Bone Marrow Transplantation:
Current Results in Leukemia

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Bone marrow transplantation offers two potential therapeutic advantages over more conventional therapy of leukemia. It allows more intensive treatment to be given without regard to marrow toxicity and allows in the case of allogeneic marrow an additional immunotherapeutic effect through graft-versus-host disease (GVHD). Initially, allogeneic transplants in HLA matched sibling donors were only employed in end-stage patients. Although there were encouraging results in terms of long-term therapeutic effects, the overall mortality was prohibitive. Subsequently, patients were transplanted in remission with a marked improvement in overall survival in both acute lymphocytic leukemia and acute non-lymphocytic leukemia. The major obstacles to further improvement in the therapeutic effects of this procedure have been identified (i.e., GVHD, viral infection, and relapse in ALL) and are subject to intensive investigations that already show encouraging results. Syngeneic marrow transplantation is limited for obvious reasons, but early results have shown significant therapeutic effects, in particular, in chronic myelogenous leukemia. These results have encouraged others to use autologous bone marrow. Marrow contamination with unseen tumor cells is being approached by pharmacologic and immunologic techniques designed to "purge" marrow of tumor cells. Animal and initial clinical studies have been encouraging.

Bone marrow transplantation (BMT) offers two potential therapeutic advantages over that of more conventional therapy in leukemia. First, it allows treatment with very intensive cytoreductive therapy without regard to marrow toxicity since the marrow infusion is able to "rescue" the patient from this otherwise lethal toxicity. In addition, allogeneic marrow transplantation may have an immunotherapeutic effect against residual tumor via graft-versus-host disease (GVHD).

In the present discussion, we will consider some of the highlights as to the present state of the art of allogeneic, syngeneic, and autologous bone marrow transplantation in the acute leukemias and chronic myelogenous leukemia (CML). For the theoretical, historical, and more extensive treatment of this subject the reader is referred to several reviews [1–5].

Marrow Donor

In all mammals studied, the major immunologic barrier to transplantation is determined by a linear array of genes; in man these are located on chromosome 6.
This complex of genetic material is called the major histocompatibility complex (MHC). A series of alleles exist for loci A, B, C, and Dr that can be identified serologically by typing (microcytotoxicity testing) the lymphocytes of the patient and the family. In addition, a fifth locus, the D locus closely associated with Dr, may be identified by determining reactivity (non-identity) or non-reactivity (identity) in one-way mixed lymphocyte cultures in vitro. In simple terms, all these laboratory tests are designed to identify the two paternal and two maternal chromosomes (haplotypes) and their inheritance in the family. Thus, after the typing is finished a genetic analysis is made by inspection of the data. Individuals sharing the same haplotypes are said to be genotypically HLA identical. These individuals, of course, differ in terms of minor histocompatibility determinants since their inheritance of other genetic material is not identical.

Although in certain situations "mismatched" donors and even unrelated donors may be used, herein when we consider allogeneic donors they will be genotypically HLA identical siblings.

Marrow is collected in heparinized syringes under general anesthesia from the posterior iliac crests in the amount of 10–20 ml/kg. The marrow is then passed through screens of decreasing mesh size and finally transferred to an empty blood bag. The marrow is then immediately brought to the ward and infused intravenously (IV) without an in-line filter [6].

Since the genes that determine major blood group antigens are not located on chromosome 6, a situation may arise where a patient with blood group O has a donor who is blood group A. Currently this poses no problem since one may simply centrifuge the collected marrow and remove the mismatched erythrocytes. This is routinely done on our unit and in no way have the results differed therapeutically from situations where donors with ABO compatible marrow were used [7,8].

The term syngeneic is used when the marrow donor is a monozygotic twin. When the patient serves as his own donor, the term autologous is employed. In these situations, of course, the marrow cells share all the genetic material of the recipient and the expected hazards as well as possible therapeutic effects of allogeneic effects are absent.

