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Total Body Irradiation, Cyclophosphamide, and Etoposide With Stem Cell Transplant as Treatment for Infants With Acute Lymphocytic Leukemia

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Background. Acute lymphoblastic leukemia (ALL) in infants has a very poor outcome with modern chemotherapy. We reviewed our experience with the infants diagnosed with ALL at Children's Memorial Hospital from 1992 to 1997. ***Procedure.*** During this time period, 10 infants were diagnosed with ALL. Seven of them were transplanted, four with marrow from HLA-matched siblings and three with umbilical cord blood. Four of the transplanted patients had the MLL gene rearrangement and the other three transplanted patients had one or more other high-risk features including CD10- blasts, age less than 6 months at diagnosis, or prior relapse. The patients were conditioned with a regimen of total body irradiation (TBI), etoposide, and cyclophosphamide (CY). Peritransplant toxicity was tolerable. The graft infused contained a median total nucleated cell dose/kg of 3×10^8 ($.3 \times 10^8$–6×10^8). The median CD34+ cell dose/kg was 5×10^6 ($.25 \times 10^6$–31×10^6). ***Results.*** All of the patients engrafted with a median of 18 days (11–29) to reach an absolute neutrophil count (ANC) of 500/μl. The median time to reach an unsupported platelet count greater than 20,000/μl was 24 days (18–64). Four of seven of the transplanted patients are leukemia-free survivors at a median follow-up of 775 days. Of the three patients who were not transplanted, one is surviving 2+ years off therapy. ***Conclusions.*** Allogeneic stem cell transplant is an alternative to chemotherapy alone as a treatment for infant ALL when a suitable donor is available. Med. Pediatr. Oncol. 32:1–6, 1999. © 1999 Wiley-Liss, Inc.

Key words: infant leukemia; bone marrow transplant; total body irradiation

INTRODUCTION

Although modern treatment approaches cure the majority of children with acute lymphoblastic leukemia (ALL), outcomes for those patients diagnosed in the first 12 months of life are significantly worse, with overall survival rates ranging from 5% to 50% [1–4]. Infant leukemia has generally been characterized clinically by hyperleukocytosis, massive hepatosplenomegaly, and a high incidence of central nervous system (CNS) disease at diagnosis [3–5]. Clinical and biologic features associated with a particularly poor prognosis include age <6 months at diagnosis, MLL gene rearrangement, CD10- leukemic cell phenotype, and elevated white blood cell count (WBC) at diagnosis [6–8]. The presence of the MLL gene rearrangement, while correlated with other unfavorable features, is the most significant, independent variable predictive of poor outcome [8–11]. These infants will require innovative treatment approaches to improve survival. One such effort has included intensive chemotherapy followed by allogeneic stem cell transplant. To date, minimal data are available concerning outcomes of this approach. We report our experience at a single institution over 5 years with the treatment of infant ALL using hematopoeitic stem cell transplants (HSCT) with a total body irradiation (TBI) containing regimen.

PATIENTS AND METHODS

Between September 1992 and January 1997, 10 infants were diagnosed with leukemia at Children's Memorial Hospital (CMH). Clinical, hematological, morphological, and cytogenetic findings at the time of diagnosis are summarized in Table I. Four patients had a WBC count greater than 50,000 at the time of diagnosis and two patients had CNS disease at the time of diagnosis defined by $\geq$ 5 WBCs and blasts in the cerebral spinal fluid. Nine of the 10 patients were classified morphologically as FAB L1 with immunophenotype revealing typical early pre-B ALL markers. Seven of these patients were CALLA (−). Patient 3 was originally diagnosed with acute nonlymphoblastic leukemia (ANLL) FAB M0 after a biopsy of skin nodules and a bone marrow aspirate

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TABLE I. Patient Characteristics*

Patient	Age at diagnosis (months)	Sex	Blast immunophenotype	WBC at diagnosis	CNS at diagnosis	Cytogenetics	Pretransplant therapy
1	4	M	HLA DR+, CD45+, CD19+, CD10−	29 k/μl	Negative	−16,t(10;11)(11;14) (p15;q14.2q25;q11)	POG 9107
2	3	M	HLA DR+, CD19+, CD10−	60 k/μl	Negative	t(5;11)(q35q23)	POG 9107
3	5	M	CD45+, CD7+, CD33+, CD15+, CD19−	38 k/μl	Positive	11q23	POG 9421 POG 9407
4	6	M	HLA DR+, CD19+, CD10+	42 k/μl	Negative	t(4,11)	POG 9107
5	7	F	HLA DR+, CD45+, CD19+, CD10−	4.3 k/μl	Negative	Unsuccessful	POG 9107
6	7	F	HLA DR+, CD45+, CD19+, CD10−	410 k/μl	Negative	11q23	POG 9407
7	7	F	HLA DR+, CD19+, CD10+	47 k/μl	Positive	46XY	CCSG 1883
8[a]	1	F	HLA DR+, CD19+, CD45+, CD10−	2.2 million/μl	Negative	46XX	POG 9107
9[a]	2	F	HLA DR+, CD19+, CD45+, CD10−	340 k/μl	Negative	t(4,11)	CCSG 1883
10[a]	7	M	HLA DR+, CD19+, CD10+	37 k/μl	Negative	46XY	POG 9107

