SCIENTIFIC SECTION

REVIEW ARTICLE

Bone marrow transplantation in Canada

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Bone marrow transplantation is an established form of therapy for aplastic anemia and severe combined immunodeficiency. It is also a therapeutic option for acute leukemia in remission. Unfortunately, compatible donors are not available for most patients who could benefit from it. Further refinement of the techniques involved may make it suitable for more patients. Graft rejection, recurrent leukemia, graft-versus-host disease and interstitial pneumonia continue to be the main unsolved complications of bone marrow transplantation, but recent advances have decreased their frequency and severity. Most of the complications of allogeneic bone marrow transplantation may be eliminated with the use of autologous stem cells. For further refinement bone marrow transplantation should continue to be performed in large centres that combine treatment with research.

La greffe de moelle osseuse est une forme reconnue de traitement de l'anémie aplastique et des déficits immunitaires combinés sévères. C'est aussi une option thérapeutique pour la leucémie aiguë en rémission. Malheureusement, pour la plupart des patients qui pourraient en profiter on ne trouve pas de donneurs compatibles. De nouveaux perfectionnements des techniques utilisées pourraient rendre la greffe de moelle applicable à un plus grand nombre de patients. Les rejets de greffes, les récidives leucémiques, les réactions du greffon contre l'hôte et les pneumonies interstitielles représentent toujours les principales complications non résolues de la greffe de moelle, mais de récents développements en ont réduit la fréquence et la gravité. La plupart des complications d'une greffe de moelle allogénéique peut être éliminée par l'utilisation de cellules souches autologues. Dans le but d'obtenir des perfectionnements plus poussés les greffes de moelle devraient continuer à être pratiquées dans des grands centres de traitement et de recherche.

Over the past 10 years bone marrow transplantation has evolved from an experimental procedure to an accepted form of therapy. Despite increasing indications for its use there is no national or provincial policy on this form of therapy in Canada. Since 1977 an advisory committee of the Canadian Hematology Society has been meeting from time to time to develop a national policy and establish guidelines for centres in Canada wishing to create a bone marrow transplantation unit. Such guidelines are required because of the high cost of bone marrow transplantation and the resulting need to concentrate expertise in a few centres.

At a recent meeting in Ottawa groups from coast to coast expressed interest in bone marrow transplantation; however, there is no consensus in this country about who should develop these programs. Several groups have already begun to perform bone marrow transplantation and will likely continue to do so whether or not they have the sanction of the advisory committee or of the federal government. Some provincial governments may agree to fund a bone marrow transplantation program whether or not federal support is forthcoming, especially since the precise contribution that the federal government is willing to make to such programs is unknown, and centres may be unwilling to await federal approval before developing a program. Furthermore, some centres may consider that they have sufficient expertise to begin serving their communities in a limited way.

Currently most Canadians who require bone marrow transplantation receive it in the United States. Undoubtedly the availability of American transplantation centres to Canadian patients will decrease sharply in view of the recent, well publicized success of the procedure. This threat has propelled some Canadian centres into the field.

Indications for bone marrow transplantation

There are two conditions for which bone marrow transplantation is probably the best available treatment: severe combined immunodeficiency (deficiency of lymphoid cells mediating both humoral and cellular immunity) and severe aplastic anemia. The value of this therapy in patients with malignant hematologic diseases is less well established. Bone marrow transplantation may be a therapeutic option in conjunction with chemotherapy and radiotherapy for patients with acute nonlymphoblastic leukemia in remission or acute lymphoblastic leukemia in second remission when a compatible sibling is available.

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Chemotherapy with or without radiotherapy can be given at lethal doses, with subsequent rescue by the grafting of bone marrow from a compatible donor.

Severe combined immunodeficiency

This rare disease is usually discovered soon after birth and is almost always fatal. The University of Minnesota pioneered bone marrow transplantation for this disorder, and it is now the preferred form of therapy if a suitable donor can be found.[1] Unrelated HLA (human leukocyte antigen)-compatible donors whose lymphocytes do not react in mixed culture with those of the patient (MLC-compatible) have been used with variable success.[2] With refinement of the techniques the results should improve.

Severe aplastic anemia

The treatment of this condition by conventional methods is discouraging: most patients die less than 6 months after the diagnosis is made.[3] It is now generally accepted that bone marrow transplantation may be the best available treatment.

