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Bone marrow transplantation for leukemia and aplastic anemia: management of ABO incompatibility

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Between February 1971 and October 1980, 34 patients with leukemia or aplastic anemia received bone marrow transplants from HLA-identical siblings whose lymphocytes did not react in a mixed leukocyte culture. The donors of 10 patients were ABO-incompatible, and for five pairs the ABO incompatibility was major. Plasma exchanges followed by a red blood cell exchange transfusion reduced the anti-A titres to 1:4 or less in these patients. The ABO incompatibility had no adverse effect on the results of marrow transplantation. Twenty-two patients, including 16 of the 20 who received their transplant after Jan. 1, 1980, are still living. Seven of the 15 patients with acute leukemia have survived 89 to 466 days, and 4 of the 6 with chronic myelogenous leukemia (CML) have survived 117 to 545 days. Of the 13 patients with aplastic anemia, 11 are alive up to 8 years after transplantation.

Marrow transplantation, when possible, is the treatment of choice for young patients with acute leukemia in remission and for patients with aplastic anemia. Marrow transplantation may also prove to be effective in patients with CML.

Entre février 1971 et octobre 1980, 34 patients souffrant de leucémie ou d'anémie aplastique ont reçu une greffe de moëlle provenant d'un frère ou d'une soeur ayant un typage HLA identique et dont les lymphocytes ne réagissaient pas en culture mixte de leucocytes. Pour 10 patients les donneurs présentaient une incompatibilité ABO, et pour cinq paires cette incompatibilité était importante. Chez ces patients un échange plasmatique suivi d'une exsanguino-transfusion de globules rouges a permis de réduire les titres d'anticorps anti-A à 1:4 ou moins. L'incompatibilité ABO n'a pas eu d'effet fâcheux sur les résultats de la greffe de moëlle. Vingt-deux patients, y compris 16 des 20 qui ont reçu leur greffe après le 1er janvier 1980, sont encore vivants. Sept des 15 patients atteints de leucémie aiguë ont survécu de 89 à 466 jours, et 4 des 6 patients souffrant de leucémie myéloïde chronique (LMC) ont survécu de 117 à 545 jours. Onze des 13 patients qui souffraient d'anémie aplastique sont vivants jusqu'à 8 ans après la greffe.

La greffe de moëlle, lorsqu'elle est possible, constitue le traitement de premier choix pour les jeunes patients ayant une leucémie aiguë en rémission et pour les patients atteints d'anémie aplastique. La greffe de moëlle peut également s'avérer efficace chez les patients souffrant de LMC.

Bone marrow transplantation may be curative treatment for patients with leukemia and aplastic anemia. After receiving marrow from a sibling who was identical at the HLA (human leukocyte antigen)-A and HLA-B loci and whose lymphocytes did not react with those of the patient in a mixed leukocyte culture, 65% of young patients with acute leukemia have had a long, disease-free survival.[1-3] Similarly, when histocompatible siblings have been used as donors, 75% of patients with aplastic anemia have had hematologic restoration and returned to normal life following marrow transplantation.[4]

Successful marrow transplantation between ABO-incompatible but HLA-compatible siblings has broadened the selection of donors.[5-12] A fatal hemolytic transfusion reaction due to the infusion of ABO-incom-

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patible marrow is avoided by plasma exchange, the infusion of blood group substance and in vivo adsorption of antibody with ABO-incompatible erythrocytes.[7,11] Marrow transplantation between siblings with a major ABO incompatibility has not carried an increased risk of graft rejection or of graft-v.-host disease (GVHD).[7,11]

This paper describes our experience in the treatment of leukemia and aplastic anemia at the Princess Margaret Hospital, Toronto with marrow transplantation between HLA-identical siblings with or without ABO incompatibility whose lymphocytes did not react in a mixed leukocyte culture. Success was achieved despite major ABO incompatibility and, on one occasion, prior sensitization with donor cells.

Materials and methods

Definitions

For this report a major ABO incompatibility is defined as one in which the recipient possesses hemagglutinins capable of reacting with the ABO antigens on the surface of the donor's erythrocytes. A minor ABO incompatibility is defined as one in which the donor possesses hemagglutinins capable of reacting with the ABO antigens on the recipient's erythrocytes.