**ALLOGENEIC TRANSPLANTATION**

For ethical reasons, initial marrow transplants in acute leukemia were performed only in end-stage patients, patients who had eventually relapsed and failed to go into another remission with the best available chemotherapy. Total body irradiation (TBI) alone, TBI in combination with cyclophosphamide (CY) [4,9], CY alone or in combination with busulfan (BU) [10,11] were used as preparative treatments in these early studies. The remarkable aspects of these early studies is that up to 15 percent of such patients showed long-term leukemia-free survivals that operationally at least appear to be cures. Unfortunately, however, early mortality was extremely high with the majority of patients not dying of leukemia but rather from complications of the treatment. Estimates of relapse rates also were in the order of 70–100 percent. The UCLA group attempted to improve the results by an even more intensive cytoreductive treatment. Although there was a suggestion of a decreased leukemic relapse rate, the overall survival was not improved because of treatment-related toxicity [12]. Patients with blastic crisis (BC) with chronic myelogenous leukemia (CML) have a notoriously poor prognosis. In a sense, they are like the end-stage patients with acute leukemia. In one series where allogeneic marrow transplantation was performed, most died of either uncontrolled leukemia or treatment complications;
However, three of 24 such patients are living in continuous remission for 30–60 months, indicating that a small salvage rate with allogeneic BMT is also achievable here [4].

New directions and strategies were clearly needed and about six to seven years ago it was decided to transplant acute leukemia patients while they were in remission. It was reasoned that such patients would be in much better condition and free of infection and, furthermore, there would be less of a body burden of tumor to contend with.

The Seattle group reported a series of patients with acute lymphocytic leukemia (ALL) who were transplanted in their second remission following preparation with CY 60 mg/kg given on each of two successive days and followed with a single dose of TBI (800–1,000 rads). At the time of the report [13] 7/22, or 32 percent, of the patients were surviving from two to four years free of disease. The majority of patients [4] who failed therapy did so because of leukemia recurrence. The transplant center at Sloan-Kettering has reported early results in a similar group of patients in second remission, using CY in combination with hyperfractionated irradiation. Initial results show a leukemia-free survival better than that reported by the Seattle group [14]. Other preliminary reports wherein fractionated TBI was used in conjunction with CY are also encouraging in this regard. Time and the addition of more patients to these series is needed before one can judge the additional therapeutic effect of fractionated radiation versus single-dose radiation. Further, the possible benefit of transplanting poor risk ALL in first remission is being currently investigated by several centers. If the situation is similar to acute non-lymphocytic leukemia (ANL), leukemia-free survival should be increased. Essentially all transplant groups employ TBI in ALL. It should be noted, however, that there is no evidence that TBI must be employed to obtain equivalent tumor control rates. One European center has suggested that chemotherapeutic regimens without TBI deserve further trial in ALL in remission [15].

In contrast with earlier series of “end-stage” patients where the majority of patients died of non-leukemic causes, leukemic relapse has been the major problem in patients transplanted in their second or subsequent remission. This strengthens the notion that patients in remission better withstand the rigors of cytoreduction because of a more favorable clinical condition.

The most exciting results have been reported for patients with ANL transplanted in first remission. The largest series of such patients has been reported by the Seattle group, using CY plus single or fractionated doses of TBI [16]. Of 58 such patients transplanted, more than half were living in continuous complete remission with a median duration of greater than 34 months at the time of the report [4]. Furthermore, at that time only three of 58, or 5 percent, had suffered a relapse. Subsequently, the Seattle group compared the effects of CY with single doses of TBI versus fractionated TBI [17]. Kaplan-Meier analysis suggested a survival advantage of the fractionated regimen but reasons for this increased survival were not clear since the incidence of acute GVHD, chronic GVHD, leukemic relapse, etc. was not statistically different in the two groups. A number of other groups employing single or fractionated TBI for transplantation of ANL in first remission have reported their initial results [18–20]. In general, their results in small series are similar or better than reported by the Seattle group.