The Seattle bone marrow transplantation team has the largest experience with bone marrow transplantation for this disease, and a review of their first 110 cases demonstrated a 50% long-term survival rate.[4] Two significant factors predisposing to failure were identified: previous blood product administration to the recipient and a marrow dose of less than 3×10^8 donor cells per kilogram of the recipient's body weight.[5] Accordingly the team tried to perform transplants before the patients had been given blood products. A recent analysis of the results in 30 such patients indicated rates of 90% for sustained grafting and 83% for survival.[6] In contrast, among the patients given blood products before transplantation and sensitized, as measured by the index of relative response[7] in mixed lymphocyte culture, the graft rejection rate was 75% and most of the patients with rejection died. This sensitization has been largely overcome with the use of viable buffy coat cells from the donor, which are collected daily on the continuous-flow blood-cell separator and infused into the bone marrow recipient for the first 5 days after transplantation. As a result the graft rejection rate has been reduced to 11% and the overall survival rate has increased to 74%. This approach has been found to be superior to more intensive immunosuppression of the recipient before bone marrow transplantation.[8]

Acute leukemia

Although intensive remission-inducing chemotherapy for acute nonlymphoblastic leukemia produces complete remission in 60% to 85% of adults, relapse occurs in most within a year or two of diagnosis despite maintenance chemotherapy.[9] At best, intensive maintenance chemotherapy may produce a 2-year survival rate of 33%.[10] In children the "cure" rate for acute lymphoblastic leukemia is about 50%. Most children with a relapse survive less than a year.[11] The Seattle group began using bone marrow transplantation for acute leukemia in 1969, when the results of conventional therapy were even worse than they are now. Initially most patients received the transplant during relapse, when they were in poor physical condition and had a large tumour load. Analysis of the results of transplants done between March 1976 and December 1977 showed that the patients who received a transplant during remission fared better than those so treated during relapse.[12] A more recent analysis of 19 cases in which bone marrow transplantation was done during remission of acute nonlymphoblastic leukemia, between March 1976 and March 1978, showed that the survival rate had levelled off at 63%; only one patient had died of recurrent leukemia.[13] How many of these patients will ultimately be cured is unknown; however, in the past most relapses have occurred within 18 months of transplantation. Therefore, it is possible that most of the 12 patients whose disease is still in remission are cured. This contrasts sharply with the results of transplantation performed during relapse: the overall survival rate was only about 10%.[14] Thus, bone marrow transplantation may offer a cure to a substantial proportion of patients with acute nonlymphoblastic leukemia without the need for maintenance chemotherapy.[13]

A recent report suggests that the results of bone marrow transplantation done during remission rather than during relapse are also better in children with acute lymphoblastic leukemia.[15] At 15 to 35 months after transplantation only 11 of 22 patients given a transplant during remission had died, whereas 22 of 26 patients given a transplant during relapse had died. Because of the poor survival after relapse of acute lymphoblastic leukemia in children treated with conventional therapy transplantation of bone marrow from an HLA- and MLC-compatible donor may be the preferred treatment. It should be performed shortly after remission is induced.

Although the results of bone marrow transplantation for acute leukemia are better mainly because the procedure is now being done during remission, there has also been improvement in other facets of the management of these patients, such as leukocyte and platelet transfusions, preventive isolation and antimicrobial therapy, hyperalimentation and pretransplantation conditioning regimens. Furthermore, the general condition of patients who receive a transplant during remission is usually far superior to that of patients who receive a transplant during relapse.

Chronic granulocytic leukemia

Stem cells collected during the chronic phase of this disease and preserved at a low temperature have been used to re-establish the chronic phase when transformation to the acute phase has occurred.[16] Transplantation with one's own stem cells only prolongs the chronic phase without eliminating the ultimate transformation into the acute phase. In the acute phase the disease often responds poorly to treatment. The length of the second chronic phase is unpredictable but may be relatively short. The only curative procedure for this disease is transplantation with allogeneic

bone marrow (marrow from the same species but antigenically distinct), which is probably best done during the chronic phase, when the patient is usually well nourished and the disease is stable. The results in twins have demonstrated two important facts: in a twin with this disease the chronic phase can be eradicated by intensive radiotherapy and chemotherapy and does not recur after subsequent transplantation with marrow from the healthy twin, and bone marrow transplantation can be successful when performed during the chronic phase.[17]

Many have been reluctant to subject a patient with chronic granulocytic leukemia in the chronic phase to bone marrow transplantation because this phase is a time of relatively good health and indefinite length (on the average, 3 to 4 years). However, with refinement of the techniques of bone marrow transplantation and supportive care several centres have begun to perform allogeneic bone marrow transplantation in such patients (R. Powles: personal communication, 1979). If this courageous step is successful it may represent an advance in treatment and a potential cure for the disease.