Patient population

Between February 1971 and October 1980, 34 patients received marrow transplants from sibling donors at the Princess Margaret Hospital (Tables I and II). Patients 1, 2 and 3 have previously been described.[13] With one exception the donor–recipient pairs were HLA-identical and their lymphocytes did not react in a mixed leukocyte culture; patient 15 differed from the donor by one antigen at the HLA-B locus, and in a mixed leukocyte culture the lymphocytes of the recipient reacted with those of the donor, though there was no

Table I—Clinical results of bone marrow transplantation in patients with leukemia

Type of leukemia and patient no.	Age (yr)	ABO–Rh type, donor/recipient	Clinical status before transplantation	Preparative regimen*	Grade of acute GVHD†	Survival to Dec. 31, 1980 (d)	Outcome
Acute myelogenous							
1	27	O+/O+	Relapse	I	0	17	Died of systemic candidiasis
3	20	O+/O+	Relapse	I	3	22	Died of systemic candidiasis and GVHD
10	42	O+/O+	Third remission	I	4	54	Died of bronchopneumonia and GVHD
17	22	O–/O+	First remission	II	2	350+	Resolving interstitial pneumonitis; otherwise well
19‡	18	O–/O–	First remission	II	4	127	Died of chronic GVHD and pneumonia due to *Pneumocystis carinii* and *Pseudomonas aeruginosa*
24§	34	O–/B+	First remission	II	3	160	Died of candidal cerebral abscess and chronic GVHD
26	41	A+/A+	First remission	II	1	215+	Well
28‖	32	A+/O+	First remission	II	2	180+	Well
33	22	A+/A+	First remission	II	3	89+	Recovering
Acute lymphoblastic							
2	34	A+/A+	Second remission	I	2	77	Died of systemic candidiasis and GVHD
9	48	O+/O+¶	First remission	I	0	75	Died of acute interstitial pneumonitis
13‡	26	O+/O+	First remission	III	3	466+	Well
16‖	19	AB+/B+	First remission	III	4	259	Died of chronic GVHD and interstitial pneumonitis
23‡	19	A+/A+	Second remission	III	3	251+	Interstitial pneumonitis
29‡	31	B+/B+¶	First remission	III	0	153+	Well
Chronic myelogenous							
5	24	A+/A+	Aplastic after busulfan therapy	I	4	67	Died of GVHD and interstitial pneumonitis
12‡	20	A+/A+	Remission after blast crisis with prednisone and vincristine	III	2	545+	Myelopathy; otherwise well
20‖	34	A–/O–	Chronic phase; receiving busulfan intermittently	II	2	305+	Well
22	28	O+/O+	No chemotherapy	II	1	264+	Well
30	31	B+/B+	Chronic phase; receiving hydroxyurea	II	4	20	Died of GVHD, pelvic cellulitis and septicemia
31§	40	A–/AB–	Chronic phase; receiving bulsulfan intermittently	II	0	117+	Well

*See Fig. 1 and text.
†Graft-v.-host disease: 1 = rash and minimal other involvement; 2 = rash and gut involvement; 3 = more severe disease and decrease in performance; 4 = additional systemic signs, such as fever and weight loss.
‡Had meningeal leukemia, previously controlled by intrathecal chemotherapy with or without cranial irradiation.
§Minor ABO incompatibility.
‖Major ABO incompatibility.
¶Donor and recipient were identical twins.

reactivity when the lymphocytes of the donor were stimulated by those of the recipient. Patients 4, 9 and 29 and their donors were identical twins. Five donor–recipient pairs had a major ABO incompatibility, and five pairs had a minor ABO incompatibility. The remaining 24 marrow transplants were between ABO-compatible siblings.

Of the 21 patients with leukemia, diagnosed according to standard morphologic criteria,[14] 9 had acute myelogenous leukemia (AML), 6 had acute lymphoblastic leukemia (ALL) and 6 had Philadelphia-chromosome-positive chronic myelogenous leukemia (CML).

