

Bone Marrow Transplantation for Cancer—An Update

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ABSTRACT

The number of allogeneic and autologous bone marrow transplants continues to grow worldwide. Bone marrow transplantation (BMT) has become standard therapy for many patients with leukemia, lymphoma, multiple myeloma and testicular cancer. Encouraging results of autologous BMT in treating patients with poor-risk breast cancer have led to this approach being tested in nationwide randomized trials. In order to increase availability and efficacy of BMT, other sources of hematopoietic cells are explored for transplantation, such as from HLA-matched unrelated volunteer donors, partially matched related donors, placental/umbilical cord blood and allogeneic peripheral blood. Relapse of

original malignancy remains the main obstacle for the success of BMT. Recent clinical investigations have demonstrated that donor-derived peripheral blood leukocytes are effective in inducing remissions in patients with hematological malignancies who relapse after allogeneic BMT. BMT procedures are associated with significant complexity and should be carried out only in transplant units that meet adequate standards. In order to better define the role of BMT in treating cancer, more phase III clinical trials are needed. The future of BMT will depend on further improvements in its efficacy and economic constraints. *The Oncologist* 1996;1:159-168

INTRODUCTION

Bone marrow transplantation (BMT) is increasingly used to treat cancer [1]. The Nobel Prize in Medicine awarded to E. Donnall Thomas and his colleagues in 1990 marked the end of the early era of clinical investigation in BMT [2]. Hematopoietic stem cells for transplantation are today obtained from sources other than bone marrow, such as peripheral blood or placental/umbilical cord blood. As a result, the traditional term “bone marrow transplantation” is expanding into a more precise description: “hematopoietic stem cell transplantation.” Current numbers of allogeneic and autologous transplants continue to grow worldwide at the rate of 15% and 20% per year (Fig. 1) [3].

The biology and indications of allogeneic and autologous BMT differ in a variety of ways, and it is important to keep these differences in mind while reviewing the results of BMT (Table 1 and Fig. 2). The most impressive trend in autologous BMT is for breast cancer: in 1989 about 15% of autotransplants were performed for breast cancer, while in 1994 this number was 35%. Although not every oncologist performs BMT, most have an opportunity to advise patients whether and when to undergo this procedure, and many will

care for these patients after they return from the transplant center. In this review we will focus on recent advances and current practice standards in BMT for malignant diseases.

CLINICAL RESULTS WITH BONE MARROW TRANSPLANTATION

A summary of the current use of either autologous or allogeneic BMT in malignant diseases is shown in Table 2.

Leukemia

Allogeneic BMT from an HLA-matched sibling donor has become the treatment of choice for patients with chronic myelogenous leukemia (CML). A five to ten year disease-free survival of 60%-70% can now be regularly observed in patients who undergo transplantation in first chronic phase [4]. Survival of matched unrelated donor (MUD) transplants at three years ranges from 35%-45% [5]. Although results of identical-twin transplants for CML indicate a possibility of cure in the absence of an allogeneic graft-versus-leukemia effect [6], attempts of autologous transplants for CML remain investigational [7].

Allogeneic marrow transplantation is the sole form of therapy able to cure patients with acute myeloid leukemia

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(AML) who fail induction therapy and is successful in 15%-20% of such patients [8]. For this reason all new patients with AML and their families should be HLA-typed. A long-term survival rate of 20%-40% has been achieved in AML patients transplanted in untreated relapse or in second remission, and cure rates of 40%-70% have been uniformly reported in patients transplanted in first complete remission [9-14]. Because of important recent advances in chemotherapy for AML, it appears that for good-risk patients characterized by t(8, 21) or inv(16), transplantation in first remission should not be considered [15]. Attempts to compare allogeneic with autologous BMT in patients with AML have generally reached the conclusion that autologous transplantation is associated with a lower treatment-related mortality but a higher relapse rate [16].

