Cancer Chemother Pharmacol (2001) 48 (Suppl 1): S79–S84
DOI 10.1007/s002800100311

**Shimon Slavin · Reuven Or · Memet Aker
Michael Y. Shapira · Soumya Panigrahi
Argiris Symeonidis · Gabriel Cividalli
Arnon Nagler**

Nonmyeloablative stem cell transplantation for the treatment of cancer and life-threatening nonmalignant disorders: past accomplishments and future goals

Abstract Allogeneic bone marrow transplantation (BMT) or blood stem cell transplantation represents an important therapeutic tool for the treatment of otherwise incurable malignant and nonmalignant diseases. Until recently, autologous and allogeneic BMT or mobilized blood stem cell transplantation was used primarily to replace a malignant, genetically abnormal, or deficient immunohematopoietic compartment, and therefore highly toxic myeloablative regimens were considered mandatory for eradication of all undesirable host-derived hematopoietic elements. Our preclinical and ongoing clinical studies have indicated that more effective eradication of host immunohematopoietic system cells could be achieved by adoptive allogeneic cell therapy with donor lymphocyte infusion following BMT. Thus eradication of blood cancer cells, especially in patients with chronic myelogenous leukemia and less frequently in patients with other hematologic malignancies, can frequently be achieved despite complete resistance of such tumor cells to the maximum tolerated doses of chemoradiotherapy. Our cumulative experience suggests that graft vs leukemia (GVL) effects might be a useful tool for eradication of otherwise resistant tumor cells of host origin. Based on the cumulative clinical experience and experimental data in animal models of human diseases, it appears that induction of host vs graft tolerance as the first step may allow durable engraftment of immunocompetent donor lymphocytes, which may be used for induction of effective biologic warfare against host-type immunohematopoietic cells that need to be replaced, whether they are malignant, genetically abnormal, or self-reactive. Based on this rationale, we speculate that the therapeutic benefit of BMT may be increased by using safer conditioning as part of the transplantation procedure, with the goal of inducing host vs graft tolerance to enable subsequent induction of GVL, possibly graft vs tumor, or even graft vs autoimmunity effects, rather than attempting to eliminate host cells with hazardous myeloablative chemoradiotherapy. Our hypothesis suggests that effective BMT procedures might be accomplished without lethal conditioning of the host, using new, well-tolerated nonmyeloablative regimens, possibly minimizing immediate and late side effects related to myeloablative procedures. Recent clinical data suggest that effective BMT procedures may be accomplished with nonmyeloablative stem cell transplantation (NST) regimens, with no major toxicity. Thus new NST approaches may make BMT procedures safer for a spectrum of clinical indications in children and elderly individuals without lower or upper age limits, while minimizing procedure-related toxicity and mortality. Our cumulative data suggest that high-dose chemotherapy and radiation therapy may be successively replaced by more effective alloreactive donor lymphocytes, thus setting the stage for innovative therapeutic procedures with safer and more effective treatment of patients requiring BMT.

Keywords Bone marrow transplantation · Blood stem cell transplantation · Nonmyeloablative stem cell transplantation · Minitransplant · Allogeneic cell therapy · Donor lymphocyte infusion · Hematologic malignancies · Nonmalignant hematologic diseases

This work was presented at the 16th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "Hematologic malignancies: pioneers in cancer therapy across the century from mustard to molecular targets and beyond," 27–28 October 2000, Nagoya, Japan.

S. Slavin (✉) · R. Or · M.Y. Shapira · S. Panigrahi
A. Symeonidis · A. Nagler
Department of Bone Marrow Transplantation
and Cancer Immunotherapy,
Danny Cunniff Leukemia Research Laboratory,
Hadassah University Hospital, Jerusalem 91120, Israel
E-mail: slavin@cc.huji.ac.il
Tel.: +972-2-6777270
Fax: +972-2-6422731

M. Aker · G. Cividalli
Department of Pediatrics, Hadassah University Hospital,
Jerusalem, Israel

Introduction

The list of diseases treatable by allogeneic bone marrow transplantation (BMT) or blood stem cell transplantation (SCT) is growing and includes those caused by deficiency of marrow stem cell products (such as aplastic anemia and severe combined immunodeficiency), genetically abnormal stem cells (hemoglobinopathy, such as beta thalassemia major, osteopetrosis, chronic granulomatous disease, Wiskott-Aldrich syndrome), enzyme deficiency diseases (such as Gaucher disease and Hurler syndrome), or malignant hematologic disorders. Acute leukemia, one of the most common malignancies in children, is highly lethal but responds initially to conventional doses of chemotherapy. Unfortunately, leukemia cells frequently become resistant to subsequent chemotherapy and this is the main cause of disease recurrence and mortality in children and the elderly.