The other 13 patients had aplastic anemia; in 11 it was idiopathic. Patient 4 received a marrow transplant during an aplastic phase of paroxysmal nocturnal hemoglobinuria. In patient 6 aplastic anemia may have developed as a complication of infectious mononucleosis: at the time of diagnosis of the aplastic anemia, in November 1976, the heterophil antibody titre was 1:1280 and, after absorption of sheep red cell agglutinins by guinea pig kidney, 1:640. The titres of antibodies to the Epstein–Barr virus (EBV) were not determined until April 1977; then the titres of antibodies to the capsular antigen and the early antigen were both 1:40.

Treatment before transplantation

Marrow transplantation was done by methods adapted from those of the Seattle marrow transplant team.[15] All the recipients except patient 12 received an infusion of donor leukocytes before preparative chemotherapy.

Preparative chemotherapy: The patients with leukemia (Fig. 1) were initially given cyclophosphamide, 60 mg/kg of body weight, intravenously on two successive days, followed by total body irradiation. When the dose of radiation was reduced to 500 rad from 1000 the chemotherapy was intensified by the addition of a 5-day continuous infusion of cytosine arabinoside, at a daily dose of 100 mg/m^2 of body surface area. The combination of cyclophosphamide and cytosine arabinoside (regimen II) is currently used to prepare patients with AML and CML for marrow transplantation. Regimen III was specifically adopted for patients with ALL, although one patient (no. 12) with CML responsive to prednisone, vincristine and L-asparaginase was prepared for transplantation according to this schedule. The drugs were given intravenously, starting with vincristine, 2 mg, and followed by five daily doses each of 200 mg of methylprednisolone and 30 000 U of L-asparaginase, then cyclophosphamide, 60 mg/kg on two successive days.

The patients with aplastic anemia (Fig. 2) were given cyclophosphamide, 50 mg/kg intravenously, on four successive days. In September 1979 total body irradiation was added to reduce the frequency and severity of GVHD; the dose was 300 rad.[16]

When a major ABO incompatibility was present, chemotherapy was completed at least 3 days prior to the day of transplantation so that serial plasma exchanges could be done. Otherwise chemotherapy was usually completed 48 hours before transplantation.

Irradiation: Total body irradiation was performed immediately prior to the infusion of donor marrow. Initially the dose was 1000 rad given at a rate of 4 to 8 rad/min, but three of the six patients who received this dose died of respiratory complications. A high incidence of radiation pneumonitis was also observed in patients receiving 800 or more rad to the upper half of the body for control of metastatic cancer.[17] Subsequently the dose of radiation for patients with leukemia has been 500 rad, given at a rate of 50 rad/min. Lung density, determined by computerized tomography, has been used to estimate the dose of radiation given to the lungs.[17]

Table II—Clinical results of bone marrow transplantation in patients with aplastic anemia‡

Patient no.	Age (yr)	ABO–Rh type, donor/recipient	Clinical status before transplantation	Preparative regimen*	Grade of acute GHVD†	Survival to Dec. 31, 1980 (mo)	Outcome
4	29	B+/B+¶	Aplastic phase of paroxysmal nocturnal hemoglobinuria	IV	0	104.5+	Well
6	19	AB+/AB+	Complication of infectious mononucleosis?	IV	2	40.2+	Disseminated herpes zoster at 13 months; now well
7	22	O+/O+	Identical twin died of aplastic anemia	IV	2	35.3+	Cutaneous GVHD; aseptic necrosis of femoral heads
8‖	29	A+/O–	Idiopathic	IV	2	28.5+	Cutaneous GVHD; herpes zoster 10 months; now well and working
11§	20	O+/A–	Idiopathic	IV	3	20.4+	Cutaneous GVHD; now well and working
14	34	B+/B+	Idiopathic	V	0	14.0+	Epstein–Barr virus infection at 6 months, then well
15	19	O+/O+	Idiopathic	V	4	< 1	Died of GVHD and systemic candidiasis
18‖	23	A+/O+	Idiopathic	V	3	11.0+	Well
21	19	A+/A+	Idiopathic	V	3	9.5+	Cutaneous GVHD; now well
25§	19	O+/B+	Idiopathic	V	2	6.3+	Well
27	21	A+/A+	Idiopathic	V	0	< 1	Died of systemic candidiasis
32§	29	O+/A+	Idiopathic	V	0	3.3+	Well
34	43	A+/A+	Hepatitis B antigen in serum; no clinical evidence of hepatitis	V	0	2.7+	Well

‡Footnotes *, †, §, ‖ and ¶ as in Table I.