Patients with myelodysplastic syndrome (MDS), when an HLA-identical sibling can be identified, can obtain long-term disease-free survival and potential cure with allogeneic BMT. In a series of 93 patients with MDS, the patients who benefited the most from allogeneic BMT were those under the age of 40 who did not have an excess of bone marrow blasts; four-year disease-free survival was 62% [17].

Results of standard therapy in children with acute lymphoblastic leukemia (ALL) are sufficiently good, and allogeneic BMT is performed as part of the primary therapy only in special situations, such as in Philadelphia chromosome positive ALL [18]. Two recent trials demonstrated superiority of allogeneic transplantation for pediatric patients during second complete remission (CR) [19, 20]. Allogeneic BMT done in first remission ALL in adults has been reported to produce long-term disease-free survival in 40%-70% of patients. However, except for high-risk patients, the superiority of this approach over an effective chemotherapy regimen has not been clearly established [21]. Autologous BMT for ALL, regardless of the disease status, is still hampered by a high rate of post-transplant relapse [22-24].

Both allogeneic and autologous transplants have been employed for younger patients with chronic lymphocytic leukemia [25]. Both approaches have produced leukemia-free survival in 50%-70% of treated patients with brief follow-up.

Multiple Myeloma

Based on global experience with more than 1,300 autotransplants and allotransplants for multiple myeloma (MM), a consensus is emerging that myeloablative therapy increases CR rates from 5% to over 40%, and significantly prolongs event-free and overall survival [26, 27]. Transplant-related mortality of autografts for MM has been reduced to 1% with the use of peripheral blood stem cells, which contrasts sharply to 30% mortality with allogeneic transplants. Final results of a recent prospective randomized trial confirmed, in

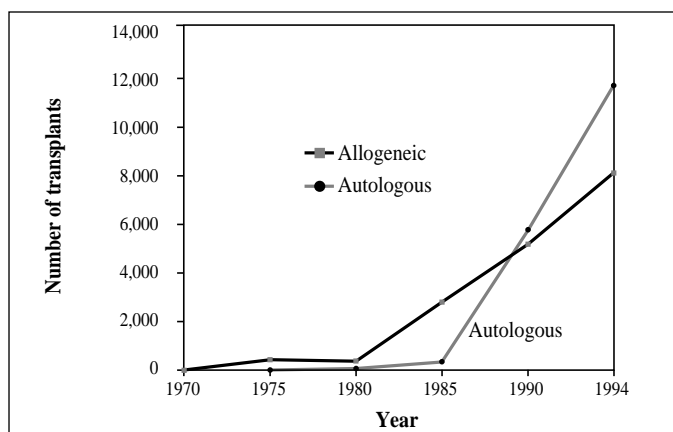


Figure 1. Continuous increase in the use of blood and marrow transplantation worldwide. Reproduced from Horowitz MM et al. by permission from the International Bone Marrow Transplant Registry (Milwaukee) [3].

an intention-to-treat analysis, superiority of autologous BMT when compared to conventional chemotherapy [28]. Because autologous stem cell transplantation can extend survival, damaging alkylating agents such as melphalan should be avoided before stem cell collection [26].

Lymphoma

Allogeneic, syngeneic and autologous BMT have all been reported to yield long-term disease-free survival and cure for patients with intermediate and high-grade non-Hodgkin's lymphomas (NHL) [29, 30]. Autologous BMT is the therapy of choice for patients with relapsed lymphoma whose tumor is still sensitive to chemotherapy [31]. Some patients who fail to achieve an initial CR can also achieve long-term disease-free survival after

