Bone Marrow Transplantation for Refractory Acute Leukemia in 34 Patients With Identical Twins


Thirty-four patients aged 4–67 yr (median 17) with acute lymphocytic leukemia (ALL) (18 patients) or acute nonlymphocytic leukemia (ANL) (16 patients) who failed to enter complete remission (CR) or relapsed on conventional chemotherapy were treated with cyclophosphamide (CY). 60 mg/kg/day for 2 days. a marrow transplant from a genotypically identical normal twin. Sixteen of the patients received additional chemotherapy within the week before CY. After the transplant, 23 patients received immunotherapy consisting of killed autologous leukemic cells and/or normal twin peripheral blood lymphocytes, 16 as part of a prospectively randomized study. One moribund patient died before engraftment. Nine patients (6 ALL, 3 ANL) continued to have detectable leukemic cells. Twenty-four patients (70%) achieved CR. One of them died of viral hepatitis at 1 mo and another of viral interstitial pneumonitis at 4 mo in CR. Fourteen patients (7 ALL, 7 ANL) relapsed 2–16 mo (median 4) after transplantation. However, 8 patients (24%) (3 ALL, 5 ANL) remain in CR without any maintenance chemotherapy at 29–103 mo (median 80) after the transplant. The end results were not significantly influenced by the type of leukemia, the immediate pre-CY chemotherapy, or the immunotherapy. The results show that this approach, even when applied to endstage patients with acute leukemia in relapse, causes tolerable morbidity, rare nonleukemic deaths, and frequent remissions, some of which represent cures.

THE AVAILABILITY of normal identical twin marrow for infusion makes it possible to administer supralethal doses of antileukemic therapy in the hope of eradicating leukemia and then to save the patient from iatrogenic death. Thomas et al.1,2 treated three acute lymphocytic leukemia (ALL) patients with supralethal doses of total body irradiation (TBI) plus infusion of normal twin marrow and demonstrated that marrow function could be readily restored. Unfortunately, the leukemia recurred in all 3 patients within 2–3 mo. A decade later, approaches to obtaining a greater antileukemic effect were initiated by adding high-dose cyclophosphamide (CY) before the TBI and marrow infusion, and immunotherapy after the transplant, in the form of autologous irradiated leukemic cells and peripheral blood lymphocytes from the normal twin. Results reported3 on 16 patients thus treated for a variety of hematologic malignancies showed that the therapy was well tolerated and induced enduring remissions in some patients, but the recurrence or persistence of leukemia continued to be the major problem and cause of death. We now report the results obtained on 34 patients with refractory ALL or acute nonlymphocytic leukemia (ANL) who received a twin marrow transplant from January 1972 through July 1978, including an update of data on 11 patients previously reported.3 In some patients, an effort was made to increase the incidence and duration of posttransplant remission by further reducing the tumor load prior to transplantation by administering additional chemotherapy shortly before the CY and TBI. In addition, some of the patients participated in a prospective randomized study to determine the contribution of immunotherapy, if any, to the end results obtained.

MATERIALS AND METHODS

Patients

The patients included in this report (each identified by a unique patient number, UPN) were treated from January 1972 through July 1978 for ALL (18 patients) or ANL (16 patients) at the University of Washington Hospital, the Fred Hutchinson Cancer Research Center, or the Children’s Orthopedic Hospital in Seattle. Of 16 patients with ANL, 10 had AML, 1 had acute promyelocytic leukemia, 2 had erythroleukemia, 1 had acute monocytic leukemia, 1 had acute myelomonocytic leukemia, and 1 had acute undifferentiated leukemia (Table I). Patients were all in relapse after various chemotherapeutic regimens and all, except UPN 731, were considered refractory and with very poor prognosis.

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Table 1. Clinical Characteristics of 34 Patients Transplanted for Refractory Leukemia From a Normal Twin Donor

<table>
<thead>
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<th>Unique Patient Number</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Remissions</th>
<th>Therapy</th>
<th>CNS Leukemia</th>
<th>Cytoreduction§</th>
<th>Immunotherapy†</th>
<th>Relapse (Day after Transplant)</th>
<th>Survival††</th>
<th>Cause of Death</th>
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<td>NR</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>NR</td>
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</table>

*ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; AMML, acute myelomonocytic leukemia; AMOL, acute mononocytic leukemia; APML, acute promyelocytic leukemia; ERY/AML, erythroleukemia/acute myelocytic leukemia; AUL, acute undifferentiated leukemia.