Meningeal leukemia: Patients 12 and 19 were found to have asymptomatic meningeal leukemia when the cerebrospinal fluid (CSF) was examined immediately before the start of the preparation for transplantation. Treatment consisted of the intrathecal administration of cytosine arabinoside, 40 mg/m^2, on five occasions and cranial irradiation at a dose of 1250 rad given over 5 days. No recurrence of meningeal leukemia was found before transplantation by cytologic examination of the CSF of patients 23 and 29, who had previously undergone the treatment for meningeal involvement with leukemia. Four 12-mg intrathecal injections of methotrexate were given to these patients during the preparation for transplantation.

Plasma exchange and antibody adsorption: The plasma exchanges were done with the use of continuous flow centrifugation and an IBM blood cell separator (IBM Corp., White Plains, New York). Pooled donor-type plasma was used; one unit of fresh frozen plasma was given for each four of stored frozen plasma used. The number and duration of plasma exchanges were estimated from the rate of fall of the ABO antibody titre in the patient's serum. The exchanges were completed on the day prior to marrow infusion. An exchange transfusion of six units of irradiated donor-type packed red blood cells was done immediately following the last plasma exchange.

Determination of ABO antibody titres

IgM anti-A titres were determined by a saline hemagglutinin technique.[18] IgG anti-A titres were estimated after incubation of serum with 2-mercaptoethanol. The tests were done immediately before and after each plasma exchange, immediately after the red cell exchange, daily during the first week after marrow transplantation and as indicated.

Other management

For the first 5 days after transplantation all patients received infusions of donor leukocytes collected with the use of continuous flow centrifugation and an IBM blood cell separator.[19] Thereafter, daily infusions of ABO-matched irradiated leukocytes were given until the absolute granulocyte count of the recipient was greater than 2 × 10^9/l. Methotrexate was given as previously described after transplantation for up to 100 days.

Acute GVHD and chronic cutaneous GVHD were diagnosed with the use of established criteria.[15,20] Initially, acute GVHD was treated with prednisone, 20 mg/d. When additional immunosuppressive therapy was required, azathioprine was given in doses of 25 to 75 mg/d. Chronic cutaneous GVHD was also treated with prednisone and azathioprine.

Results of marrow transplantation

For leukemia

Of the 15 patients with acute leukemia, marrow engraftment was successful in all, and no graft rejection has occurred. At the time of writing, seven of the patients are alive, 89 to 466 days after transplantation. All seven were prepared for transplantation with regimen II or III, which included total body irradiation at a dose of 500 rad. None of the five patients prepared with