Experience suggests that administration of more aggressive chemoradiotherapy is likely to cause increased toxicity with minimal or no improvement in disease-free survival rates. Whereas a certain proportion of patients with relapsing or primary resistant leukemia or other hematologic malignancies not expected to be cured with conventional chemotherapy may respond to more intensive, myeloablative chemoradiotherapy followed by rescue with autologous bone marrow or blood stem cells, the large majority are likely to relapse. In contrast, bone marrow or blood stem cells obtained from a genetically matched family member or matched unrelated donor (MUD) are likely to be more effective due to graft vs leukemia (GVL) effects mediated by alloreactive donor lymphocytes, usually but not exclusively in association with anti-host responses causing graft vs host disease (GVHD) [5, 12, 24]. Myeloablative conditioning with the goal of eliminating or minimizing the number of resistant tumor cells or otherwise abnormal host cells followed by SCT was considered until recently the most effective treatment available for patients with hematologic cancer not expected to be cured by other therapy. A similar approach was considered the treatment of choice for numerous nonmalignant diseases curable by SCT.

The use of myeloablative conditioning was considered mandatory until recently, since it was believed that it was essential both for elimination of undesirable host hematopoietic cells (malignant, genetically abnormal) or immune system cells (self-reactive T cells or B cells, or plasma cells) in autoimmune diseases or plasma cell dyscrasias, as well as for establishing marrow space (a "niche") for donor stem cells. Starting in the early 1970s we documented that durable engraftment of donor stem cells could be achieved following immunosuppressive but nonmyeloablative conditioning [13, 15]. The resulting state of mixed chimerism could be reversed by increasing the number of donor bone marrow cells or by increasing the intensity of the conditioning [16]. Experimental data confirmed durable engraftment after immunosuppression rather than myeloablation and subsequent infusion with a large inoculum of donor stem cells including immunocompetent lymphocytes.

Adoptive allogeneic cell therapy with donor lymphocyte infusion for nonmyeloablative SCT

Starting in early 1987, we introduced a new treatment modality for patients who relapsed following BMT and who were then considered incurable based on transfer of donor immune system cells collected from the blood. The procedure became known as donor lymphocyte infusion (DLI) [18, 19, 20]. In contrast to chemo- and radiation therapy, adoptive allogeneic cell-mediated immunotherapy may eliminate all tumor cells of host origin despite resistance to available anticancer agents. Therefore immunotherapy mediated by DLI may be the most effective modality for treating otherwise resistant hematologic cancers, especially minimal residual disease after conventional doses of chemotherapy in the early stage of the disease. For patients at high risk of relapse or at risk from continuous chemotherapy, immunotherapy mediated by donor lymphocytes in principle offers the best prophylaxis against relapse [11].

More recently, we have documented that DLI may also be able to displace nonmalignant hemopoietic cells of host origin in patients with genetic diseases [6]. Thus infusion of donor blood stem cells or bone marrow cells following nonmyeloablative stem cell transplantation (NST), followed by DLI in cases where residual host stem cells are present, may be used for effective myeloablation of the hematopoietic compartment of patients with malignant and nonmalignant diseases, including residual malignant and normal stem cells, immune system cells, and circulating and tissue-bound reticuloendothelial cells of host origin.

Cell-mediated post-transplantation immunotherapy was developed originally in animal models of human disease, focusing on the first spontaneous B cell leukemia/lymphoma in mice which resembles human disease, and was subsequently introduced for treatment and prevention of relapse post-BMT in patients with leukemia and lymphoma [17]. The clinical application of similar procedures for patients with metastatic solid tumors resulted in well-documented anticancer effects. However, procedure-related toxicity and mortality were too high for wider clinical application [3].