†V, vincristine; P, prednisone; MP, 6-mercaptopurine; CY, cyclophosphamide; L-ASP, L-asparaginase; ARA-C, cytosine arabinoside; TG, 6-thioguanine; RT, radiation therapy; MTX, methotrexate; it, intrathecal; COAP, a combination of CY, V, ARA-C and P; BCNU, bis-chlorethyl nitrosourea; BMT, bone marrow transplant; DNR, daunorubicin; ADR, adriamycin; VAMP, a combination of V, MP, MTX and P; POMP, a combination of V, P, MP and MTX; AZC, azacytidine; HDMTX, high dose MTX and leucovorin rescue; VAPA-10, a combination of V, P, ARA-C and ADR; DMB, dimethyl busulfan.

††Lumbar puncture on admission for transplant revealed leukemia cells (+ +), no leukemia cells (--), or was not done (ND).

§Systemic antileukemic chemotherapy administered within a week or less before CY-TBI.

¶All patients received 1000 rad TBI, except UPN 295 who received 1130 rad.

*See text for details.

**The first 9 patients (No) were transplanted before a randomized trial of immunotherapy was initiated. Thereafter, patients were randomized (Yes) to receive or not to receive both tumor and lymphocytes, but if tumor or lymphocytes were not readily available, patients were nonrandomized (NR) and received whichever was available.

††As of June 30, 1980.
Details of the clinical characteristics of each individual patient are provided in Table 1. The patients were 4-67 yr old (median 17) and had experienced 0-4 complete remissions (CR). Twelve of the 34 patients (4 of 18 ALL and 8 of 16 ANL) had never achieved a CR. On admission, most patients were in relatively poor clinical condition due to the leukemia and/or their previous chemotherapy. Twelve of 34 patients had central nervous system (CNS) leukemia at some time—4 treated with intrathecal methotrexate (MTX), 1 with CNS radiation, and 7 with both. Nine of the 12 patients had CNS leukemia on admission for transplantation. One patient, UPN 524, was transplanted solely for refractory CNS leukemia while still in her first marrow remission.

Identity between twins was determined by physical resemblance, HLA typing, mixed leukocyte culture tests, and erythrocyte antigen typing and often by dermatoglyphic studies, erythrocyte enzyme electrophoretic phenotype determinations, and pathologic reports of the placenta.

Informed Consent and Donor Information

All protocols were reviewed and approved by the Human Subjects Review Committee of the University of Washington or the Fred Hutchinson Cancer Research Center. The procedures, along with potential risks and benefits to recipients and donors, were explained in detail to appropriate family members.

Donor marrow was obtained under anesthesia by multiple aspirations from the anterior and posterior iliac crests bilaterally. The average volume of marrow mixed with blood was 586 ml (range 300-780). The marrow was infused intravenously (i.v.) within 3 hr after it was obtained. Donors were hospitalized for 1-2 days and experienced postoperative pain at the aspiration sites without other complications.

Pretransplant Chemoradiotherapy and Marrow Transplantation

All patients received CY i.v. 60 mg/kg on each of 2 successive days, and 2-4 days later, a supralethal dose of TBI from 2 opposing 60Co sources, as previously described. Until September 1975, the midline tissue dose was 1000 rad delivered at 5.6 R/min. Thereafter, it was 920 rad at 8.0 R/min. Marrow transplantation was performed within 24 hr after TBI. Patients received 0.8-9.0 x 10^6 nucleated marrow cells/kg body weight (median 3.2). The day of marrow infusion was designated day 0, and subsequent days are numbered from that point.