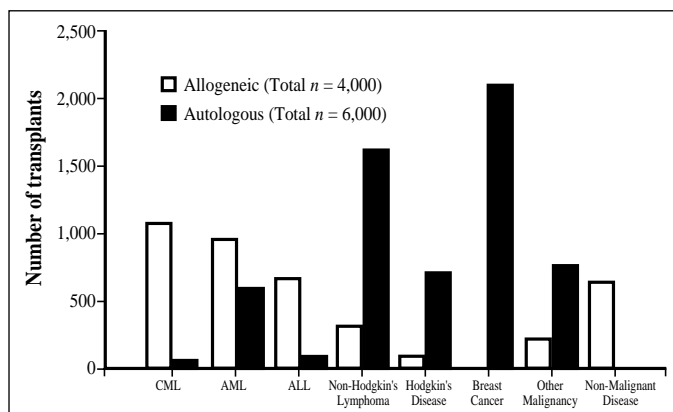


Figure 2. The most common indications for allogeneic and autologous transplants in North America in 1994. Reproduced from Horowitz MM et al. by permission from the International Bone Marrow Transplant Registry (Milwaukee) [3].

Table 1. Comparison of allogeneic and autologous bone marrow transplantation

	Allogeneic	Autologous
Most important complication	Graft-versus-host disease	Relapse of original malignancy
Main limiting factor	Finding a closely HLA-matched donor	Tumor contamination of the graft
Upper age for candidates	50-60 years	60-70 years
Graft-versus-tumor effect of infused cells	Proved or suspected in a number of malignancies	Unproved but possible
Main indication	Malignant diseases and nonmalignant diseases	Only in malignant diseases at present

BMT [32]. Two recent trials addressed the issue of the utility of high-dose therapy and autologous BMT in NHL for patients transplanted in first partial remission (PR). The French-Belgian LNH87-2 study showed a superior disease-free survival rate of 63% for patients transplanted in first PR versus 46% with conventional salvage chemotherapy [33]. A Dutch trial, however, failed to demonstrate improvements in outcome for patients in PR after three cycles of conventional chemotherapy with CHOP, who were randomized between autologous BMT or five additional cycles of CHOP [34]. Ongoing studies indicate that autologous BMT may be of benefit if used early, as initial therapy for patients with high-risk NHL or as a consolidation for high-risk patients in first remission [35, 36].

For patients with low-grade NHL autologous BMT can result in disease-free survivals of 40%-50% with follow-up periods of four years [37-40]. These studies show a continued pattern of relapse, and it is yet unclear if any patients are cured. Recent results with allogeneic BMT for low-grade NHL show that this approach has promise [41].

High-dose therapy and autologous or allogeneic BMT have been widely performed in patients with recurrent Hodgkin's disease [42]. Because of lower treatment-related mortality, autologous transplantation is preferred by most investigators. Current results support use of autologous BMT for all patients with Hodgkin's disease as early as possible after failure from a front-line therapy [43].

Breast Cancer

Autologous BMT can produce complete responses in a higher proportion of patients with breast cancer than seen with traditional doses of chemotherapy [44]. The results in large numbers of patients have shown that disease-free survival at two to five years is seen in 10%-30% of breast cancer patients with chemotherapy-sensitive, stage IV disease [44-46]. In a recent trial from South Africa, 90 patients with newly diagnosed metastatic breast cancer were randomized between autologous BMT and six to eight courses of conventional chemotherapy with CNV (cyclophosphamide, mitoxantrone, vincristine). Complete response rate (51% versus 4%), duration of responses (80 months versus 34 months)

Table 2. The application of bone marrow transplantation in selected malignancies

Malignancy	Preferred type of transplant	Optimal timing	Standard therapy*
CML	Allogeneic	Early in the first chronic phase	Yes
AML, ALL	Allogeneic	Primary refractory or advanced, poor-risk in first remission	Yes
Myelodysplastic syndrome	Allogeneic	No excess blasts	Yes
CLL	Controversial	Younger patients	No
Multiple myeloma	Autologous	<12 months of prior therapy	Yes
NHL aggressive	Autologous	Sensitive relapse	Yes
NHL indolent	Controversial	Younger patients	Yes
Hodgkin's disease	Autologous	Early after relapse	Yes
Breast cancer	Autologous	Unknown	Not yet
Neuroblastoma	Controversial	High-risk for relapse	No
Testicular cancer	Autologous	Sensitive relapse	Yes
Other solid tumors	Autologous	Unknown	No

*Standard therapy is defined as treatment that is widely accepted by physicians and routinely reimbursed by most third-party payers.

and median survival (90 months versus 45 months) were significantly better in the high-dose therapy arm [47]. If ongoing randomized studies show that survival with transplantation is superior to conventional chemotherapy, high-dose therapy is likely to become a standard approach for younger women with chemotherapy-sensitive metastatic disease. Encouraging results of incorporation of autologous BMT into primary therapy of patients who present with poor prognostic factors have led to this treatment being tested in an adjuvant setting in controlled trials [48].