Our group is the only major transplant group that does not employ TBI in our preparative regimen for transplantation in ANL without a history of CNS disease. Based on extensive study in the rat [21–23] and studies in “end-stage” patients with
ANL in relapse [10,11], we prepare patients with ANL with 4 mg/kg of BU given orally on each of four successive days (total dose of 16 mg/kg), followed immediately by CY (50 mg/kg) given on each of four consecutive days (total dose, 200 mg/kg). Prophylaxis for CNS leukemia is provided with a course of intrathecal chemotherapy 50–70 days following transplantation. At the time of this writing, we have transplanted 33 patients in first, second, and third remission or early relapse. Fifteen survive free of leukemia for 53 to 1,124 days (median, 470 days). There has been only one relapse to date. This was in a 35-year-old male who relapsed in the marrow 349 days following transplantation in his third remission. He was retransplanted using CY and fractionated TBI and survives free of leukemia 246 days after the second transplant and 607 days after the first transplant. It is hoped that, as more patients are added to the series and it matures with time, comparisons can be made to other series where TBI is employed regarding late toxicities (i.e., cataracts, pulmonary function deficits, growth rates, sterility, malignancies, etc.).

The decision to perform marrow transplantation, particularly in first remission, has met with some resistance and it has been argued that survival curves for transplanted patients are not yet statistically different from survival curves of similar patients treated only with chemotherapy [24]. Clearly this matter will not be settled without clinical trials that prospectively compare transplantation versus more conventional cytoreductive therapy. It is hoped that the answer will soon be apparent from several such trials that have already begun.

**COMPLICATIONS OF ALLOGENEIC MARROW TRANSPLANTATION**

The most serious complications following allogeneic marrow transplantation are viral infections in the form of gastroenteritis and interstitial pneumonitis and acute and chronic GVHD.

During the first month following transplantation, patients are highly susceptible to bacterial infections, particularly those gram-negative in origin. Patients in “good” clinical condition (i.e., in remission) are able to weather this period much better than the “end-stage” patients. The appropriate use of some of the newer antibiotics, isolation procedures, and judicious use of granulocyte transfusions have markedly decreased the severity of these complications (unless complicated by severe acute GVHD). Currently, mortality from bacterial infection is less than 5 percent in our center.

Following marrow transplantation, there is a severe combined immunodeficiency that, in its gradual repair, mimics what one would expect in a recapitulation of ontogeny [25]. We have found both B-cell, T-helper cell and T-suppressor cell abnormalities [26]. It is, therefore, not surprising that these patients are, for a variable length of time, susceptible to life-threatening fungal (i.e., candidiasis, aspergillosis), protozoan (*Pneumocystis Carinii*), and viral infections [herpes simplex (HSV), cytomegalic virus (CMV) and varicella zoster (VZV)]. Despite the use of Amphotericin B, fungal infections account for 10 percent of deaths. The problem of *Pneumocystis Carinii* has largely been eliminated with the use of trimethoprim-sulfamethoxazole. Similarly, the morbidity and mortality from HSV infections should, in the future, be markedly decreased with the use of acyclovir [27].

Interstitial pneumonitis, 60 percent of which are associated with CMV, remains a particularly serious problem in most transplant centers. The incidence in various centers is 30 to 50 percent of allogeneic transplants with a fatality of 50–60 percent. Preliminary observations from our own group suggest that it is less in those patients who have received BU and CY or fractionated TBI as opposed to single high doses
of TBI [unpublished observations]. Recent observations from our center indicate that the prognosis of CMV infections correlates with cytotoxic T and other cytotoxic cell responses [28]. Efforts to augment these responses by direct or indirect measures should, in the future, decrease the mortality from this complication.