Cytoreductive chemotherapy. Sixteen patients (7 with ANL, 9 with ALL) received additional chemotheraphy shortly before the CY. Although all patients admitted for a transplant had received chemotherapy at some time, the additional "cytoreductive chemotherapy" is defined as having been completed within a week or less before the CY. The regimens employed (Table 1) varied from patient to patient through the years, partly depending on previous drug history and clinical condition. Patients were not selected to receive the additional chemotherapy on the basis of specific criteria but because they were admitted at a time when the possible benefit of such therapy on a larger group of patients was being tested.

Therapy for CNS leukemia. The week before the transplant, we administered intrathecal MTX to 7 (UPN 175, 397, 501, 524, 562, 670, 799) of the 9 patients who had active CNS leukemia, to 1 (UPN 381) of 3 patients who had a history of CNS leukemia but had no active disease on admission, and to 10 of the 22 patients who had no CNS leukemia by history or on admission (UPN 316, 560, 594, 702, 722, 728, 731, 766, 793, 864). Patient UPN 731 also received intrathecal MTX every 2 wk from day 32 through 74 after marrow transplantation. Patients who received only intrathecal MTX are not included in the analysis as part of the group receiving aggressive cytoreductive chemotherapy before the CY.

Immunotherapy

After marrow transplantation, some of the patients received immunotherapy in the form of normal twin lymphocytes for 3 wk and the patients' own irradiated tumor cells for 1-5 wk, as previously described. Beginning in 1974, patients for whom leukemic cells and donor lymphocytes were accessible were randomized to receive or not to receive both leukemic cells and lymphocytes. If either tumor cells or lymphocytes were not readily accessible, then the patient was not randomized but received whichever were available, i.e., tumor cells or lymphocytes.

Supportive Care

Beginning in 1977, Hickman-type right atrial catheters were placed in every patient and used for administration of fluids, antibiotics, and blood products, and for hyperalimentation. To maintain a platelet count of at least 20,000/cu mm, most patients initially received platelet transfusions from random donors; platelets from the twin donor were given when the patient became refractory to random platelets. When twin buffy coat cells were used for immunotherapy, they usually contained enough platelets for support. Blood products from non-twin donors were always irradiated with 1500 rad to inactivate immunologically competent cells so as to avoid a possible graft-versus-host reaction.

All patients were managed in single rooms with conventional hospital reverse isolation, except UPN 766 who was treated in a laminar air flow room with gut sterilization and a sterile diet. Fever of unknown origin above 38°C was treated with broad spectrum antibiotics.

No antitumor maintenance chemotherapy was administered to patients who went into CR after transplantation except intrathecal MTX in UPN 731. When leukemia recurred in the marrow, various chemotherapy regimens were sometimes used by the referring physician, but no substantial responses were induced. Two patients (UPN 560 and 728) underwent a second twin marrow transplant following relapse.

RESULTS

Overall Results

Data on each of the 34 patients are shown in Table 1, and the end results are summarized in Table 2. One moribund patient with refractory CNS leukemia became comatose on day 0 and died of a cerebellar herniation syndrome on day 5 after transplantation. Nine patients continued to have detectable leukemic cells and never experienced a CR. Twenty-four patients went into CR. Two of them died without evidence of leukemia—1 of viral hepatitis at 1 mo and 1 of viral interstitial pneumonitis at 4 mo after transplantation. Leukemia recurred in 14 patients. Although the relapses usually occurred within a few months, 3 patients did not relapse until 13-16 mo. Finally, 8 patients remain alive and well in CR without any maintenance therapy at 29-103 mo (median 80 mo) after marrow transplantation.

Using the method of Kaplan and Meier, a plot of the survival of the 34 patients (Fig. 1) shows a
decreasing death rate after marrow transplantation. The slope of the curve, on a semilogarithmic scale, estimates the instantaneous death rate at any point in time assuming that the patient has lived up to that time. The early high rate of death reflects failure to induce CR. The middle and somewhat lower rate of death reflects relapse after CR has been induced. The last death occurred on day 773 after the original marrow transplant, and no deaths have occurred beyond that point.

Figure 2 shows a plot of the Kaplan-Meier product limit estimates of the probability of being in remission as a function of time after marrow transplantation. The 9 patients who had refractory leukemia and never went into CR are plotted in this figure as having relapsed on day 0. The slope of the curve indicates a relatively constant rate of relapse for the first year after transplantation and a low rate thereafter. The latest relapse in this series of patients occurred 16 mo after transplantation.