Other Malignancies

Autologous and allogeneic BMT have been used with some success in patients with advanced neuroblastoma [49, 50]. However, randomized trials are needed to determine the role of transplantation in this disorder.

In patients with testicular carcinoma who fail to be cured with platinum-based chemotherapy regimens, autologous BMT has resulted in disease-free survival of 10%-20% at two years [51]. Results are better in patients with chemotherapy-sensitive relapse [52]. The role of high-dose therapy as a primary treatment for patients with poor risk features is unproven and needs further confirmation in controlled trials [53].

Autologous BMT has been used to treat patients with other solid tumors [54]. For malignant melanoma, colon cancer and non-small cell lung cancer the results of transplantation have been sufficiently discouraging to preclude larger clinical trials. For gynecological cancers, small cell lung cancer, soft-tissue sarcomas and brain tumors, however, transplantation has had some positive results stimulating further trials.

OTHER SOURCES OF HEMATOPOIETIC CELLS

Unrelated Volunteer Donors

Fewer than 40% of BMT candidates have an HLA-matched sibling. In order to extend the benefits of allogeneic BMT to those who lack a suitable related donor, the late 1980s witnessed an increase in transplants from closely HLA-matched unrelated volunteer donors (Fig. 3). Establishing the

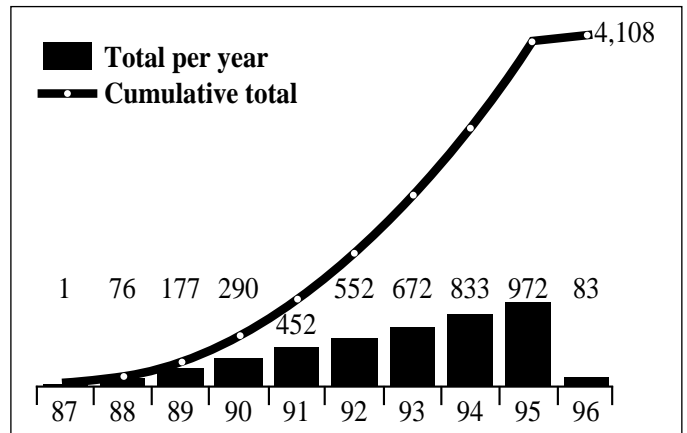


Figure 3. Updated cumulative and total per-year number of matched unrelated donor bone marrow transplants performed through the National Marrow Donor program from 1987 to February 1996. The data were provided by the National Marrow Donor Program (Minneapolis).

National Marrow Donor Program in 1986 was instrumental in these efforts [55]. With the current number of registered volunteer donors around 1,500,000, the odds for a patient to have an unrelated match are 40%-50%. A considerable effort is done to expand the donor pool to the ethnic-minority groups with less common HLA phenotypes whose chance of finding a donor could be less than 5% [56]. MUD BMT is still associated with significantly higher nonrelapse-related mortality than HLA-matched sibling BMT [57]. Factors related to an improved outcome with MUD BMT include younger age, degree of HLA-matching and early-stage disease. With relapse rates generally lower after MUD transplants and further improvements in clinical care, outcome is expected to approach the results of a sibling-donor BMT. Standards of practice and recommendations for using MUD transplants have been published recently [58] (Table 3).