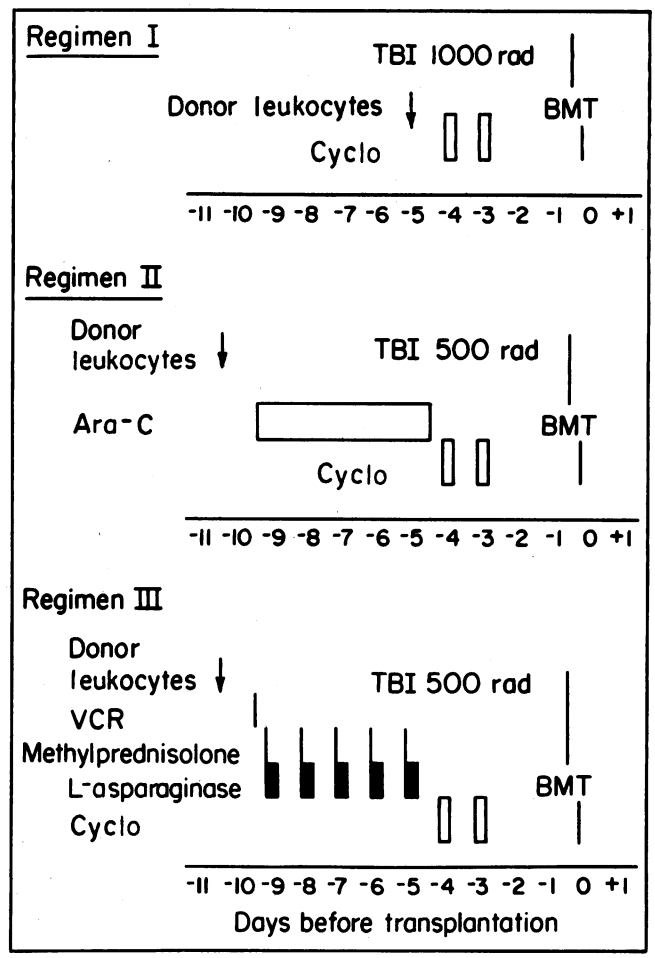

FIG. 1—Preparation for bone marrow transplantation (BMT) for patients with leukemia. TBI = total body irradiation; Cyclo = cyclophosphamide; Ara-C = cytosine arabinoside; VCR = vincristine. TBI was given on the day of transplantation (day 0), shortly before infusion of the marrow.

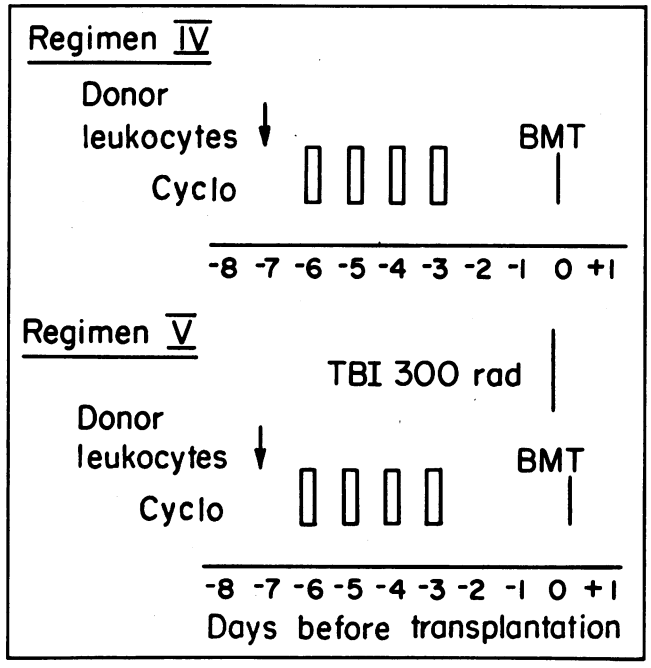

FIG. 2—Preparation for bone marrow transplantation for patients with aplastic anemia. Abbreviations as for Fig. 1.

regimen I, which included 1000 rad of radiation, survived more than 77 days; at the time of transplantation two of these patients had leukemia in relapse, and a third was in his third remission. To date no case of recurrent leukemia has been observed following marrow transplantation.

Of the six patients with Philadelphia-chromosome-positive CML four are surviving, 117 to 545 days after transplantation, and the Philadelphia chromosome has not been observed in marrow specimens examined following transplantation. Only one of the six patients (no. 22) underwent splenectomy before transplantation; this patient had received no chemotherapy prior to preparation for transplantation, and the marrow showed a minor second anomaly before transplantation.

For aplastic anemia

Of the 13 patients with aplastic anemia 11 are alive and well, and have essentially normal peripheral blood counts. When cytogenetic analysis has been done, the marrow cells after transplantation have been of the donor karyotype. In one of the two patients who died, pneumonia developed during the preparatory period; the other received marrow from a non-HLA-identical sibling. Two patients had disseminated herpes zoster 10 and 13 months after transplantation, and one other had an EBV infection characterized by acute hepatitis about 6 months after transplantation; the three patients recovered uneventfully from these infections.

