Bone Marrow Transplantation in Children with Acute Leukemia: A 1990 View

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Introduction

Since the first case report in 1959 of total body irradiation and bone marrow transplantation (BMT) in a child with acute leukemia, the popularity of this approach has steadily increased [1]. The introduction of human leukocyte antigen typing and mixed leukocyte cultures and improved methods of supportive care made BMT a successful way of treating certain immunodeficiency disorders, severe aplastic anemia, chronic myeloid leukemia, and certain other blood dyscrasias as well as acute leukemia [2]. The purpose of this essay is to examine critically the practice of myeloablation and marrow transplantation in children with acute leukemia.

Acute Myeloid Leukemia

The first generally accepted use of allogeneic BMT in children with leukemia was for those with acute myeloid leukemia (AML) in hematological remission after initial chemotherapy [2]. It was thought that relapse was almost inevitable in these patients, so the reports of apparently permanent remission after BMT convinced most hematologists that BMT was the treatment of choice if a histocompatible sibling donor were available. However, in the past 10 years it has become apparent that combination chemotherapy alone without BMT may be as effective as BMT. This is reflected in a 1989 statement of the International Bone Marrow Transplant Registry (IBMTR): "It is not known whether chemotherapy or bone marrow transplantation is the more effective treatment for acute myelogenous leukemia in first remission" [3].

A recent 6-year follow-up report from St. Jude Children's Research Hospital of a 1980–1984 study of therapy of AML describes no significant difference in 6-year continuous complete remission rates between BMT and chemotherapy [4]. Nine of 19 BMT patients remained in continuous complete remission for a median of 68 months and 13 of 42 chemotherapy patients for a median of 74 months (Fig. 1 a). Similar experience has been reported from the Johns Hopkins Oncology Center in young adults with AML [5]. When corrected for patient selection, their data indicate that the frequency of lengthy continuous complete remissions was similar for 41 patients treated with allogeneic BMT and 46 patients who received intensive chemotherapy without BMT (Fig. 1 b).

From January 1986 to February 1989 the Children's Cancer Study Group admitted 617 children with AML into a study in which those with histocompatible sibling donors underwent BMT after remission induction while the others received intensive chemotherapy for 3 months with or without subsequent maintenance chemotherapy [6]. The actuarial 2-year event-free survival from the time of BMT or intensive chemotherapy is not significantly different, 41% for

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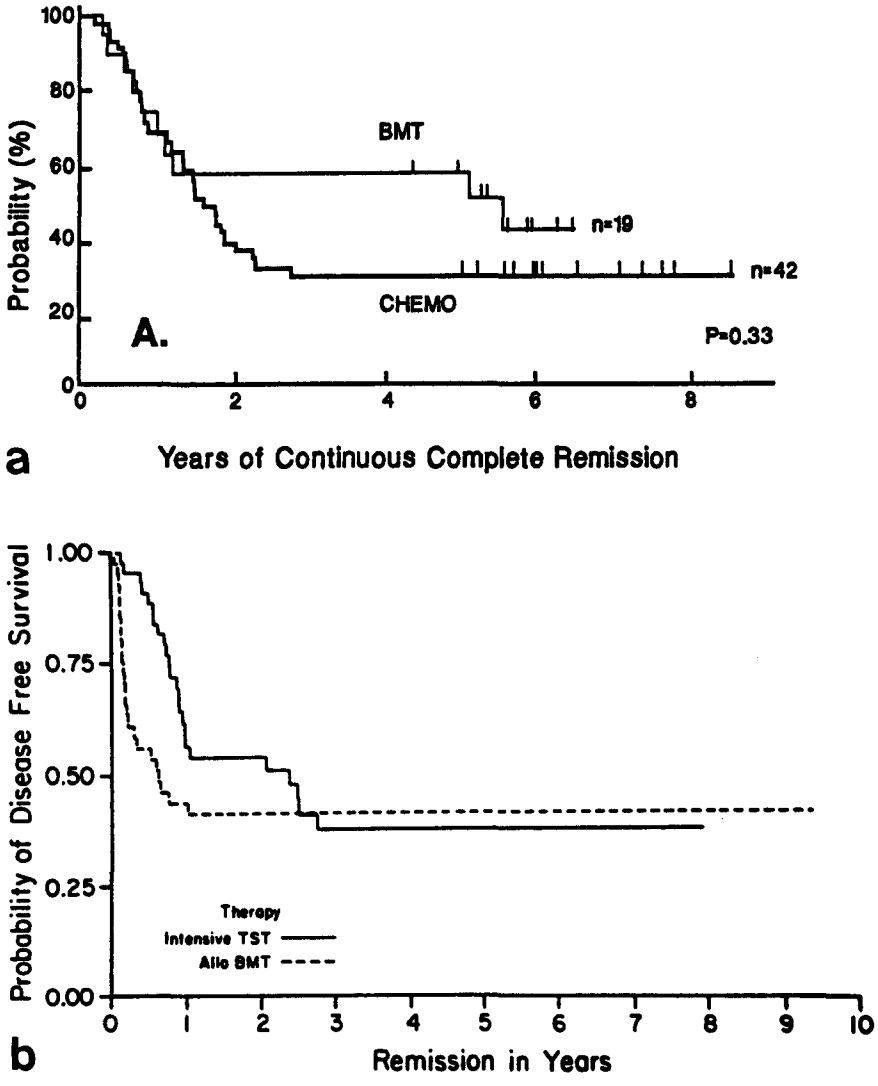