**Graft-versus-host Disease**

Acute GVHD remains a major cause of morbidity and mortality following allogeneic marrow transplantation, despite the use of genotypical HL-A identical sibling donors and post-transplant immunosuppression with methotrexate (MTX) or CY. This iatrogenic disease shows a varied clinical spectrum ranging from a mild skin rash to severe involvement of the skin, gut, liver, and bronchial mucosa. Depending upon its severity it is also associated with profound immunodeficiency and susceptibility to opportunistic infections. Severe acute GVHD may occur in 30–50 percent of patients with a mortality of 30 to 60 percent.

Acute GVHD has been well studied in animal models. It is clear that the disease is initiated by cytotoxic T cells reactive to host minor antigens. On the basis of studies in a variety of species, it appears to be a self-limited disease from which individuals may recover if they are able to survive the critical period when immunologic defenses and anatomic (i.e., skin and gut) barriers are broken and susceptible to invasion by bacterial, mycotic, and viral agents. Eventually specific suppressor cells of T lymphocyte origin arise that are able to terminate the generation of new cytotoxic T cells [29]. Animal studies suggest that at least some thymic function is required for amplification of the T suppressor response [29].

Treatment of the disease with steroids and/or antithymocyte globulin, although partially successful, is far from satisfactory. A more rational approach would be a prophylactic treatment to prevent the disease. The aim ideally would be to prevent the development of cytotoxic T-cell responses and yet permit the development of specific T suppressor responses. Cyclosporin A, a novel immunosuppressant agent, appears to be an agent capable of accomplishing this aim in rodents [30]. Clinical studies with Cyclosporin are currently under way at several centers [31,32].

Another promising approach being evaluated in several centers is to attempt to rid the marrow inoculum of post-thymic T cells that initiate acute GVHD. A variety of physical, immunologic (i.e., monoclonal antibodies), and pharmacologic methods are being vigorously pursued, some showing initial clinical promise. For a more complete discussion of this fascinating subject the reader is referred to other reviews [33].

A chronic form of GVHD has been recognized in 25 to 40 percent of patients undergoing allogeneic marrow transplantation. The disease is polymorphous in nature and has a number of clinical manifestation similar to the collagen vascular disorders: dyspigmentation, scleroderma-like lesions of the skin, mucositis, malabsorption, and pulmonary insufficiency. Chronic GVHD appears to represent a severe imbalance of humoral and cellular immunity without the fine control system that regulates a normal immune response. Less is known about the mechanisms involved in chronic as opposed to acute GVHD; however, it is a subject of intense investigation both in the laboratory and clinic. Mortality in this disease used to be as high as 80 percent, primarily because of the associated immunodeficiency and death due to gram-positive organisms. Currently this mortality has been reduced to about 10 percent with empiric treatment with corticosteroids and azathioprine [34] which appears to restore immunologic balance in the majority of cases.

With the variety of approaches being taken, it is this author's opinion that the
prevention of clinical acute and chronic GVHD is highly likely in the next few years. Paradoxically this may create new problems. For instance, it has been shown that GVHD may have a therapeutic effect in preventing clinical relapse of leukemia. Will leukemic relapses be increased if the practical problems of GVHD are solved? In anticipation of an affirmative answer to this question, efforts in laboratory models are being directed toward replacing the therapeutic effect of GVHD with alternative immunologic or chemotherapeutic treatments.

SYNGENEIC MARROW TRANSPLANTATION

Marrow transplantation with monozygotic twin donors (syngeneic) offers a unique opportunity to study transplantation without the problems associated with GVHD. A series of 34 such patients with refractory leukemia in relapse (18 ALL, 16 ANL) have been transplanted following treatment with CY and single-dose TBI [35]. Recurrence of leukemia (13 ALL and 10 ANL) was the principal cause of death. Three patients with ALL and five with ANL remain in complete remission without maintenance therapy from 29 to 103 months. Mortality in this group due to non-leukemic causes is much reduced over that seen in a similar allogeneic series; however, this is balanced by the increase in leukemic relapse due to the absence of GVH.