Compatibility of donor and recipient

Donor and recipient need not be ABO- and Rh-compatible for successful bone marrow grafting.[18,19] Plasma exchange can be performed in the recipient before transplantation to reduce the level of hemagglutinins if there is blood group incompatibility,[20] and new methods are being developed for the in vivo adsorption of hemagglutinins.[21] Although HLA and MLC compatibility is desirable, only one sibling in four, theoretically, is compatible in both respects. It may be possible to perform bone marrow transplantation when there is HLA incompatibility if the lymphocytes of donor and recipient are nonreactive in mixed culture.[22]

Autotransplantation

Many of the complications of bone marrow transplantation could be avoided if there was a method of selectively preparing disease-free bone marrow cells and preserving them from the effects of chemotherapy and radiotherapy. Transplantation of a person's own bone marrow is appealing for several reasons. No donor is needed and graft-versus-host disease cannot occur; thus, immune suppression is not required after transplantation.

Techniques for long-term cryopreservation of autologous stem cells are established and reliable.[23] However, there must be some normal stem cells within the stored marrow, and there must be a way of separating normal from diseased stem cells before the autologous stem cells are reinfused. Leukemic stem cells withstand preservation at low temperatures well, and this may be the reason for the unimpressive results of autotransplantation in patients with acute leukemia.[24] Autotransplantation may be of value in the treatment of solid tumours that do not involve the bone marrow.

Complications

The main complications of bone marrow transplantation are graft rejection, recurrent leukemia, graft-versus-host disease and interstitial pneumonia. The frequency of recurrent leukemia may be significantly reduced by transplantation during remission; however, graft-versus-host disease and interstitial pneumonia account for many deaths.

Graft-versus-host disease develops in over half the patients who undergo bone marrow transplantation, and many die of it.[25] Although there are some novel approaches to the management of this complication none has been very successful, and the disease is still the subject of intensive research. Its prevention and treatment are unsolved problems. Methotrexate, steroids in high doses, antithymocyte globulin and cyclosporin A are being investigated as therapeutic agents. A recent analysis suggested that graft-versus-host disease has a beneficial antileukemic effect. Therefore, aggressive management of this complication may be detrimental to patients with leukemia;[26] however, the patient's condition and quality of life with chronic graft-versus-host disease is often poor, and death sometimes ensues.

Interstitial pneumonia may be infective or idiopathic. New radiotherapeutic techniques should reduce its frequency, but clearly this problem too is unresolved.[27]

The latent effects of chemotherapy and radiotherapy at lethal doses plus immunosuppression after transplantation are unknown. A second malignant disease may be significantly more frequent in long-term survivors. The role of immunosuppression in the treatment of aplastic anemia needs further evaluation, as bone marrow transplantation may be the most suitable mode of therapy for patients with this disease who have nonimmune stem cell failure.[28,29] Some patients with aplastic anemia have responded to plasma exchange or prednisone therapy alone[28] (unpublished observations). The use of antithymocyte globulin with or without mismatched bone marrow for patients with aplastic anemia for whom there is no compatible donor has been controversial and disappointing.[30,31]

Cost

The costs of bone marrow transplantation are difficult to estimate, and they differ considerably. Some provinces have paid up to $131 000 for a single transplant — more than twice the usual amount. The cost varies with the amount of research incorporated into the transplant program, the support services available, the complications encountered, the medical care system supporting the program and so on. The transplantation procedure is simple and cheap; it requires an anesthetist, three hardy souls to aspirate and strain the marrow and a couple of hours in the operating room. The marrow is infused intravenously without delay into the recipient, who has been conditioned by chemotherapy, with or without radiotherapy. The stay in hospital can be as short as 2 to 3 weeks or much longer if complications arise or the research protocol demands it. As there are no really good therapeutic alternatives for severe aplastic anemia when a compatible donor is available, the cost of the

procedure should not be an issue. Undoubtedly, if it can be shown to be cheaper and more successful than conventional chemotherapy for acute leukemia, bone marrow transplantation will be a more attractive therapeutic option.

Where should it be done?

The impressive refinement of bone marrow transplantation over the past 10 years has been largely due to concentrated efforts in several large centres. The results I have mentioned have come from units that combine treatment with research. Now that bone marrow transplantation is established therapy for a few diseases and promising for others, some small centres in Canada may wish to use it.

Is a small centre without research interests that will do the procedure infrequently the best place to care for these patients and invest medical research funds? If bone marrow transplantation had reached the end of its development one could argue that such a centre might handle patients on a service basis. However, a bone marrow transplantation program requires highly skilled, multidisciplinary expertise and extensive support services, such as cell separator and intensive care units, which a small centre may not have. Sufficient experienced attending physicians need to be available for periods of up to 3 months to provide almost constant care to transplant recipients.

As experience in this field depends on the number of patients undergoing transplantation, large centres will acquire the greatest expertise in bone marrow transplantation. Accordingly, in Canada the benefits will likely be greatest if bone marrow transplantation is limited to a few large centres that will further refine it and thus avoid widespread, costly duplication of facilities.

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