Fig. 1. **a** Duration of continuous complete remissions of children with AML in first remission treated with chemotherapy alone vs. chemotherapy (*chemo*), myeloablation and allogeneic marrow transplantation (BMT) in St. Jude study AML-80. Transplantation did not affect the probability of lengthy complete remission. (From [4]). **b** Duration of complete remissions in young adults treated with intensive timed sequential (*TST*) chemotherapy vs. myeloablation and allogeneic marrow transplantation (*Allo BMT*) at the Johns Hopkins Oncology Center. (From [5])

intensive chemotherapy and 50% for BMT ($p = 0.41$). It is possible that late deaths from chronic graft vs. host disease and its complications, secondary neoplasms, or late relapses might modify this outcome in favor of one or the other methods.

Acute Lymphoid Leukemia at High Risk of Relapse

BMT has been employed in first remission of acute lymphoid leukemia (ALL) with features considered to augur an unfavorable outcome. One report describes 50% disease-free survival of patients with "poor-risk" ALL in complete remission after BMT [7]. The median delay from diagnosis to BMT in these patients was 179 days. Since estimates of relapse risk in ALL are based on complete remission duration, this 6-month delay likely excluded those who were at "poorest risk." A similar report with a higher proportion of survivors, but shorter follow-up, is subject to the same criticism [8]. The achievement of re-

mission and the delay of BMT for 1–12 months again tends to exclude the patients with the greatest risk of unfavorable outcome.

Young adults have a higher risk of relapse of ALL than do children. Recently the IBMTR compared the remission experience of 484 young German adults with ALL who received intensive chemotherapy and 251 treated with allogeneic BMT during the same period [9]. Statistical corrections were applied for selection factors. The 5-year leukemia-free survival was similar for both groups.

Acute Lymphoid Leukemia in Second Remission

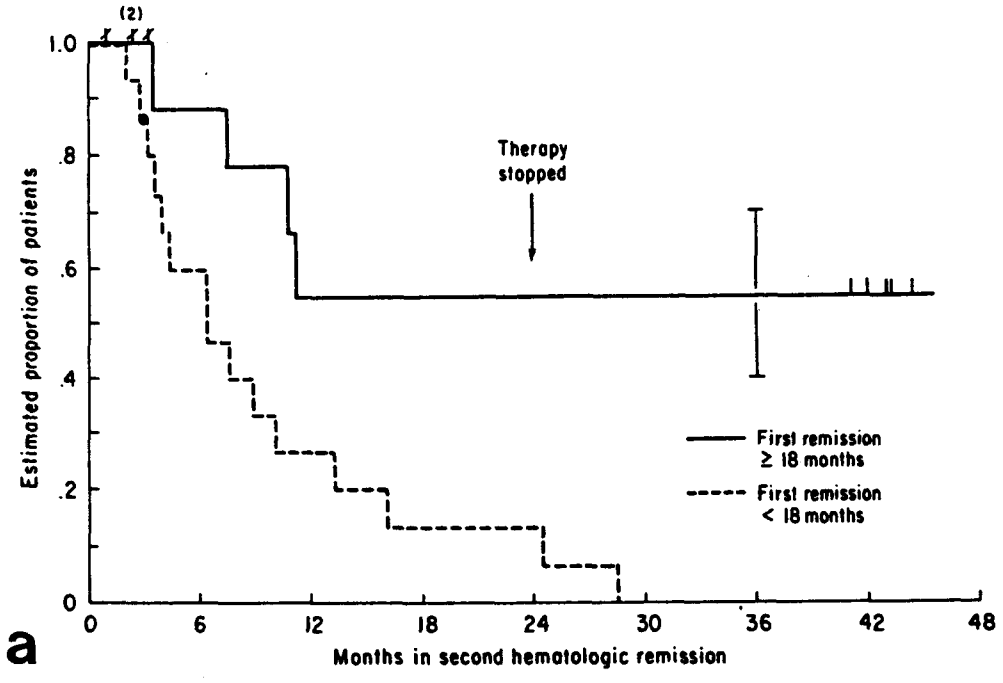
One of the early publications concerning allogeneic BMT is second remission of ALL concluded that "marrow transplantation offers the best chance of long term remission and potential cure after a child with ALL has had a relapse in the marrow" [10]. This was based on a non-random comparison in which 9 of 24 children survived in remission after BMT and only 1 of 21 after chemotherapy alone. However, scrutiny of the published data reveals that 11 of the 24 BMT patients had isolated extramedullary relapse, which has a more favorable response to treatment [11], rather than marrow relapse. This contrasted with 4 of 21 chemotherapy patients who had extramedullary relapse. The median duration of first remission, an important prognostic factor for second remission [12], was 25 months for BMT patients and 13 months for chemotherapy patients. Finally, the delay between remission induction and BMT ranged up to 17 months, thus tending to exclude patients with early relapse and, therefore, the worst prognosis. In retrospect, the data did not justify the conclusion.