It therefore appeared logical to induce host vs graft transplantation tolerance in patients with a sibling matched for human leukocyte antigen (HLA) to enable durable engraftment of donor lymphocytes for more effective GVL or graft vs tumor (GVT) effects in all patients with cancer. Since the results of our earlier studies showed that host vs graft transplantation tolerance following engraftment of donor stem cells could be achieved following nonmyeloablative conditioning, we

have focused on developing nonmyeloablative protocols to induce host vs graft transplantation [21]. This procedure is referred to as a "mini-transplant", although it results in full replacement of host with donor marrow and immune compartments in the majority of the cases, thus avoiding the need for myeloablative conditioning using high-dose chemo- and radiation therapy.

Biologic principles of NST

The success of NST depends on initial engraftment of donor stem cells for induction of host vs graft transplantation tolerance to prevent rejection of donor cells and permit durable engraftment of donor lymphocytes. An optimal and well-tolerated regimen for conditioning of recipients of HLA-matched sibling or MUD allografts is a combination of fludarabine and anti-T lymphocyte immunoglobulin (ATG) in addition to low-dose busulfan or cyclophosphamide, which were used until recently in higher doses for all indications.

Following step 1, which is based on nonmyeloablative yet immunosuppressive conditioning that is tolerated well even by elderly individuals (there is no upper age limit), donor lymphocytes can be accepted without rejection and mediate GVL or graft vs lymphoma effects against residual tumor cells escaping chemotherapy. Following NST, donor lymphocytes can eliminate the "last tumor cell" even in patients who cannot be cured by "lethal" doses of chemotherapy including total body irradiation (TBI). Basically, the patient's own lymphocytes (T cells) ignore tumor cells, which is why the tumor continues to grow indefinitely, whereas donor T cells that are foreign to the tumor may recognize residual malignant cells and destroy them. This is the rationale behind allogeneic cell therapy, which provides an option for cure of patients with otherwise incurable hematologic cancer or lymphoma.

We are currently attempting to use the same rationale to treat patients with metastatic solid tumors for whom no alternative option for cure exists. Thus new concepts involving the use of NST (step 1 and step 2, followed by step 3) have been shown to be effective in all hematologic malignancies. Encouraging results from animal experiments in a model of metastatic breast cancer justify a similar approach in patients with otherwise resistant metastatic solid tumors.

NST in malignant diseases treatable with BMT

We have developed NST using a fludarabine-based regimen (30 mg/m^2 per day $\times$6) in conjunction with oral busulfan (4 mg/kg per day $\times$2) with ATG (Fresenius, Munich, Germany) (5 to 10 mg/kg per day $\times$4), or using single low-dose TBI 200 cGy. Intravenous or higher doses of busulfan (4 mg/kg per day $\times$4) may be preferred in children with genetic diseases (e.g. beta thalassemia major) with many stem cells per kilogram due to diminished and uncontrolled absorption and more rapid pharmacokinetics. Busulfan was replaced with cyclophosphamide (5 mg/kg per day $\times$2) in patients with Fanconi anemia [7] or in patients with severe aplastic anemia (60 mg/kg $\times$2) [21]. In patients with poor performance status, or when radiation therapy is preferred, busulfan can be replaced with TBI 200 cGy (avoiding the use of ATG) [9, 22]. This regimen has been used to treat patients with hematologic malignancies (acute and chronic leukemia, lymphoma, myelodysplastic syndrome) and patients with nonmalignant hematologic diseases (aplastic anemia, Fanconi anemia, Gaucher disease, osteopetrosis, chronic granulomatosis disease, beta thalassemia major, and Diamond-Blackfan syndrome).

NST was also tried in a cohort of patients with MUD transplantation, as well as in patients who had failed prior myeloablative SCT. Engraftment was observed in all patients with an HLA-matched donor available with minimal or no aplasia. Low-dose cyclosporine A (CSA) 3 mg/kg was administered for 30–100 days for prophylaxis against GVHD [4]. Other centers have used different conditioning regimens based on a similar rationale [1, 4, 8, 9].

The NST protocol developed in Jerusalem was well tolerated by patients in all age groups [21]. Rapid, durable engraftment was observed in 99% of patients, including all patients who received HLA-matched sibling donor cells. Procedure-related toxicity and mortality were low, but GVHD was still a major problem. The mortality rate on day 100 was 2.6%: 0% in 21 patients with nonmalignant disease, 4% in patients with hematologic malignancy who received HLA-matched sibling donor cells, and 10% in MUD recipients. Persistent evidence of disease or recurrent disease in mixed chimeras was treated with earlier discontinuation of CSA or by graded increments of DLI in 10 of 15 responders.