*POG 9107, vincristine, prednisone, cytarabine, cyclophosphamide, daunorubicin, etoposide, methotrexate, mercaptopurine, triple intrathecals; POG 9407, vincristine, decadron, daunorubicin, cyclophosphamide, asparginase, methotrexate, etoposide, triple intrathecals; POG 9421, daunorubicin, cytarabine, thioguanine, etoposide, mitoxantrone, cyclosporine, intrathecal cytarabine; CCSG 1883, vincristine, prednisone, daunorubicin, cytarabine, asparaginase, methotrexate, cyclophosphamide, mercaptopurine, intrathecal methotrexate.
[a]Patients not transplanted.

revealed blasts with immunophenotype (CD33+, CD15+, CD7+, CD13−, CD19−, CD10−, CD5−, and CD7−). Cytogenetically, this patient had the MLL gene rearrangement. This patient was treated on the Pediatric Oncology Group (POG) AML protocol 9421 and subsequently relapsed with blasts that had a lymphoid immunophenotype (CD45+, CD19+, HLA-DR+, CD10−, and CD33−). Six of the ten patients had documented chromosomal abnormalities (Table I). Of significance, five patients had the MLL gene rearrangement documented by cytogenetics or polymerase chain reaction.

All patients were initially treated with modern intensive multidrug therapy. Six of the ten patients were induced into remission with the POG 9107 protocol. Two patients were induced into remission (patient 3 into a second remission) using POG protocol 9407. Two patients were treated as per the Children's Cancer Study Group (CCSG) protocol 1883. One of these patients (patient 7) continued on this protocol through consolidation, interim maintenance, and intensification. She relapsed while on maintenance therapy. She was reinduced with a four-drug regimen consisting of vincristine, decadron, daunomycin, and asparginase along with triple intrathecal chemotherapy and was transplanted in second remission. The other patient treated on this protocol was transferred to another institution and died of infection-related complications during the interim maintenance phase of chemotherapy. Three of the ten patients who were diagnosed and initially treated at our institution were not transplanted as no suitable donor was available. The remaining seven underwent allogeneic stem cell transplant and are the emphasis of the discussion in this article.

The transplant characteristics of this group of patients are shown in Table II. The mean time from diagnosis to transplant was 293 days and the median was 308 days (68–741). Five of the seven patients were transplanted in first remission. Four patients received bone marrow stem cells from HLA-identical siblings. Three patients received umbilical cord blood stem cells (UCBSC), one HLA-matched unrelated, one 5/6 HLA DR-matched unrelated, and one haploidentical sibling.

Pretransplant conditioning for related transplants consisted of TBI at a total dose of 1,200 cGy given in 150 cGy fractions twice daily on days −10, −9, −8, and −7; etoposide at 1,000 mg/m^2/day as a continuous infusion for 24 hours on days −6 and −5; and cyclophosphamide (CY) at 500 mg/m^2/dose for a total of nine doses every 8 hours on days −4, −3, and −2. Instead of the dose schedule of CY cited above, unrelated transplant recipients received CY at a dose of 60 mg/kg/day on days −4, −3, and −2. Unrelated transplant recipients also received one dose of thiotepa (TT) at 10 mg/kg on day −6. None of the stem cell grafts were T cell depleted.

Graft-vs-host disease (GVHD) prophylaxis for the

TABLE II. Transplant Characteristics

Patient	Age at transplant (months)	Diagnosis to transplant (days)	Status at transplant[a]	Stem cell source[b]	Conditioning regimen	GVHD prophylaxis	G-CSF
1	17	408	CR1	6/6 (related)	TBI, etoposide, CY	CSA, MTX	No
2	6	78	CR1	6/6 (related)	TBI, etoposide, CY	CSA, MTX	No
3	17	371	CR2	UCBSC 6/6 (unrelated)	TBI, etoposide, CY, TT	CSA,MTX,ATG	Yes
4	8	68	CR1	6/6 (related)	TBI, etoposide, CY	CSA, MTX	No
5	17	308	CR1	UCBSC 5/6 DR matched (unrelated)	TBI, etoposide, CY, TT	CSA,MTX,ATG	Yes
6	10	80	CR1	6/6 (related)	TBI, etoposide, CY	CSA, MTX	Yes
7	32	741	CR2	UCBSC 3/6 (haploidentical sibling)	TBI, etoposide, CY	CSA, MTX	No