Table 2 shows no significant difference between the results obtained in patients with ALL and those with ANL. Age also did not determine prognosis after transplantation. Thus, patients who failed to enter a CR were 4-37 yr old (median 16), those who relapsed were 5-67 yr old (median 19), and those who remain in long-term CR are 8-57 yr old (median 17).

Cytoreductive Chemotherapy

Additional chemotherapy shortly before CY had no significant effect on persistence or recurrence of leukemia (Table 1). Thus, of 16 patients who received additional chemotherapy, 10 (4 AML, 6 ALL) either never went into CR or went into CR and then relapsed, 2 died while in CR, and 4 are long-term survivors. Similarly, of 18 patients who received no additional chemotherapy, 1 died on day 5, 13 (6 AML, 7 ALL) exhibited persistent leukemia or leukemia that relapsed, and 4 are long-term tumor-free survivors. Thus, the additional chemotherapy did not increase either the probability of CR induction or the CR duration.

Immunotherapy

Analysis of data presented in Table 1 reveals that immunotherapy also had no significant effect. Of the 34 patients, 1 patient died on day 5 before any immunotherapy and 9 others had been part of a nonrandomized study that could not be evaluated. Of the remain-
ing 24 patients, 7 were randomized to receive both tumor cells and lymphocytes and 5 to receive neither. Twelve patients could not be randomized: 3 received neither lymphocytes nor tumor cells and 9 received only lymphocytes. No significant differences were detected between these very small groups.

**Engraftment**

Following TBI, severe pancytopenia occurred in every patient with total disappearance of granulocytes from the blood. Histologic evidence of marrow engraftment was usually detectable within 2 wk after transplantation. The absolute granulocyte count rose to 500/cu mm by day 9–35 (median 16) after marrow transplantation, and platelets were no longer necessary to maintain a count above 20,000/cu mm by day 10–32 (median 16).

No relationship was noted between the number of nucleated marrow cells infused and the time to rising peripheral blood counts. For example, patients who received 3.0–9.0 x 10⁶ marrow cells/kg did not differ significantly in their kinetics of hemopoietic restoration from patients who received only 0.8–2.9 x 10⁶, as reflected by days to attainment of an absolute granulocyte count of 200 or 500/cu mm. Chemotherapy shortly before CY and TBI also had no detectable effect on posttransplant hemopoietic recovery.

**Early Side Effects and Complications**

The acute side effects of the CY and TBI have been previously described and were manageable. Infusion of the filtered marrow caused no problems. Immuno-therapy caused erythema at the site of tumor inoculation, which usually disappeared in 12 hr.

The gastrointestinal toxicity of the chemoradiotherapy was extremely variable in severity and duration, with nausea and anorexia (exacerbated by oral mucositis) occasionally persisting for 2–3 wk. Significant weight loss occurred in all patients until hyperalimentation was adopted as a routine supportive measure.

**Infections.** Fever above 38°C occurred in every patient sometime during the first 2 wk after marrow transplantation and usually disappeared as the granulocyte count rose. In 10 patients with fever, no specific infectious organism was ever identified but the fever disappeared as the peripheral granulocyte count rose. Bacterial infections were documented in 11 patients during granulocytopenia. Bacteremia occurred in 8 patients—1 with coagulase positive *Staphylococcus aureus*, 1 with *Diplococcus pneumoniae*, 5 with *E. coli*, and 1 (UPN 175) with *Pseudomonas aeruginosa* as well as *E. coli* and *D. pneumoniae*. The only other bacterial infections consisted of a staphylococcal sinusitis, staphylococcal cellulitis, and an *E. coli* infection in the urinary tract. All bacterial infections responded to appropriate antibiotics.

 Cultures positive for fungus—all *Candida albicans*—occurred in 13 patients. The fungus was cultured from the mouth alone in 6 patients, the esophagus in 1, the urine in 3, the skin in 3, and blood in 1 (UPN 175). Most patients were treated with Mycostatin alone, but several received amphotericin. No patient died of fungal infection.