After 4 years, with a median observation period of 30 months, the actuarial probability of disease-free survival is approximately 50%. Among patients with chronic myelogenous leukemia (CML) in first chronic phase who received HLA-matched sibling donor cells, the disease-free survival rate is 89% at 4 years, and among non-Hodgkin's lymphoma patients, it is approximately 40%. Corresponding rates for MUD recipients at 12 months were 75% and 70%, and at 18 months 48%, respectively. Survival and disease-free survival rates at 2 years in patients with nonmalignant diseases were 100% and approximately 80%. Although acute and chronic GVHD appeared to be the major problem in patients with hematologic malignancies, severe acute GVHD was not observed in patients with nonmalignant diseases. Based on our preliminary data, NST appears promising, but larger cohorts of patients and longer observation periods are required to confirm the advantages of NST compared with conventional BMT.

The data suggest that following induction of host vs graft tolerance, donor immunocompetent cells can

displace and replace host with donor immunohematopoietic cells. NST may thus become the treatment of choice for patients requiring allogeneic SCT for malignant and nonmalignant diseases, replacing conventional myeloablative BMT in patients without bulky or advanced disease.

NST in the treatment of metastatic solid tumors

As clinical experience increased with nonmyeloablative hematopoietic SCT in the treatment of acute and chronic leukemia, lymphoma, multiple myeloma, and genetic diseases such as enzyme deficiency disorders, Fanconi anemia, and beta thalassemia major, it became evident that the method has potential for immunotherapy of metastatic solid tumors. This was reinforced by demonstrations in animals of the GVT effects mediated by allogeneic lymphocytes [10]. For this reason, the success of the nonmyeloablative protocol used by Childs et al. [2] in treating metastatic renal cell cancer is cause for hope [14]. The therapy they used has two main phases: pretreatment with immunosuppressive agents to induce acceptance of HLA-matched hematopoietic stem cells from a normal sibling, followed by one or more DLIs to attack the tumor. Additional immunosuppressive therapy with CSA to prevent or ameliorate GVHD was also required in most patients. A measurable response was observed in 10 of 19 patients (53%) who enrolled in the study, and durable complete responses occurred in three patients. The potential use of NST in the treatment of renal cell cancer and other metastatic solid tumors should be investigated further but appears to be promising.

Several approaches may enhance the efficacy and reduce the risks of immunotherapy with donor lymphocytes. Recent experiments in our laboratory suggest that anticancer effects can be significantly improved while eliminating or reducing the severity of GVHD by using immune rather than naive donor T cells. Such immune T cells can be generated in vitro by culture of lymphocytes with tumor-specific peptides or patient tumor cells. Donor cytotoxic and helper T cells can be generated in vitro by a method that disables the reactivity of T cells against the prospective host's histocompatibility antigens, leaving a population of tumor-specific T cells. Another approach that could be used in patients lacking a histocompatible sibling uses T cell-depleted hematopoietic stem cells to render the recipient incapable of rejecting the graft, followed by administration of graded increments of donor T cells (or tumor-specific T cells), with careful titration until elimination of all tumor cells of host origin or until the first evidence of GVHD. It is also possible to manipulate donor lymphocytes in vitro by insertion of a suicide gene, such as the herpes simplex virus thymidine kinase gene, which provides an option for limiting the lifespan of the infused lymphocytes once all tumor cells are eliminated, thus reducing the risk of uncontrolled GVHD [14].