[a]CR1 = first complete remission; CR2 = second complete remission.
[b]All matching was done by serology at the A and B antigens. The DR was confirmed with DNA oligonucleotides.

matched sibling transplants consisted of cyclosporine A (CSA) 1.5 mg/kg/dose every 12 hours and short-course methotrexate (MTX) 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3 and +6. The unrelated transplants received GVHD prophylaxis with continuous infusion CSA at a dose of 5 mg/kg/day, short course MTX as above, and antithymocyte globulin (ATG; UpJohn, Columbus, OH) at 20/mg/m^2 (premedicated with methylprednisolone at 2 mg/kg/dose) on days +1, +3, +5, and +7.

All patients were cared for in positive pressure laminar air flow rooms. Additional supportive care included prophylactic fluconazole 3–5 mg/kg/day and acyclovir 250 mg/m^2 daily through day +100, IVIG given at a dose of 250 mg/kg weekly for 3 months then monthly for 3 months after transplant, and pentamidine 4 mg/kg every month beginning at day +30 for *Pneumocystis carinii* prophylaxis. Three of seven patients received granulocyte-colony stimulating factor (G-CSF) at a dose of 5–10 μg/kg starting at day +7. Broad spectrum antibiotics were started empirically for febrile neutropenia.

RESULTS

Engraftment data, GVHD, and outcome are shown in Table III. The graft infused contained a median total nucleated cell dose/kg of 3×10^8 ($.3 \times 10^8$–6×10^8). The median CD34+ cell dose/kg was 5.0×10^6 ($.25 \times 10^6$–31×10^6). The median time to reach an ANC greater than 500/μl was 18 days (11–29). The median time to reach an unsupported platelet count greater than 20,000/μl was 24 days (18–64). All patients had engraftment documented through restriction fragment length polymorphisms (RFLP), HLA typing of bone marrow, or cytogenetics. Time to engraftment appeared somewhat longer in UCBSC transplants, but numbers are too small for statistical comparison.

Mucositis developed in all patients; grade 1 (n = 2), grade 2 (n = 4), and grade 3 (n = 1). There were no episodes of veno-occlusive disease of the liver. All patients developed fever and neutropenia and three had positive blood isolates. One patient did require blood pressure support associated with *Klebsiella pneumonia* sepsis, but responded to antibiotic therapy and had no significant sequelae. Patient 7 died of sepsis with *Enterococcus faecalis* and *Staphlococcus epidermidis* related to an acute bowel obstruction. Three patients developed grade 1 GVHD of the skin and one patient developed extensive chronic skin GVHD.

At this time, four of seven patients transplanted are alive with a median follow-up of 775 days. The mean follow-up is 1,002 days (485–1,975). Two patients died of progressive disease (patients 3 and 4) 90 days and 274 days posttransplant, respectively.

Of the four patients alive at this point, three are below the 5% for height and two are also below the 5% for weight. One of these patients is on growth hormone replacement. All of the patients show consistent linear growth. Posttransplant neuropsychological evaluation has not been formally performed at this time. The oldest patient, age 7, attends regular school and receives speech therapy. Two patients appear to have normal to a slight delay in achievement of their developmental milestones. One patient has significant delay in motor skills that is most likely related to his chronic skin GVHD that resulted in significant contractures. He continues to improve and to gain ground with intensive physical therapy.

DISCUSSION

The poor survival of infants with ALL treated with conventional chemotherapy has prompted the search for new approaches including marrow ablative therapy with allogeneic stem cell transplant. Concerns about acute toxicity, the long-term sequelae associated with the preparative regimens for stem cell transplant, and the limited availability of matched related donors have led to restraint in the application of this therapy in infancy.

TABLE III. Engraftment Data, GVHD, and Outcome*

Patient	TNC dose/kg ($\times 10^8$)	CD34+ cells/kg ($\times 10^6$)	ANC >500 (days)	Platelets >20,000 (days)	GVHD	Follow-up (days)
1	3	15	16	18	None	NED 1975+
2	6	31	18	64	Extensive chronic (skin)	NED 790+
3	5	0.25	29	36	None	DIR/90
4	5	5	13	24	Grade 1 (skin)	DIR/274
5	1	2	20	20	Grade 1 (skin)	NED 760+
6	5	10	11	24	Grade 1 (skin)	NED 485+
7	0.3	0.33	19	—	None	Toxic death/20
Mean	3	9.2	18	26		1002
Median	3	5	18	24		775

*TNC, total nucleated cell; NED, no evidence of disease; DIR, death in relapse. Data updated 3/31/98.

