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Monoclonal-Antibody-Purged Autologous Bone Marrow Transplantation for Relapsed Non-T-Cell Acute Lymphoblastic Leukemia in Childhood

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A. Introduction

Acute lymphoblastic leukemia (ALL) in childhood is a curable disease for the majority of patients [1]. Most children who relapse, however, have a poor prognosis. Although second complete remission can usually be obtained, the long-term disease-free survival in most series is less than 10% [2, 3]. Therefore, allogeneic bone marrow transplantation has been considered the treatment of choice for children with ALL in second hematologic remission who have an HLA-identical mixed leukocyte culture (MLC) nonreactive sibling donor. An alternative approach has been autologous bone marrow transplantation.

Since leukemic cells almost certainly contaminate remission bone marrow, methods to eradicate leukemic cells in vitro have been developed. The essential elements of in vitro purging are removal of leukemic cells and in vivo hematopoietic reconstitution by the treated bone marrow. The two strategies for in vitro removal of contaminating leukemic cells include the use of pharmacologic agents, mainly the cyclophosphamide derivatives ASTA Z 7557 [4] and 4-hydroperoxycyclophosphamide [5], and the use of heteroantisera [6] or monoclonal antibodies directed against cell surface antigens of leukemic cells. Monoclonal antibodies are utilized with exogenous complement [7, 8] or immunotoxins [9, 10] or immunophysical methods [11]. In a model system that utilizes leukemic cell lines, one can demonstrate that monoclonal antibodies, complement, and drugs have a higher efficacy in the selective elimination of clonogenic cells than either modality alone [12, 13].

There are a number of practical and theoretical obstacles to overcome. Chemotherapeutic agents might have excessive toxicity to stem cells, and, thus, hematopoietic recovery would be impossible. The antigenic heterogeneity of malignant cells in the individual patient might mitigate against in vitro cytolysis of all blast cells. Furthermore, antibodies may cross-react with normal cells, especially progenitors or stem cells. The phenotype of a small population of progenitor cells for leukemic blasts may not be the same as the phenotype for the majority of blast cells [14]. It would be more important to purge these malignant progenitor cells and perhaps their precursors. Finally, none of the clinical studies that apply one or the other method of in vitro purging of remission bone marrow has been done in a setting where the efficacy of the in vitro manipulation could be compared to the use of nonpurged bone marrow.

In this report, we provide an update and critical evaluation of our clinical experience in autologous bone marrow transplantation for children with ALL in second and subsequent remissions. Moreover, we will compare these results with our concurrent allogeneic transplant experience.

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B. Methods and Materials

Between November 1980 and June 1986 we transplanted 31 children under the age of 18 for non-T-cell ALL.

I. Elimination of Leukemic Cells from Remission Bone Marrow In Vitro

Two murine monoclonal antibodies, J5 [15] and J2 [16, 17], were utilized with rabbit complement. The J5 antibody reacts with the common acute lymphoblastic leukemia antigen (CALLA), a 100-kd glycoprotein expressed on leukemic cells of approximately 80% of patients with non-T-cell ALL. J2 recognizes an associated 26-kd glycoprotein (gp26). Although in the majority of cases of non-T-cell ALL leukemic cells express both CALLA and gp26 antigen, there are instances when only one of these antigens is present [18]. In over 90% of cases, leukemic cells will express at least one of these antigens, which independently might serve as a target for monoclonal antibody binding and complement lysis. The generation, characterization, and utilization of the monoclonal antibodies in the in vitro elimination of leukemic cells have been described previously [7, 19, 20]. The first 13 patients had marrow treated with only one antibody: J5 in 12 patients and J2 in 1 patient. After an experimental in vitro system indicated that two antibodies resulted in higher cell kill [21], the next 18 patients had their marrow treated with both antibodies.

II. Cytoreductive Chemotherapeutic Treatment and Radiation Therapy In Vivo

Patients with relapsed ALL were eligible if their leukemic cells expressed CALLA or gp26. Patients with HLA-compatible donors, as well as those in whom a complete remission could not be induced with chemotherapy alone, were excluded. After remission induction (usually with vincristine, prednisone, and asparaginase), all children received at least one course of intensification therapy consisting of VM-26, cytosine arabinoside (ara-C), and asparaginase, together with intrathecal hydrocortisone and ara-C (Table 1). Patients who had not previously

Table 1. Intensification therapy

		Day			
		1	3	7	10
Vm-26	200 mg/m² i.v.	×	×	×	×
Ara-C	300 mg/m² i.v.	×	×	×	×
Asparaginase	25000 IU/m² i.m.	×		×	
Ara-C	40 mg i.t.	×	×	×	×
Hydrocortisone	15 mg i.t	×	×	×	×