NST for adoptive allogeneic cell-mediated immunotherapy of malignant and nonmalignant disorders

Clinical data show that a fludarabine-ATG regimen [21] prevents rejection of donor stem cells, eliminating the need for myeloablative conditioning with high-dose chemotherapy or TBI. The NST protocol is based on a three-step procedure in which the first step is designed to debulk without necessarily attempting to ablate the "last cancer cell". This avoids major toxicity while inducing transient immunosuppression to enable durable acceptance of donor bone marrow cells. Step 1 is preferably an outpatient procedure. Subsequently, donor lymphocytes are infused together with stem cells collected from the blood following mobilization with granulocyte-colony stimulating factor or from the marrow without mobilization for induction of host vs graft transplantation tolerance, as well as for induction of GVL or GVT effects by donor lymphocytes present in the graft (step 2). Following the immunosuppressive procedure, donor T cells, and possibly natural killer (NK) cells, are expected to eliminate residual leukemia or other tumor cells resistant to chemotherapy. Patients with more resistant disease may require additional infusions of donor lymphocytes posttransplantation on an outpatient basis (step 3). DLI may be amplified with recombinant interleukin-2 (rIL-2) administration or with infusions of donor lymphocytes activated in vitro with rIL-2. Using donor lymphocytes specifically immune against the tumor may further activate immunotherapy mediated by DLI. This procedure can be considered when tumor cells are available for "immunization" of donor lymphocytes.

Since the majority of patients with hematologic malignancies in all age groups, with the exception of low-risk acute lymphoblastic leukemia in childhood, are anticipated to relapse even after achieving complete remission, NST immunotherapy should be regarded as an additional therapeutic option for high-risk patients in the early stage of disease. As experience with NST accumulates and its safety is confirmed, its use for additional indications at earlier disease stages will be accepted.

NST can provide a platform for down- or upregulation of immune function by adoptive transfer of donor immune lymphocytes. Host reactivity to donor alloantigens is downregulated following NST, which should permit allotransplantation of cells or perfused organ allografts, as well as the use of organs or tissues derived from the stem cell donor. Similarly, upregulation of host immune function can be accomplished when donor-derived lymphocytes are used to correct host immunodeficiency.

Another potential use of NST is the elimination of self-reactive lymphocytes in patients with resistant or life-threatening autoimmune diseases. As shown in experimental animals, which led to pilot clinical studies, self-reactive lymphocytes can be eliminated with high-

dose chemoradiotherapy, followed by autologous SCT. Unresponsiveness to self antigens of newly generated lymphocytes is reestablished due to a mechanism of central clonal deletion. We hypothesized that self-reactive lymphocytes causing autoimmune disease might be eliminated by highly immunosuppressive, yet not necessarily myeloablative, conditioning in conjunction with allogeneic blood SCT, since immunocompetent alloreactive lymphocytes of donor origin can effectively eliminate residual host-type hematopoietic cells, including self-reactive lymphocytes, by a mechanism resembling the GVL effect.

We have recently confirmed the existence of graft vs autoimmunity (GVA) effects in parallel with amplification of the alloreactive potential of donor lymphocytes following allogeneic NST [23]. We identified a patient with severe psoriatic arthritis who also had Philadelphia chromosome (bcr/abl)-positive CML and therefore was eligible for NST. Both diseases responded initially to nonmyeloablative conditioning with fludarabine 30 mg/m^2 ×6, ATG 10 mg/kg ×4, and busulfan 4 mg/kg ×2. The initial NST procedure was uneventful and resulted in elimination of all signs of autoimmunity (psoriasis and arthritis) as well as all evidence of CML. Recurrence of polyarthritis and exacerbation of psoriasis were observed in parallel with a significant increase in the proportion of male (host) DNA, and 5% of the mitoses were again bcr/abl positive, indicating an increase in the clone of host cells. Both bcr/abl-positive cells identified by reverse transcription-polymerase chain reaction (RT-PCR) and psoriatic arthritis were eliminated following discontinuation of anti-GVHD prophylaxis with CSA. The discontinuation resulted in activation of the alloreactive potential of donor T cells, accompanied by GVHD, suggesting the existence of GVA effects. RT-PCR for bcr/abl has remained consistently negative for nearly 3 years, and all DNA is of the donor type.

The response of autoimmune disease manifestations to GVA effects in parallel with elimination of all host-derived hematopoietic cells supports our working hypothesis that autoimmune diseases caused by self-reactive lymphocytes may be treated by elimination of alloreactive self-reactive lymphocytes following induction of host vs graft tolerance. This is analogous to replacement of malignant or genetically abnormal host cells following DLI. It is therefore suggested that intentional GVA effects may be inducible by DLI following a conventional nonmyeloablative regimen in recipients with life-threatening autoimmune diseases resistant to conventional treatment modalities. Adoptive immunotherapy of autoimmunity, like treatment of hematologic malignancy, may thus involve a two-step procedure: first, inducing host vs graft and graft vs host transplantation tolerance through a transient stage of mixed chimerism; and second, inducing controlled GVA effects, initially by discontinuation of CSA and then, if indicated, by late outpatient DLI to eradicate residual hematopoietic cells of host origin, including self-reactive lymphocytes.