Partially Matched Related Donors (PMRDs)

An alternative approach for patients who lack an HLA-matched sibling donor or a MUD is to use the marrow from

Table 3. Recommended criteria for considering a patient for a matched unrelated donor bone marrow transplant according to World Marrow Donor Association [58]

Diagnosis	Generally accepted	Research only	Not generally accepted
AML, ALL	High risk CR	In relapse	Refractory relapse
Chronic myelogenous leukemia	Chronic phase	Advanced	Refractory blast phase
Myelodysplastic syndrome	Poor risk RA or RARS	RAEB or RAEB-t	Refractory RAEB or RAEB-t
Lymphoma	Poor risk lymphoma	—	Chemoresistant
Myeloma	Poor risk myeloma	—	Chemoresistant

CR: complete remission; RA: refractory anemia; RARS: refractory anemia with ringed sideroblasts; RAEB: refractory anemia with excess blasts; RAEB-t: refractory anemia with excess blasts in transformation.

a related donor who is a less than perfect match [59]. A single-antigen mismatch among family members is available in 10% of cases, two-antigen mismatch to another 25% and three-antigen mismatch (haploidentity) to almost all patients. The potential advantage of such transplants is immediate availability to almost all patients, even to those with rare HLA haplotypes. Initial results with such PMRD transplants were dismal [60]. However, after modifications in techniques and more experience some centers are reporting results with partially matched family donors that are comparable to matched sibling or MUD data [61-63]. Currently BMT from a PMRD is indicated in selected cases, particularly when relapse is an imminent risk.

Placental/Umbilical Cord Blood Transplantation

Since 1988 allogeneic sibling placental/umbilical cord blood has been increasingly explored as an alternative source of hematopoietic stem cells [64]. At present this is a highly investigational procedure limited to a few specialized centers. Postulated advantages of such stem cell source are increased availability of stem cells, no risk for the donor, and less graft-versus-host disease (GVHD) as a result of the immature immune system of such donors. The recent International Umbilical Cord Blood Registry report on 25 pediatric patients with malignant diseases shows the probability of survival as 46%, probability of relapse 49%, probability of acute GVHD 3%, and chronic GVHD 6% [65]. The limiting factor for umbilical cord blood transplants is the small number of hematopoietic progenitors, making it unsuitable for safe engraftment in adults. Current studies are focused on expansion of unrelated cord blood banking programs and on developing in vitro stem cell expansion techniques that would make this procedure available to adults [65, 66].

Allogeneic Peripheral Blood Stem Cell Transplantation

Peripheral blood stem cells (BSC) mobilized by colony stimulating factors became, in recent years, the predominant source of stem cells for autografting [3]. The use of BSC for allografting could have several potential advantages over the bone marrow, such as more rapid engraftment, convenience for the donor, no tumor contamination and, because of a much larger number of lymphocytes in such products, an increased graft-versus-leukemia effect [67]. In 1989 it was reported that allogeneic blood stem cells resulted in rapid hematopoietic recovery [68]. This source of stem cells was not pursued until recently due to the large number of apheresis procedures and the theoretical concerns of increased GVHD. After clinical introduction of hematopoietic growth factors, it became feasible to collect sufficient numbers of progenitors from normal

donors with only two to three leukaphereses. Results of several clinical trials that have begun over the last three years show that using allogeneic BSC for transplantation results in rapid engraftment with, surprisingly, no increase in acute GVHD [69-72]. Long-term superiority and safety of such an approach need yet to be established.

LONG-TERM FOLLOW-UP AND RELAPSE

A number of issues related to late effects of high-dose therapy and immune reconstitution can arise after both allogeneic and autologous BMT [73]. Recovery after allogeneic BMT is further modified by the need for immunosuppression and the occurrence of chronic GVHD. Most BMT patients return to their normal function after one year post-transplant [74]. Because recipients of allogeneic marrow and a large proportion of those receiving autologous BMT lose immunity to poliovirus, tetanus, diphtheria and other diseases, a reimmunization program at one and two years post-transplantation is necessary [75].