Between ABO-incompatible siblings

Marrow transplantation was done between 10 ABO-incompatible donor–recipient pairs. Neither major nor minor transfusion reactions occurred in the immediate period after transfusion. In all five instances of a major ABO incompatibility transient hyperbilirubinemia with jaundice developed 5 to 10 days after transplantation. In the five instances of a minor ABO incompatibility the degree of hyperbilirubinemia was less and the patient did not become jaundiced during this period.

The hematologic reconstitution and survival of these 10 patients have been similar to those of the patients receiving marrow from an ABO-compatible sibling. Following complete reconstitution of the marrow there was no evidence of continuing hemolysis in the recipients of ABO-incompatible marrow. The reticulocyte counts have remained within the normal range, the erythrocytes have been morphologically normal, and repeated marrow aspirations have not demonstrated erythroid hyperplasia.

Plasma exchange and antibody adsorption

The fall in the anti-A titre with plasma exchange was rapid and proportional to the height of the titre before the exchange. The highest titre was in patient 8, who had received a leukocyte transfusion from the donor sibling 8 weeks before marrow transplantation. The changes in the anti-A titres in this patient during and after plasma exchange (Table III) were typical: the IgM titre fell rapidly, and the IgG titre tended to rise between the exchanges as the intravascular antibody levels equilibrated with the extravascular levels.

The anti-A titres of all five recipients of marrow from donors with a major ABO incompatibility were reduced before transplantation to 1:4 or less (Table IV). Patient 16, prepared with regimen III, had three plasma exchanges while receiving vincristine, methylprednisolone and L-asparaginase. Four days later the IgG anti-A titre was 1:32 and the IgM anti-A titre was 1:28, which suggested that this therapy had not inhibited the synthesis of anti-A. Two further plasma exchanges after cyclophosphamide therapy reduced the titre of circulating anti-A to less than 1:2.

The plasma exchange procedures and the red blood cell exchanges were well tolerated by all the patients.

GVHD

Acute GVHD developed in 25 of the 34 marrow transplant recipients (Table V). It was severe in 14, 8 of whom also had severe infection and died. In contrast, only 4 of the 20 patients with no GVHD or mild disease died. Of the nine patients in whom GVHD did not develop, three had identical twins as donors and three died within 30 days of receiving the transplant. In seven patients acute GVHD was followed by chronic cutaneous GVHD; three of these patients subsequently died.

The incidence and severity of acute and chronic cutaneous GVHD were not increased in the recipients of ABO-mismatched marrow transplants. Only one patient who had a major ABO incompatibility with his donor has died.

Discussion

This study has demonstrated that marrow transplan-

Table III—Changes in serum anti-A titre with serial plasma exchanges before marrow transplantation in patient 8

	Reciprocal of titre					
	IgM		IgG		Volume of plasma (ml)	
Day	Before exchange	After exchange	Before exchange	After exchange	Removed	Replaced
–4	4 096	64	4 096*	512	4 506	4 308
–3	64	4	1 024	64	6 616	6 177
–2	64	2	512	16	14 255	14 703
–1†	2	0	256	4	16 725	15 987
Total					42 102	41 175

*Hemolysins present.
†Immediately after the last plasma exchange six units of irradiated type A packed red blood cells were transfused. Beforehand the IgM and IgG titres were 0 and 1:2 respectively; afterwards both were less than 1:2.

tation can be performed successfully between histocompatible siblings despite ABO differences. When there was a major ABO incompatibility the chemotherapy regimen eliminated the production of ABO antibodies, and the plasma and red blood cell exchanges depleted the recipient of circulating anti-A. Patient 8 was unique in that marrow transplantation was successful despite marked sensitization to A substance because of a prior leukocyte transfusion from the donor. No evidence of compensated hemolysis has been found in any of the recipients of marrow from ABO-incompatible donors. This study has confirmed reports that marrow transplantation can be accomplished without increased morbidity between ABO-incompatible siblings who are otherwise well matched.[5-12]

Following the initial plasma exchanges the IgG anti-A titres in our patients tended to increase, but to lower levels than prior to the plasma exchange. This increase is attributable to the IgG antibody's entering the circulation from the tissues. The IgM anti-A titres showed this rebound phenomenon to a much lesser extent, which suggests that the IgM antibody is intravascular or is unable to enter the circulation readily. The anti-A titres were reduced to 1:4 or less prior to the infusion of ABO-incompatible marrow. Other studies have shown that when the anti-A titre is 1:8 or less, ABO-incompatible marrow can safely be given.[7] The total volume of plasma exchange necessary to reduce the serum anti-A level to 1:4 or less can be anticipated by plotting the anti-A titres in the patient's serum before and after each procedure against the volume of plasma exchanged.