Table 2. Ablation therapy

			Pretransplant day									
			−9	−8	−7	−6	−5	−4	−3	−2	−1	0
Vm-26	200 mg/m²		×				×					
Ara-C	500 mg/m² × 5	n = 22	▨	▨	▨	▨	▨					
	500 mg/m² × 7	n = 6										
	3 g/m² × 6	n = 3										
Cyclophosphamide	60 mg/kg							×	×			
TBI 850 cGy		n = 12										
1200 cGy	(200 cGy × 6)	n = 16								×	×	×
1300 cGy	(216 cGy × 6)	n = 3								×	×	×
Bone marrow reinfusion												×

N: number of patients treated;
TBI: total body irradiation.

received intensive treatment with an anthracycline were also given a single dose of doxorubicin. After recovery from intensification therapy, bone marrow was harvested and ablation initiated (Table 2). During the study period, several dose adjustments were implemented. All patients received cyclophosphamide (60 mg/kg) in the days immediately preceding radiation therapy. They also received ara-C during the days preceding cyclophosphamide treatment. Twenty-two patients were given ara-C (500 mg/m^2) per day for 5 days by continuous infusion. In an effort to improve antileukemic efficacy, six children were given the same daily dose for 7 days. This schedule was abandoned because of concern about increased morbidity secondary to prolonged marrow aplasia. The most recently treated patients were given 3 gm/m^2 for six doses. VM-26 was administered on the first and last day of the ara-C infusion. Additionally, eight patients were treated with asparaginase at the time of the first VM-26 dose. All patients received total body irradiation at 5 cGy per minute. During the trial the total dose was increased and fractionated. The first 12 patients received 850 cGy in a single fraction, and the following 16 patients received 1200 cGy fraction in six 200 cGy doses delivered twice daily. Most recently, the total dose was further increased to 1300 cGy with 216 cGy fraction twice daily. Small lead shields were used to attentuate the pulmonary dose by 15%. Following the last dose of total body irradiation, the antibody-treated autologous bone marrow was thawed and directly infused by rapid intravenous bolus. No chemotherapy was administered after transplantation.

III. Study Population

Of the 31 patients, 21 were transplanted in second remission, 8 in third remission, and 1 child in fourth remission. The analysis also includes one child transplanted in first remission. This child had required more than 100 days to enter remission. Thirteen of the children had experienced an initial relapse while receiving therapy, and 17 had relapsed after stopping treatment. The median duration of first remission was 24 months (range 2–84), and the median duration of the second remission for the nine children transplanted in subsequent remissions was 8 months (range 2–54). The last remission prior to transplant had a median duration of 2 months (range 1–7).

Analysis of the sites of relapse prior to transplantation showed that 18 patients had bone marrow (BM) relapse, 2 had central nervous system (CNS) disease, and 2 had isolated testicular relapses only. Either consecutively or simultaneously, five children had recurrent BM and CNS disease, two had BM and testicular disease, and one had involvement of BM, CNS, and testis. The median age at the time of transplantation was 7.4 years (range 3.2–15.7). There were 24 males and 7 females.

Beginning in 1979, we adopted a treatment policy of allogeneic bone marrow transplantation for all patients with relapsed ALL who had histocompatible donors. This policy was modified in 1981 to exclude individuals whose relapse occurred more than 1 year after stopping chemotherapy. Twenty-two patients received an allogeneic bone marrow transplant at our own center, the Memorial Sloan-Kettering Cancer Center, the Seattle Bone Marrow Transplantation Center, the University of Kentucky, or the University of Iowa. The autologous and allogeneic transplant populations were comparable with respect to age and white blood count at diagnosis, as well as to the duration of the initial complete remission. There were two major differences between the groups. Most patients in the allogeneic group had relapsed after intensive chemotherapy, whereas the majority of patients in the autologous group had relapsed after more conventional chemotherapy. Ablative therapy for the allogeneic patients included only cyclophosphamide and total body irradiation, as compared to the more intensive preparative regimen for the autologous patients.

IV. Statistical Methods

For analysis of event-free survival, events were defined as relapses or remission deaths. Times were calculated from the day of bone marrow transplantation. The Kaplan-Meier

method was used to estimate survival distributions for event-free survival [33]. The two-sided log-rank procedure was utilized to assess the statistical significance of treatment differences between time distributions [34]. The Fisher exact test was used to compare outcome with respect to prognostic features which were categorized [34].

C. Results

After autologous bone marrow transplantation, the probability of event-free survival at 5 years was 27% ± 16% (Fig. 1). Of the 31 patients, 21 had an event and 10 remained in continuous complete remission. There was a high incidence of remission deaths (9 patients), with all deaths secondary to toxicity occurring within 3 months of transplantation. Four patients died of aspergillosis, three of hemorrhage, and two of interstitial pneumonitis of unknown etiology. The majority of transplants were performed in single isolation rooms without high-energy particulate filtration. Hematologic recovery was noted in all patients who survived more than 20 days.

