chemoradiotherapy with bone marrow transplantation as consolidation treatment in neuroblastoma: An unselected group of stage IV patients over 1 year of age. J Clin Oncol 1987;5:266-71.
59. de Kraker J, Boon F, van Leeuwen EF, Voûte PA. Autologous bone marrow transplantation in the treatment of children with neuroblastoma; 30 patients in 10 years. Ned Tijdschr Geneeskd 1994;138:2097-100.
60. Pritchard J, McElwain TJ, Graham-Pole J. High-dose melphalan with autologous marrow for treatment of advanced neuroblastoma. Br J Cancer 1982;45:86-94.
61. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med 1996;335:91-7.
62. Bensinger WI, Buckner CD, Clift RA, Petersen FB, Bianco JA, Singer JW, et al. Phase I study of busulfan and cyclophosphamide in preparation for allogeneic marrow transplant for patients with multiple myeloma. J Clin Oncol 1992;10:1492-7.
63. Barlogie B, Gahrton G. Bone marrow transplantation in multiple myeloma. Bone Marrow Transplant 1991;7:71-9.
64. Fujiwara T, Yoshioka J, Ohmoto T. Treatment of malignant glioma with high dose intra-arterial ACNU and autologous bone marrow transplantation--case report. Neurol Med Chir (Tokyo) 1991;31:654-7.
65. Nomura K, Watanabe T, Nakamura O, Ohira M, Shibui S, Takakura K, et al. Intensive chemotherapy with autologous bone marrow rescue for recurrent malignant gliomas. Neurosurg Rev 1984;7:13-22.
66. Shibui S, Watanabe T, Miki Y, Nomura K, Ohira M. High-dose chemotherapy with autologous bone marrow transplantation for malignant brain tumors. No Shinkei Geka 1983;11:723-9.
67. Hochberg FH, Parker LM, Takvorian T, Canellos GP, Zervas NT. High-dose BCNU with autologous bone marrow rescue for recurrent glioblastoma multiforme. J Neurosurg 1981;54:455-60.
68. Hildebrand J, Badjou R, Collard-Ronge E, Delforge A, Malarme M, Spiro T, et al. Treatment of brain giomas with high dose of CCNU and autologous bone marrow transplantation. Biomedicine 1980;32:71-5.
69. Broun ER, Nichols CR, Kneebone P, Williams SD, Loehrer PJ, Einhorn LH, et al. Long-term outcome of patients with relapsed and refractory germ cell

tumors treated with high-dose chemotherapy and autologous bone marrow rescue. Ann Intern Med 1992;117:124-8.
70. Nichols CR, Andersen J, Lazarus HM, Fisher H, Greer J, Stadtmauer EA, et al. High-dose carboplatin and etoposide with autologous bone marrow transplantation in refractory germ cell cancer: An Eastern Cooperative Oncology Group protocol. J Clin Oncol 1992;10:558-63.
71. Nichols CR, Tricot G, Williams SD, van Besien K, Loehrer PJ, Roth BJ, et al. Dose-intensive chemotherapy in refractory germ cell cancer--a phase I/II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation. J Clin Oncol 1989;7:932-9.
72. Mulder PO, de Vries EG, Koops HS, Splinter T, Maas A, van der Geest S, et al. Chemotherapy with maximally tolerable doses of VP 16-213 and cyclophosphamide followed by autologous bone marrow transplantation for the treatment of relapsed or refractory germ cell tumors. Eur J Cancer Clin Oncol 1988;24:675-9.
73. Gavhane YN, Shete AS, Bhagat AK, Shinde VR, Bhong KK, Khairnar GA, et al. Solid tumors: Facts, challenges and solutions. International Journal of Pharma Sciences and Research (IJPSR) 2011;2:1-12.