A recent report comparing allogeneic BMT vs. chemotherapy without BMT in children with ALL in second remission attempts to address the problems of other such comparisons [13]. The patients who received chemotherapy alone had "risk factors" for relapse comparable to the BMT patients and had been in complete remission for 2–3 months prior to entry into the study. However, BMT was delayed up to 13 months and no description is given of the drug schedules and medical care of the chemotherapy patients. For these reasons the reader cannot be certain whether the superior outcome of BMT was related to the exclusion of patients with early relapse, the most reliable prognostic factor. Also, one is unable to assess whether medical care was comparable in the two groups and whether the chemotherapy alone patients received optimal drug therapy.

Bone Marrow Autografts in Acute Leukemia

There is a surge of interest in treating childhood acute leukemia with myeloablation and autografting of cryopreserved bone marrow obtained during hematological remission and subjected to "purging" with biological or chemical agents.

A recent report concludes that this may be a treatment option for children with ALL in second or subsequent remission whose first remissions were longer than 24 months [14]. Of 44 patients grafted, 15 were in continuous second remission 10–94 months; all 15 had initial remissions longer than 24 months. Children with T-cell ALL or B-precursor ALL without CD10 or CD9 surface antigens were excluded. Delays of 1–11 months between remission and autograft excluded other patients with more aggressive or resistant leukemia. The event-free survival was similar to that reported previously for a group of 28 children with ALL in second hematological remission treated with chemotherapy alone [12]. In both the autograft and the chemotherapy alone series those with brief initial remissions had short second remissions while those with long first remissions had longer and sometimes durable second remissions (Fig. 2). There is no evidence



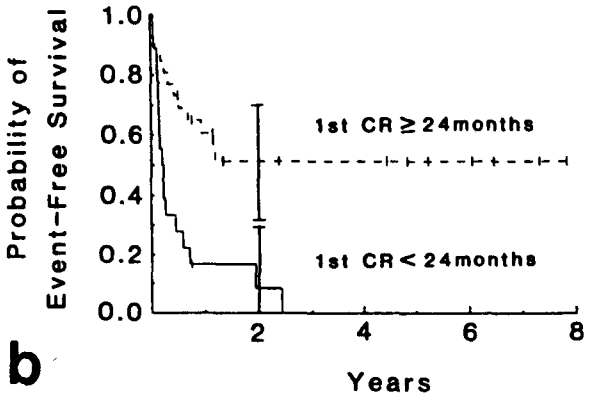


Fig. 2a, b. Duration of remission. **a** In 44 children with ALL in second or subsequent remission who received ablative chemotherapy and autografts of purged bone marrow. All patients with initial remissions of less than 24 months experienced relapse but one half of those with initial remissions longer than 24 months survived free of leukemia. (From [14]). **b** In 28 children with ALL in second hematological remission who received chemotherapy alone in Pediatric Oncology Group study 8201. All children with initial remissions of less than 18 months experienced relapses but one half of those with initial remissions longer than 18 months remained in complete remission after completion of treatment. Note the similarity with the bone marrow autograft results. (From [12])

that adding a marrow autograft procedure to chemotherapy changed the outlook for survival. In contrast to the chemotherapy only regimen, all long-term survivors of the autograft procedure had growth failure and 9 of 28 patients in remission 3 months after grafting experienced hemolytic-uremic syndrome.

A report from the IBMTR summarizes their view: "Whether autotransplants are equivalent or superior to other therapies... is uncertain, since prospective trials are not reported and data analysis is confounded by selection of subjects and time-censoring" [15].