Viral infections occurred in 13 patients. Perioral herpes simplex with mucositis occurred in 6 patients during the granulocytopenic period and tended to improve dramatically with a rise in granulocyte count. Three patients developed herpetic esophagitis. 1 patient had a scalp infection by herpes simplex virus and cytomegalovirus (CMV) in the throat, and 2 patients excreted CMV in the urine. One child. UPN 267, contracted non-A, non-B viral hepatitis and died 1 mo after transplantation. The only other patient who died without evidence of leukemia was UPN 316, who developed viral interstitial pneumonitis and died at 4 mo after transplantation.

Six additional patients (UPN 258, 524, 525, 670, 766, and 793) also developed interstitial pneumonitis 11–85 days (median 58) after marrow transplantation. Patient UPN 670 underwent a lung biopsy, but no etiology was found and the pneumonitis resolved. Patient UPN 524, who had persistent CNS leukemia, had a similar finding on biopsy but died with pneumonitis. The other 4 patients had clinically less severe pneumonitis, did not undergo lung biopsy, and the pneumonitis resolved in all. Additional chemotherapy before CY or immunotherapy administered after transplantation had no significant effect on the incidence or type of infections observed.

**Other side effects.** Generalized rashes occurred in 18 of the 34 patients beginning on day 0–17 (median 10) after marrow transplantation, which usually disappeared within a week. The rash was quite variable in character and distribution but often was maculopapular, erythematous, and occasionally pruritic, and usually generalized. Rashes were usually associated temporally with granulocytopenia, fever, multiple antibiotics, and transfusions of blood products. Almost all were thought to be drug induced. Skin biopsies performed on 9 patients were either nondiagnostic or consistent with drug rash or “chemotherapy or radiation effect.” No therapy was administered, but drugs were discontinued whenever possible. Rashes disappeared in all patients before they were discharged from the hospital and none become chronic.

Transient and mild elevations in the bilirubin and/or in the transaminases were noted in 7 patients 1–28
days after transplantation. In 5 other patients, LFTs, which were abnormal before the transplant, became normal after the transplant. No patient developed chronically abnormal liver function tests. No cases of veno-occlusive disease of the liver were observed.

The median duration of hospitalization after marrow transplantation was 25 days (range 12–39). Patients were usually discharged from the hospital directly home to the outpatient care of their referring physician. Bone marrow examinations were performed every 1–2 mo during the first year and less frequently thereafter.

Late Complications

Recurrence of leukemia. The principal problem has been recurrence of leukemia. The recurrence was always in the bone marrow except for UPN 562 who relapsed in the CNS at 4 mo, in the parotid gland and orbit at 14 mo, and in lymph nodes at 15 mo after transplantation. Various chemotherapeutic regimens were used for recurrence, usually without significant benefit so that the patients died with leukemia 6–345 days after marrow relapse (median 42).

Two patients were treated with a second marrow transplant. UPN 560 failed to clear her marrow of blasts after the first transplant. She then received dimethyl busulfan and a second twin marrow transplant. The percentage of leukemic cells in the marrow decreased, but the patient died of cerebral hemorrhage 2 mo after the second transplant. Patient UPN 728, who relapsed 13 mo after the first marrow transplant, received a second marrow transplant after vincristine, daunomycin, cytosine arabinoside, prednisone, and 400 rad TBI. A CR was induced and maintained with MTX and 6-mercaptopurine. Marrow relapse occurred at 10 mo after the second transplant and the patient died.

CNS leukemia. Data in Table 1 show that of 9 patients with active CNS disease at the time of admission for marrow transplantation, 7 exhibited persistent leukemic cells (including UPN 618 who died on day 5), 1 relapsed in the CNS at 4 mo, and 1 (UPN 501) remains in CR at 70 mo. Of 3 patients without active disease but with a history of CNS leukemia due to ALL, 1 (UPN 258) relapsed both in the CNS and marrow at 7 mo, 1 (UPN 381) relapsed in the marrow at 13 mo, and 1 (UPN 339) remains in CR 73 mo after marrow transplantation.