Conclusions

NST appears to be a relatively safe approach for patients with high-risk disease, especially those with minimal residual disease failing front-line chemotherapy or high-dose chemoradiotherapy following autologous stem cell rescue. NST has already proven to be effective in the treatment of patients with hematologic malignancies and nonmalignant indications for BMT. Innovative immunotherapy mediated by donor lymphocytes offers a rational chance for eradication of tumor or otherwise abnormal host cells by introducing foreign immune system cells that can eliminate undesirable host hematopoietic cells more effectively, at the risk of GVHD. The use of NST as a replacement for conventional BMT needs to be investigated further, although it is clear that a combination of fludarabine and ATG with low-dose cyclophosphamide, busulfan, or TBI allows stable engraftment and full donor chimerism. This avoids the need for myeloablative doses of chemoradiotherapy associated with retardation of growth and development in children, cataract formation, and sterility, among other complications. Conventional conditioning should still be considered for high-risk patients with bulky disease for better tumor debulking prior to immunotherapy with donor lymphocytes or posttransplant DLI. While minimizing procedure-related toxicity and mortality, NST may permit safer early application of an ultimate therapeutic modality involving allogeneic SCT in conjunction with additional innovative posttransplantation immunotherapy with allogeneic donor lymphocytes. Thus new modalities based on biologic tools rather than chemoradiotherapy may be developed for the treatment of life-threatening malignant, genetic, and autoimmune diseases in all age groups.

Acknowledgements We wish to thank Baxter International Corporation, the German-Israel Foundation, Gabrielle Rich Leukemia Research Foundation, Danny Cunniff Leukemia Research Laboratory, Cancer Treatment Research Foundation, Szydlowsky Foundation, Novotny Trust, Joanne and David Morrison, Ronne and Donald Hess, and Pep and Jerry Silverstein for their continuous generous support of our ongoing basic and clinical research in cell therapy.

References

1. Carella AM, Champlin R, Slavin S, McSweeney P, Strob R (2000) "Mini-allografts": ongoing trials in humans. Bone Marrow Transplant 25:345
2. Childs R, Chernoff A, Contentin N, Bahceci E, Schrump D, Leitman S, Read EJ, Tisdale J, Dunbar C, Linehan WM, Young NS, Barrett AJ (2000) Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. N Engl J Med 343:750
3. Eibl B, Schwaighofer H, Nachbaur D, Marth C, Gächter A, Knapp R, Böck G, Gassner C, Schiller L, Petersen F, Niederwieser D (1996) Evidence for a graft-versus-tumor effect in a patient treated with marrow ablative chemotherapy and