Unfortunately, relapse of the original malignancy remains the main problem after BMT, and it is, in general, increased in recipients of nonallogeneic marrow. Success of traditional approaches in treating relapse after BMT, such as additional chemotherapy or second transplants, is poor [76]. Clinical investigations over the last five years demonstrated that donor-derived peripheral blood leukocytes are effective in inducing remissions in patients who relapse after allogeneic BMT [77]. Donor leukocyte infusions (DLI) result in a remission rate in excess of 70% in patients who relapse in chronic phase after allogeneic BMT for CML [78]. The effectors of such a process are assumed to be donor T cells. The rate of inducing remissions with DLI is lower after relapse with advanced-phase CML and AML, and the lowest for relapses after allogeneic BMT for ALL [77]. DLI infusions are still associated with significant mortality, close to 20%, usually due to secondary marrow aplasia or GVHD. In acute leukemia, chances for responding to DLI appear to be better if leukocytes are delivered after a second remission obtained with standard chemotherapy. A recent study indicates that some patients after allogeneic BMT with DLI-resistant relapse may achieve remission if donor cells are exposed to interleukin 2 [79]. Anecdotal responses to DLI have been reported also for patients with Epstein-Barr virus-associated lymphomas, multiple myeloma and chronic lymphocytic leukemia [80-82].

COSTS

A high-technology procedure such as BMT is associated with significant cost. However, costs are not fixed and tend to decrease with time and the increasing experience of the transplant center [83]. At the University of Nebraska Medical

Center in-hospital mortality rates for patients with Hodgkin's disease and NHL after autologous BMT decreased between 1987 and 1991, from 20% to 0% and 29% to 4%, respectively. This was associated with a yearly decrease in costs of 10% and 8%, respectively. Multivariate analysis indicated that the number of previously performed transplants was the most important factor associated with better survival and low-cost care (Fig. 4).

DONORS

Extreme diligence is required from transplant teams to prevent and treat complications in healthy donors. Bone marrow harvesting is associated with some morbidity. In a Seattle series of 1,549 bone marrow donors the incidence of major complications was 3% and life-threatening complications 0.4% [84]. Patients with pre-existing medical problems were at increased risk of bone marrow donation, but no deaths were recorded. With widespread use of autologous blood storage the donors' risks of getting an allogeneic blood transfusion have been decreased to a minimum.

The collection of growth-factor mobilized peripheral BSC instead of a bone marrow harvest is an attractive option to the majority of healthy donors. Limitations of BSC collection are an occasional need for central venous access and the inability to collect blood from small children. At the University of Nebraska Medical Center, 25 healthy donors received low-dose G-CSF for the mobilization of allogeneic stem cells, and nine donors required placement of a central venous catheter. The most frequent toxicities observed were myalgias, arthralgias, headache and fever. All side-effects of growth factor administration and apheresis procedure were mild and well tolerated [85].

PRACTICE STANDARDS

High-dose therapy procedures followed by hematopoietic stem cell transplants are associated with significant complexity and should be carried out only in transplant units where facilities are adequate. The American Society of Hematology, American Society of Clinical Oncology, European Bone Marrow Transplant Group and, most recently, the American Society for Blood and Marrow Transplantation issued a series of guidelines and minimal requirements which should be followed in order to ensure safe and efficient performance of hematopoietic stem cell transplants (Table 4) [86-88].

FUTURE OF BONE MARROW TRANSPLANTATION

Based largely on the success of phase II trials during the 1980s and early 1990s, hematopoietic stem cell