Twelve patients relapsed between 2 and 14 months (median 4.5 months) after transplantation. Nine of them relapsed in the BM only, two simultaneously in the BM and an extramedullary site, and one in the retro-orbital space. The three patients with recurrent extramedullary disease were all individuals who had previously relapsed in only extramedullary sites prior to the procedure. Of the five patients with only extramedullary disease prior to transplantation, one is in continuous complete remission at 53 months, one died of toxicity, and three relapsed, all within the BM and an extramedullary site.

The occurrence of an isolated or combined extramedullary relapse prior to transplantation was not a prognostic factor, nor was the initial presenting white blood count. The duration of the initial remission, however, was prognostically highly significant ($p = 0.0028$) for event-free survival post-transplantation (Fig. 2). Of the 14 patients with an initial remission of more than 24 months, 3 died secondary to toxicity, 2 relapsed, and 9 remained in continuous complete remission. Of the 17 children whose initial remission was shorter than 24 months, 6 died

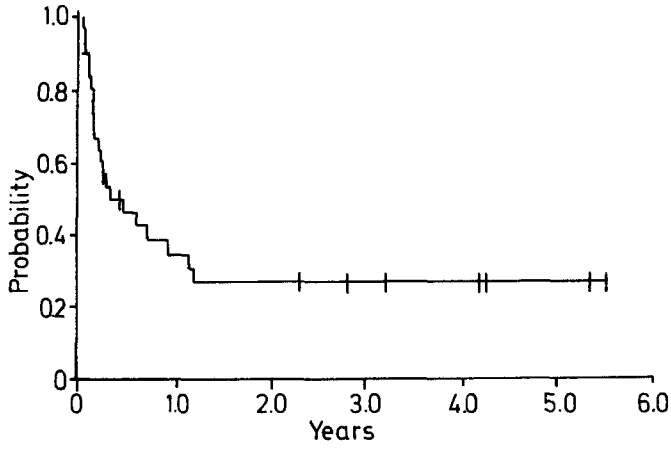

Fig. 1. Probability of event-free survival after autologous bone marrow transplantation

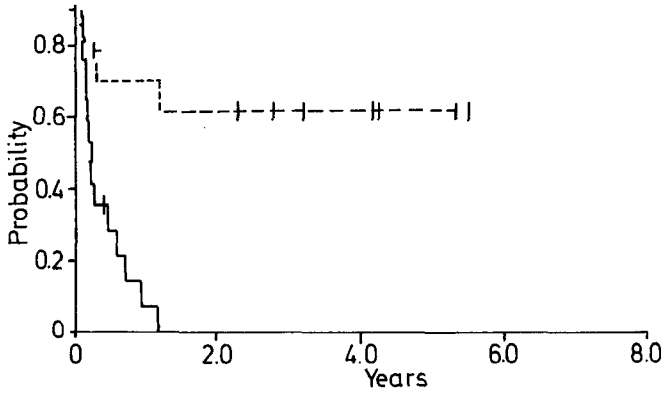

Fig. 2. Probability of event-free survival as a function of duration of longest remission prior to transplantation. (—— less than 24 months; – – – more than 24 months)

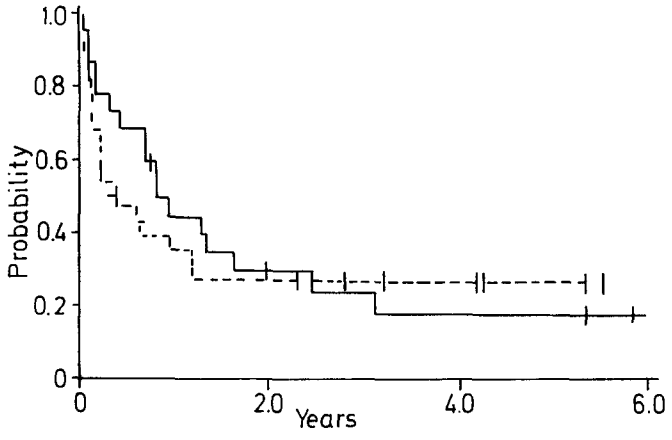

Fig. 3. Probability of event-free survival of allogeneic (——) versus autologous (– – –) bone marrow transplantation

from toxicity, 10 relapsed, and 1 is in continuous complete remission 3 months after transplantation. None of the children transplanted after a remission of 30 months or longer has relapsed.

When the outcome of the 31 autologous transplant patients was compared with that of the 22 allogeneic patients, the probability of event-free survival at 5 years was seen to be very similar, with $27 \pm 16\%$ for the autologous patients and $18\% \pm 18\%$ for the allogeneic transplant patients (Fig. 3) [25]. The median time to failure was shorter for the autologous group owing to acute toxicity and relapse.