allogeneic bone marrow transplantation for breast cancer. Blood 88:1501
4. Giralt S, Estey E, Albitar M, Van Besien K, Rondon G, Anderlini PS, Khouri I, Gajewski J, Mehma R, Claxton D, Andersson B, Beran M. Przepiorka D, Koller C, Kornblau S, Körbling M, Keating M, Kautarziah H, Champlin R (1997) Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 89:4531
5. Horowitz M, Gale RP, Sondel PM, Goldman JM, Karsay J, Kolb HJ, Rimma A, Ringden O, Rozman C, Speck B (1990) Graft-versus-leukemia reactions after bone marrow transplantation. Blood 75:555
6. Kapelushnik J, Or R, Aker M, Cividalli G, Nagler A, Naparstek E, Varadi G, Ackerstein A, Amar A, Slavin S (1996) Allogeneic cell therapy of severe beta thalassemia major by displacement of host stem cells in mixed chimera by donor blood lymphocytes. Bone Marrow Transplant 19:96
7. Kapelushnik J, Or R, Slavin S, Nagler A (1997) Fludarabine based protocol for BMT in Fanconi anemia. Bone Marrow Transplant 29:1109
8. Khouri I, Keating M, Przepiorka D, O'Brien S, Giralt S, Körbling M, Champlin R (1996) Engraftment and induction of GVL with fludarabine based non-ablative preparative regimens in patients with chronic lymphocytic leukemia and lymphoma. Blood 88 [Suppl 1]:301a
9. McSweeney PA, Wagner JL, Maloney DG, Radich J, Shizuru J, Bensinger WI, Bryant E, Chauncey TR, Flowers MED, Kauffman M, Minor CS, Nash RA, Blume K, Storb R (1998) Outpatient PBSC allografts using immunosuppression with low-dose TBI before, and cyclosporine (CSP) and mycophenolate mofetil (MMF) after transplant. Blood 92 [Suppl 1]:519a
10. Moscovitch M, Slavin S (1984) Anti-tumor effects of allogeneic bone marrow transplantation in (NZB×NZW)F1 hybrids with spontaneous lymphosarcoma. J Immunol 132:997
11. Naparstek E, Nagler A, Or R, Slavin S (1996) Allogeneic cell mediated immunotherapy using donor lymphocytes for prevention of relapse in patients treated with allogeneic BMT for hematological malignancies. In: Ceka JM, Tarasaki PI (eds) Clinical transplantation. Tissue Typing Laboratory, Los Angeles, p 281
12. Ringden O, Horowitz MM, for the Advisory Committee of the International BMT Registry (1989) Graft-versus-leukemia reactions in humans. Transplant Proc 21:2989
13. Slavin S (1987) Total lymphoid irradiation. Immunol Today 3:88
14. Slavin S (2000) Cancer immunotherapy with alloreactive lymphocytes. N Engl J Med 343:802
15. Slavin S, Strober S, Fuks Z, Kaplan HS (1976) Long-term survival of skin allografts in mice treated with fractionated total lymphoid irradiation. Science 193:1252
16. Slavin S, Fuks Z, Kaplan HS, Strober S (1978) Transplantation of allogeneic bone marrow without graft vs host disease using total lymphoid irradiation. J Exp Med 147:963
17. Slavin S, Weiss L, Morecki S, Weigensberg M (1981) Eradication of murine leukemia with histoincompatible marrow grafts in mice conditioned with total lymphoid irradiation (TLI). Cancer Immunol Immunother 11:155
18. Slavin S, Or R, Naparstek E, Ackerstein A, Weiss L (1988) Cellular-mediated immunotherapy of leukemia in conjunction with autologous and allogeneic bone marrow transplantation in experimental animals and man. Blood 72 [Suppl 1]:407a
19. Slavin S, Naparstek E, Nagler A, Ackerstein A, Kapelushnik Y, Or R (1995) Allogeneic cell therapy for relapsed leukemia following bone marrow transplantation with donor peripheral blood lymphocytes. Exp Hematol 23:1553
20. Slavin S, Naparstek E, Nagler A, Ackerstein A, Samuel S, Kapelushnik J, Brautbar C, Or R (1996) Allogeneic cell therapy with donor peripheral blood cells and recombinant human interleukin-2 to treat leukemia relapse post allogeneic bone marrow transplantation. Blood 87:2195
21. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, Varadi G, Kirschbaum M, Ackerstein A, Samuel S, Ben-Tal O, Eldor A, Or R (1998) Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and non-malignant hematologic diseases. Blood 91:756
22. Slavin S, Nagler A, Naparstek E, Varadi G, Ben-Yosef R, Panighari S, Samuel S, Ackerstein A, Or R (1999) A new non-myeloablative protocol using fludarabine and low-dose TBI in preparation for allogeneic blood stem cell transplantation for high risk patients with malignant and non-malignant disorders. Blood 94:10 [Suppl 1]:388b
23. Slavin S, Nagler A, Varadi G, Or R (2000) Graft vs autoimmunity following allogeneic non-myeloablative blood stem cell transplantation in a patient with chronic myelogenous leukemia and severe systemic psoriasis and psoriatic polyarthritis. Exp Hematol 28:853
24. Sullivan KM, Weiden PL, Storb R, Witherspoon RP, Fefer A, Fisher L, Buckner CD, Anasetti C, Appelbaum FR, Badger C (1989) Influence of acute and chronic graft-versus-host disease on relapse and survival after bone marrow transplantation from HLA-identical siblings as treatment of acute and chronic leukemia. Blood 73:1720