The major life-threatening complication in this series of marrow transplants was GVHD. Acute GVHD occurred in 74% of the marrow recipients, and acute and chronic GVHD were major factors in 8 of the 12 deaths. Improved methods of supportive care and new approaches to immunosuppressive therapy may decrease the morbidity and mortality associated with GVHD.[21]

Marrow transplantation is now the treatment of choice for patients with aplastic anemia who have a suitable sibling donor.[4,22]* Transplantation early, prior to erythrocyte and platelet transfusions, has reduced the frequency of graft rejection, reduced the severity of GVHD and been associated with long survival. The role of marrow transplantation for patients with acute leukemia is becoming established. Results from large centres suggest that for young adults with a suitable sibling donor, transplantation is indicated during the first remission of AML and ALL.[1-3]

In our six patients with CML who underwent allogeneic marrow transplantation no recurrence of the Philadelphia chromosome has been observed to date. Thus, marrow transplantation is a promising form of therapy for CML. A previous report described successful marrow transplantation in four patients with CML for whom identical twins were donors.[23]

Marrow transplantation has thus emerged as an effective and potentially curable form of therapy for selected patients with leukemia and aplastic anemia. Our study, as well as others, has shown that ABO incompatibility between donor and recipient is not a barrier to marrow transplantation. The investigation of

*The National Advisory Committee on Marrow Transplantation of the Canadian Hematology Society has estimated an annual incidence of aplastic anemia of 4 per million population or 90 cases per year across Canada. Of the 90 patients, 12 to 18 will be less than 45 years of age, have a compatible donor and be suitable for marrow transplantation. Similarly, it can be estimated that between 130 and 140 patients with acute leukemia will present annually for marrow transplantation. This estimate is based on an annual incidence of acute leukemia in Canada of 65 per million population. If a remission rate of 60% is assumed, then in 900 of the 1500 patients seen annually there will be a remission; of these, 45% or 405 will be under 45 years of age, and about one third will have a compatible sibling and therefore be candidates for marrow transplantation (communicated by E.A. McCulloch to the Federal–Provincial Advisory Committee on Institutional and Medical Services).

Table V—GVHD and mortality in marrow transplant recipients and relation to ABO mismatching

Type of GVHD	No. of patients			
	All		ABO-mismatched	
	Total	Dead	Total	Dead
Acute, grade				
0	9	3	2	0
1	2	0	0	0
2	9	1	4	0
3	8	2	3	1
4	6	6	1	1
Total	34	12	10	2
Chronic cutaneous	7	3	4	2

Table IV—Plasma and red blood cell exchanges and anti-A titres in recipients of marrow from sibling with major ABO incompatibility

Patient no. and ABO–Rh type, donor/recipient	Plasma exchanges		Volume of red blood cell exchange (ml)	Antibody type	Reciprocal of titre		
	No.	Total volume (ml)			Before plasma exchanges	Just before transplantation	Peak after transplantation*
8, A+/O–	4	41 175	1 464	IgG	4 096	< 2	32
				IgM	512	< 2	< 2
16, AB+/B+	6	41 406	1 899	IgG	64	< 2	< 2
				IgM	128	< 2	< 2
18, A+/O+	3	24 209	1 963	IgG	256	< 2	ND
				IgM	32	< 2	ND
20, A–/O–	3	27 972	1 840	IgG	512	< 2	4
				IgM	64	< 2	< 2
28, A+/O+	3	20 280	1 892	IgG	2 048	4	ND
				IgM	128	< 2	ND

*ND = not determined.

other histocompatibility antigen systems will likely increase the number of individuals who can be used as marrow donors.[24]

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