Status of Long-Term Survivors

Patients who remain in long-term CR live relatively normal active lives. They are not particularly susceptible to infections. Of 11 patients in CR 1 yr or more after marrow transplantation, 2 (UPN 295 and 793) developed localized herpes zoster infections at 5 and 12 mo after transplantation and recovered normally without specific therapy.

One late effect, attributed to the TBI, has been the development of cataracts in 3 of the 8 long-term survivors at 3–5 yr after grafting. Two required surgical correction.

None of the 34 patients have had acute or chronic graft-versus-host disease. Moreover, the 8 long-term survivors have not exhibited any of the clinical features associated with chronic graft-versus-host disease.10

Patients (UPN 133, 142, 283, 339) who received the transplant as children experienced some growth retardation and remain shorter than their twins. Patient UPN 133 who was transplanted at age 13 became pregnant at 19 but was aborted at 3 mo.

Secondary malignancies have not been a problem. However, patient UPN 793 who had been treated for a diffuse poorly differentiated lymphocytic lymphoma developed acute myelomonocytic leukemia 3 yr later, received a twin marrow transplant for it and then underwent resection for rectal carcinoma 14 mo after marrow transplantation for leukemia. He is now well without evidence of any malignancy.

All marrow donors remain well without evidence of hematologic disease.

DISCUSSION

The possibility that normal identical twin marrow infusion might overcome the potentially fatal aplasia induced by the large doses of drugs and/or radiation required to eradicate a hematologic malignancy was first tested 2 decades ago. The results11,12 demonstrated that the approach could indeed restore normal hematopoiesis but failed to induce long-term remissions. After a long hiatus, an attempt at a greater antileukemic effect was made by adding to the regimen of TBI and twin marrow a form of potential immunotherapy and/or chemotherapy.11,12 This combined approach, when applied to 16 patients with various hematologic malignancies, was associated with tolerable morbidity and some long unmaintained CRs.13 Indeed, 6 of the patients were reported13 as “cured,” including 4 patients presented in this report (UPN 133, 142, 283, 295). However, there were too few patients in that heterogeneous group to permit any conclusions about the benefit, if any, of the additional chemotherapy or immunotherapy. This report presents our experience with 34 patients who are less heterogeneous in that all had ALL or ANL in relapse, all were refractory to the therapy available at the time, and all received CY plus 920–1000 rad TBI. Eleven of the 34 patients were reported previously13 and are updated here.
The results show that CR can often be induced even in patients who are in poor clinical condition with endstage refractory leukemia. Although the duration of the CR tended to be quite short, 3 patients who relapsed did not do so for 13–16 mo. Since no patient relapsed after 16 mo, the plateau in recurrence rate is consistent with the probability that patients remaining in CR beyond 16 mo are cured. Indeed, 8 of the 24 patients who went into CR remain in unmaintained CR for 29–103 mo and 6 of the 8 are beyond 5 yr and are leading normal active lives. The morbidity experienced by the 34 twin marrow transplant recipients was extremely variable but generally comparable to that of aggressive combination chemotherapy. No patients were lost due to bacterial or fungal infections. The only nonleukemic deaths were due to a viral hepatitis and a viral interstitial pneumonitis.

In an effort to induce more and longer remissions, we added cytoreduction in the form of chemotherapy shortly before the CY and TBI. The cytoreductive chemotherapy varied from one patient to another, partly depending on the drug history and the anticipated ability of the patient to tolerate the toxicity and time required for the additional therapy. Since many patients had already received the known active chemotherapeutic agents, the additional chemotherapy often included drugs to which the patient had already been exposed. The gastrointestinal morbidity was perhaps somewhat greater in patients receiving cytoreduction. Moreover, the 2 nonleukemic deaths in CR occurred in patients given cytoreduction, as did the 1 death due to idiopathic interstitial pneumonitis in the presence of CNS leukemia (UPN 524). No significant difference was noted in the frequency or duration of posttransplant CR between 16 patients who received cytoreduction and the 18 who did not. Cytoreductive chemotherapy might be expected to be more effective if it were to consist of drugs to which patients have not previously been exposed and which have significant antileukemic efficacy.