The possible therapeutic effect of GVH in ANL is strongly suggested by the fact that of 20 cases of ANL known to the author [unpublished observations] transplanted in their first remission using monozygotic twin donors, 10 of 20, or 50 percent, have relapsed as compared to the 5 percent seen in the Seattle series of allogeneic BMT for ANL in first remission.

Patients with CML in BC have a poor prognosis; however, one of six such patients given an identical-twin transplant survives in continuous unmaintained remission for 52 months [4]. The transplantation of such patients in the chronic phase of their disease using identical twin donors, however, has demonstrated remarkable results with 10 of 12 such patients showing complete continuous remission, free of Ph' positive cells for 9 to 53 months (median 21) [36]. These results suggest that an additional therapeutic effect of GVHD may not be required in all malignancies in order to obtain long-term disease-free survival and possible cure. Encouraged by these results, allogeneic transplantation in the chronic phase of CML has begun at several centers. Initial results appear promising [33].

AUTOLOGOUS MARROW TRANSPLANTATION

Currently there is a fair amount of interest in autologous marrow transplantation partly because of the results of allogeneic marrow transplantation but more so because of what can be accomplished with syngeneic transplants. The technology and early results of clinical trials are presented in recent reviews [37–41].

Although some patients with acute leukemia have been transplanted with marrow obtained in initial remission and cryopreserved without further treatment, none have exhibited prolonged disease-free survival equivalent to that seen in syngeneic transplants. An analysis of actuarial leukemia-free survival from data pooled from several centers showed a median duration of remission of four to six months with no evidence of a plateau of long-term disease-free survivors [42]. This suggests the autologous marrow may contain viable leukemic cells. It would appear, therefore, that an important requirement for autologous marrow transplantation in acute leukemia would be the use of marrow that has been "purged" of tumor cells prior to cryopreservation.
Elsewhere, we have reviewed details of studies in animal model systems that indicated it was possible to “purge” tumor cells from marrow by pharmacologic or immunologic methods [40]. We, for instance, were able to show that a congener of CY, 4-hydroperoxycyclophosphamide (4HC) was able to eliminate tumor cells from a marrow-tumor cell suspension with a short in vitro incubation without inhibiting the ability of this treated marrow to protect irradiated rats from lethal aplasia [43]. Currently we are engaged in a phase I study designed to determine the maximum concentration of 4HC that can be used for in vitro incubation without destroying the capacity of the marrow to effect hematologic recovery after otherwise lethal intensive cytoreductive therapy. So far, early results indicate that satisfactory hematologic recovery may be obtained at drug concentrations that inhibit over 90 percent of the marrow colony forming units in culture (CFU-c) [44]. The current concentrations are several orders of magnitude above what is even feasible if given in vivo.

Immunologic approaches to the elimination of tumor cells in vitro have also been successful in animal model systems. Marrow-tumor cell mixtures have been incubated with ordinary antibody (prepared in other species) and complement and more recently with monoclonal antibodies and complement. Recently a number of clinical trials have begun with this approach [33]. Although this method appeals to the intellect because of its simplicity and specificity and offers the exciting possibility of increasing its therapeutic effect by coupling a toxin to the antibody, the pharmacologic approach may indeed turn out to be more practical. Theoretically, all one needs to do is to destroy all the tumor cells without destroying the restorative properties of hematopoietic stem cells. It may make little difference whether or not other cells in the marrow infusate are destroyed.

CONCLUSIONS

Prior studies have established that marrow transplantation is the treatment of choice for severe aplastic anemia and severe combined immunodeficiency. Current clinical results suggest that marrow transplantation in acute leukemia is at the very least a viable option for the patient. Most of the major obstacles for a successful outcome have been identified and solutions are being actively pursued. With the current pace of laboratory and clinical research in this area, it seems reasonable to predict that marrow transplantation will become the treatment of choice for acute leukemia early on in the disease.

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