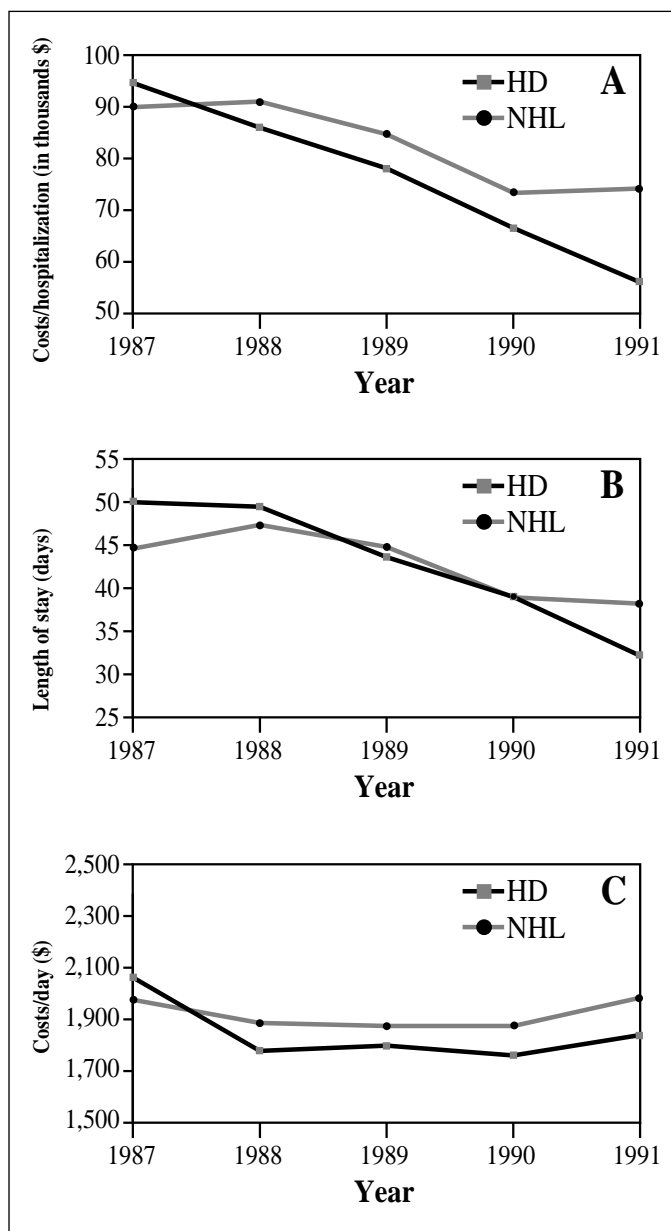


Figure 4. A) Average hospitalization costs, B) length of stay and C) daily costs for patients undergoing autologous bone marrow transplantation at the University of Nebraska Medical Center (1987-1991). Reproduced from Bennett CL et al. by permission from the *Journal of Clinical Oncology* [83].

transplantation has become the treatment of choice for relapsed or high-risk cancer. In today's managed care environment, the task for physicians and insurers is how to fit this high-technology procedure effectively into the spectrum of existing oncologic therapies. Many important questions about the optimal usage of BMT remain unanswered and more effort is needed in order to include larger numbers of patients in important phase III clinical

Table 4. Some of the recommended criteria for the performance of blood and bone marrow transplantation [86-88]

Characteristic	Recommendation
Patient volume	Minimum 10-20 transplants/year (10 allogeneic, 10 autologous if both are performed)
Number of transplant beds	Two or more
Marrow processing laboratory	To meet FAHCT ¹ standards
HLA-typing laboratory	Needs ASHP ² accreditation
Isolation facilities	Including air-handling systems
Outpatient facility	Adjacent to BMT unit, seven days/week, ability for lifelong follow-up
24-hour support	Clinical laboratory, radiology, consultations, microbiology, clinical pathology, blood bank, MD on-call
Radiotherapy unit	If TBI part of preparative regimen
Personnel	Board-certified program director, physicians and nurses trained in BMT, ability to deliver ICU standard of care, BMT coordinators, social workers, dietitian, pharmacy, physical therapy, data manager
Treatment outcome	An occasional poor-risk patient should be discouraged from undergoing BMT, continuous data evaluation of outcomes, implementation of improvements, reporting to international registries, publishing important observations

¹Foundation for Accreditation of Hematopoietic Cell Therapy; ²American Society of Histocompatibility and Immunogenetics.

trials. The ultimate future of BMT will depend on improvements in its efficacy, parallel developments in nontransplant cancer therapies and economic constraints.

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