D. Discussion

Thirty-one children received an autologous bone marrow transplant for treatment of ALL in second or subsequent remission. Event-free survival at 5 years was $27\% \pm 16\%$. Toxicity rate was high, with 9 out of 31 children suffering a remission death. Duration of initial remission prior to transplantation was prognostically highly significant for long-term event-free survival after transplantation. The outcome of autologous transplantation compared favorably with that of our allogeneic transplant experience.

At the University of Minnesota, two consecutive studies of autologous bone marrow transplantation for recurrent ALL have been conducted since 1982 [8, 22]. Both studies utilized the same monoclonal antibodies, BA-1 (pan B cell), BA-2 (anti-gp26), BA-3 (anti-CALLA), and complement for in vitro purging of the harvested bone marrow. The preparative regimen differed in the sequential studies.

In the first study, 23 children and 5 adults were treated with two doses of cyclophosphamide (60 mg/kg) and total body irradiation (1320 cGy) delivered twice daily in 165 cGy fractions. The second study utilized a single fraction irradiation dose of 850 cGy followed by ara-C to a total dose of 38 gm/m^2. Thirteen patients were enrolled on this study prior to December 1985. Toxicity in both studies was low, with three toxic deaths from infection: one in Study One and two in Study Two [22]. Twenty-one of the 28 patients in the first study relapsed 1–9 months after transplantation, with a median time to relapse of 3.3 months. Seven of the 13 patients in the second study relapsed. The relapse-free survivals at 1 year are 22% and 30%, respectively. The duration of longest remission prior to transplantation was not of prognostic significance for post-transplant event-free survival [22].

In contrast to our study, all the Minnesota patients' initial relapses occurred while they were receiving treatment. Furthermore, a higher percentage of patients were transplanted in third or fourth remission, and the median duration of the longest remission prior to transplantation was 14 months [23], as opposed to 24 months in our study.

The high relapse rate after autologous bone marrow transplantation for ALL could be due to an insufficient conditioning regimen or to inadequate removal of leukemic cells during the in vitro treatment. At the University of Minnesota, the same conditioning regimen was used for allogeneic and autologous transplants. A review of 121 patients transplanted between 1978 and

1985 showed that patients with autografts and allografts had a similar event-free survival at 2 years of 28% ± 14% and 34% ± 16%, respectively [24]. Patients with autografts relapsed earlier and more frequently than patients with allografts. However, patients who received allogeneic transplants and did not have graft-versus-host disease had the same relapse rate as those who received autologous grafts. This suggests that the relapses in autologous transplant patients were due to refractory disease in vivo, and possibly the lack of graft-versus-leukemia effect, rather than to reinfused leukemic cells.

The Seattle transplant group reported similar survival rates for allogeneic transplantation of children with ALL in second or subsequent remission, with 13 out of 15 patients in long-term remission [26]. Better results for allogeneic transplantation have been reported by the Memorial Sloan-Kettering Cancer Center, with a projected 2-year disease-free survival for 22 patients in second remission of 67% ± 10% [27].

In our study, two out of ten patients in continuous complete remission after autologous bone marrow transplantation had experienced an initial relapse more than 1 year off therapy. It could be argued that those children could have been treated as effectively with an intensive chemotherapy regimen without total body irradiation and transplantation. Johnson and coworkers compared the outcome of 24 children who received allogeneic transplants in second or subsequent remission to that of 21 children treated with conventional chemotherapy [28]. A follow-up of that study showed that all 21 children treated with chemotherapy died within 3.5 years of entering the study, whereas 6 out of 21 children who were transplanted remained leukemia-free from 4.5–8 years after transplantation [29]. That study, however, was hampered by the fact that the median duration of initial remission was only 13 months for the chemotherapy group, as compared to 25 months for the transplant group. A report from the Hospital for Sick Children in London found no advantage for 15 children treated with allogeneic transplantation, compared to 40 children treated with chemotherapy only [30]. In both groups, there was a highly significant correlation between the lengths of initial remission and disease-free survival after transplantation.

The relative efficacy of autologous or allogeneic transplantation versus more intensive chemotherapy without transplantation remains unresolved at this time. Our current policy offers autologous or allogeneic bone marrow transplantation for all children with ALL who relapse at any site while receiving therapy or within 12 months after elective cessation of therapy. If an HLA-matched donor is available, an allogeneic transplant is recommended; if not, the child who is CALLA-positive is eligible for an autologous marrow transplant. Children who relapse more than 12 months after elective cessation of therapy are treated with only intensive chemotherapy.

Children with relapsed ALL have a dismal prognosis. Recent reports [31, 32] suggest that for a selected group of patients the outcome of intensive chemotherapy might be as good as that reported with bone marrow transplantation. For some time to come, we will continue to be confronted by the problem of optimal therapy for treatment of children with relapsed ALL.

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