There are few reports in the literature of infant ALL patients who have undergone myeloablative therapy with allogeneic stem cell transplant. Reports focused on infant transplants have included patients transplanted at less than 1–2 years of age for a variety of underlying conditions including ALL, acute myelogenous leukemia (AML), and nonmalignant disorders [12–15]. Our report centers on infants with ALL in our institution selected for transplant based on a combination of risk factors including the presence of the MLL gene rearrangement, CD10(−) blasts by flow cytometry, age, relapse, and the availability of an appropriate donor.

The choice of a preparative regimen including TBI and CY was based on data available on acute toxicity and engraftment. Studies in patients with ALL transplanted in second or third remission using a TBI-based regimen have acceptable acute toxicity and demonstrate excellent results with regards to engraftment and relapse-free survival [16–20]. It is well documented, however, that TBI-containing regimens can cause significant long-term sequelae including growth deficiencies, hypothyroidism, hypogonadism, cataracts, and neuropsychological/cognitive deficits [21–24]. Very few studies have looked at the long-term implications of a TBI-containing regimen in infants less than 1 year of age at the time of transplant [3,16,25,26]. Psychosocial variables such as length of hospitalization, length of isolation, and parenting skills may impact significantly on long-term neuropsychological outcome and they need to be studied prospectively. Neuropsychological difficulties secondary to TBI are not known at this time in our series of patients due to the relatively short median follow-up of 775 days in the surviving patients and need to be studied. Close follow-up with anticipatory aggressive early intervention may ameliorate or decrease potential long-term neuropsychological problems and needs to be studied.

Other preparative regimens reported in the literature use busulfan in the place of TBI in conjunction with CY +/− cytarabine and/or melphan [12–15]. We elected to use a TBI-based regimen due to the difficulties that can be encountered in maintaining adequate levels of the drug in the pediatric population to produce ablation without unacceptable toxicity [27,28]. There is minimal information on the use of busulfan for pretransplant conditioning in infants with ALL. Target drug levels necessary to minimize graft rejection and toxicity and to prevent disease recurrence are not well defined in the very young patient [12,14,15]. Long-term sequelae such as neuropsychological difficulties are not known in the group of patients treated with busulfan in their preparative regimen due to the limited number of patients available to study and the length of follow-up needed to confirm significant changes.

One of the reasons for failure in stem cell transplantation is relapse of disease. Etoposide was included in the ablative regimen for our series of patients for this reason. Etoposide, a topoisomerase inhibitor, is a potent antileukemic agent which has a different mechanism of action than CY [29]. Importantly, the nonhematologic toxicities are not overlapping. A regimen combining TBI, CY, and etoposide has proven to be well tolerated and will possibly improve the relapse-free survival of patients with ALL [30,31].

In our experience with seven infants undergoing stem cell transplant, the acute toxicity was minimal and engraftment was good. There was no significant acute GVHD. Only one patient developed extensive chronic GVHD limited to the skin that required splinting, physical therapy, and continues to require treatment with low-dose steroids and CSA. The low incidence of severe GVHD in our patient population may be related to several factors including the immaturity of our patients' immune system at the time of diagnosis and transplant, the use of umbilical cord blood donors in some patients, the degree of matching at the DR locus, and the efficacy of the GVHD prophylaxis regimen.

All patients engrafted at a median time of 18 days, reflecting the efficacy of a preparative regimen containing TBI and CY. Of the transplanted patients who died in this series both had the MLL gene rearrangement (patients 3 and 4). Patient 3 was the previously described patient whose initial morphology and flow cytometry

were consistent with biphenotypic leukemia and who was transplanted in second remission. Only one of the three infants diagnosed with ALL at CMH who was not transplanted remains in remission for 2+ years since the end of therapy. This patient was >than 6 months at the time of diagnosis, with a WBC of <50,000, CD10+ blasts by flow cytometry, and had normal chromosomes by cytogenetics, features which are relatively good prognostic factors in infant ALL. The other two patients died less than 6 months from diagnosis of progressive disease and from infection-related complications.

CONCLUSIONS

In summary, infant leukemia, especially when characterized by the MLL gene rearrangement, remains a difficult disease to cure. In our series of infants, stem cell transplant using a conditioning regimen including TBI, CY, and etoposide was feasible, with minimal acute toxicity and good engraftment. The overall survival to date in this small series is improved compared to historical results in patients treated with chemotherapy alone. Neuropsychological testing is scheduled to be performed when the infants achieve an age that is suitable for testing. Long-term sequelae and event-free survival from this aggressive treatment regimen are not known at this time and will need to be studied. These preliminary results suggest that infants with leukemia characterized by the presence of the MLL gene rearrangement or other poor prognostic features may benefit from a treatment approach which includes high-dose chemotherapy followed by allogeneic stem cell transplant in first remission when an appropriate donor is available.

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