Immunotherapy had no detectable effect on CR induction and duration and did not affect the incidence of infectious complications. The most obvious effect of lymphocyte infusion was a decreased need for random platelet transfusions. Despite the absence of a detectable antitumor effect of immunotherapy in this study, several recent observations encourage the continued evaluation of twin lymphocytes in marrow transplantation for leukemia. In addition to an older report that a mouse lymphoma could be cured by lethal dimethyl myleran and normal syngeneic spleen and marrow cells, a mouse leukemia and a rat leukemia were recently reported to be curable by CY plus normal syngeneic spleen and/or marrow cells. A major additional impetus for lymphocyte infusion studies is provided by the recently reported statistical analysis of the leukemic relapse rate after allogeneic versus syngeneic marrow transplantation, which strongly implied that there exists a graft-versus-leukemia effect in man, as originally suggested by studies in animals. The implication that an antileukemic effect can be exerted by adoptive transfer of cells represents a cogent justification for continued studies of lymphocyte infusions.

Interstitial pneumonitis occurred in 7 patients in this series and caused the death of 2 patients. Although 2 other patients died early of nonleukemic causes while still at risk of ISP, the incidence of interstitial pneumonitis in this series of identical twin marrow transplants is somewhat lower than that observed in comparable patients transplanted with HLA-compatible sibling marrow, and the fraction of the interstitial pneumonitis being fatal is also lower than that reported in allogeneic marrow transplant recipients (77%). The differences must be attributable to the clinical or subclinical graft-versus-host reaction, the prophylactic use of MTX for graft-versus-host disease, and/or the therapy for graft-versus-host disease in the allogeneic setting.

Skin rashes were common, usually remained undiagnosed, and always resolved. The possibility has recently been raised that rashes in recipients of identical twin marrow might reflect graft-versus-host disease. Although some of the rashes seen in our twin transplant recipients were clinically similar to those observed in allogeneic marrow transplant recipients, they tended to disappear fairly rapidly, often in association with withdrawal of a suspected offending agent. None of the twin marrow recipients experienced persistence or chronicity or recurrence of their rashes. Most significantly, their coded skin biopsies differed significantly from skin biopsies obtained from allogeneic transplant recipients with rashes thought to reflect graft-versus-host disease.

Bone marrow transplantation should be considered—and is now being performed—for patients in chemotherapy-induced CR when such remissions are anticipated to be of relatively short duration, such as the first CR in ANL for all age groups, the first CR in ALL for adults, the second or subsequent CR for ALL in children, or in first CR for high-risk childhood ALL. Recently reported results of allogeneic marrow transplants for acute leukemia in remission (especially for ANL in first chemotherapy-induced CR) are extremely encouraging and represent a strong argument for the same approach in identical twins. For the older patient who may be considered at high risk for vigorous combination chemotherapy
induction regimens, it may be appropriate to use twin marrow transplantation as the first line therapy.

Twin marrow transplantation should also be considered for patients with hematologic malignancies other than acute leukemia. Thus, for example, twin marrow transplantation has been used successfully in patients with chronic myelogenous leukemia while still in the chronic phase and in several patients with lymphosarcoma-leukemia, one of whom represents the longest tumor-free survivor of a twin marrow transplant, now at 117 mo. Finally, the approach need not be restricted to patients with hematologic malignancies but should be tested in other malignancies that are known or suspected to be sensitive to high doses of chemotherapy or TBI. The results would not only define the therapeutic utility of marrow transplants in twins but may also have significant implications to autologous marrow transplantation. Twin marrow transplantation illustrates what can be achieved by supralethal chemoradiotherapy and marrow without the complication presented by possible presence of tumor in the infused marrow. In fact, unless autologous marrow is postulated to exert an antitumor effect greater than that of twin marrow, twin marrow transplantation probably represents the best results that one can expect with autologous marrow. Therefore, twin marrow transplantation can be used to develop or identify the most effective chemoradiotherapy regimens to be used for autologous marrow transplantation.

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Bone marrow transplantation for refractory acute leukemia in 34 patients with identical twins

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