Sequelae of BMT in Children with Acute Leukemia

From the earliest reports of curative approaches to children with acute leukemia pediatricians have been concerned about the quality of survival. Studies have focused on anthropometric and neuropsychological measurements of surviving children. Cure has been defined as not only eradication of leukemia but restoration of normal health and normal capacity for physical, intellectual, social, and emotional growth and development.

The need for weighing the value of each component of treatment against its ultimate risk to normal health, growth, and development of the children has been emphasized.

Children who survive leukemia have the potential for a much longer life than adult survivors and thus a longer period of risk for delayed effects such as second cancers or organ failures. In addition, the growing tissues and more rapidly replicating cell systems of children are more vulnerable to cytotoxic agents. For example, preschool children are more likely to experience neuropsychologic deficits after cranial irradiation than older children and adults [16]. Children's hearts are apparently more vulnerable to delayed anthracycline cardiomyopathy than adults [17]. For these reasons one must necessarily be concerned about the late effects of treatment of children.

There are relatively few descriptions of the delayed sequelae of BMT. Growth failure is universal in the Seattle series, probably as a result of total body irradiation [18]. Survival must therefore be considered dysfunctional despite the courage and vigor of the children, their families, and their physicians in overcoming the problem. This contrasts with the outcome of chemotherapy alone in which "catch-up" growth usually occurs after cessation of therapy in those children whose growth is slowed on treatment [19].

Although gonadal failure may follow treatment with alkylating agents, the majority of children with leukemia receive little or no drugs of this class and fertility is usually preserved [20]. In contrast, approximately 70% of BMT survivors experience gonadal failure [18, 21]. Other endocrine deficiencies, rare in chemotherapy survivors, are reported in about one third of BMT survivors.

Chronic graft vs. host disease occurs in approximately one third of children after allogeneic BMT [18, 21]. This can result in crippling organ failure as well as a continuous risk of life-threatening infection. Obstructive and restrictive pulmonary disease, often fatal, is another complication of BMT not seen in children with leukemia treated with chemotherapy alone [22].

Second malignant solid tumors 10–30 years later are among the delayed sequelae of childhood cancer. Some may be related to the first neoplasm but the greatest risk appears to arise from treatment with radiation therapy and alkylating agents [23]. The administration of total body irradiation and high dosages of alkylating agents such as busulfan and cyclophosphamide are customary methods of myeloablation in marrow transplant and autograft procedures. Given the long life expectancy of children cured of cancer and the carcinogenic effects of radiation and alkylating agents, it can be anticipated that children with leukemia treated with BMT or autografts will experience a very high incidence of malignant solid tumors as young adults.

In summary, available data indicate that the human "price of cure" is appreciably higher in children treated with BMT than with current chemotherapy regimens.

Discussion

The difficulties in comparing outcomes of alternative treatments of cancer are well known. Among them are patient selection, lack of randomization, enthusiasm for test therapy, differences in quality or level of medical care, misuse of survival curves, and failure to describe fully the sequelae of treatment so that its human cost can be compared to its benefits.

In the evaluation of reports of BMT in acute leukemia of children there are some specific problems [24]. First is the exclusion of potentially eligible patients. BMT is usually performed during hematological remission. Therefore, patients who fail to experience remission are excluded from the procedure. Because of delays between remission and the BMT procedure patients who experience relapse prior to BMT are also excluded. Since

failure to enter remission and early relapse tend to signify more resistant, more aggressive leukemia with poor prognosis for survival, these exclusions are highly selective for providing BMT candidates that have a relatively favorable outlook.

An example of this selective process was demonstrated in the Pediatric Oncology Group (POG) 8710 study of treatment of children with ALL in first hematological relapse [25]. Of 100 patients registered in the study, 74 had HLA-typing. Of 16 children found to have a fully matched sibling donor, only seven underwent BMT. The other nine children either failed to experience a second hematological remission or suffered another relapse before BMT could be performed. Thus, one half of the eligible patients, the half with the worst outlook for survival, were excluded from BMT.

The effect on apparent therapeutic outcome of excluding patients who have early relapses from BMT can be appreciated by consideration of expected failure rates for patients under 21 years of age during the first few months after remission induction of acute nonlymphoid leukemia (ANLL) [26]. Almost one fifth of patients experience relapse during the first 3 months of remission. Therefore, any intervention introduced after 3 months of remission will be followed by an apparently better relapse-free survival than no intervention because these early relapses are discounted. If a comparison is made between patients who receive the intervention and cohorts who do not, the relapse-free survival of those who do not receive the intervention will appear to be less because their number will include *all* the patients who experienced relapse in the first 3 months. In other words, the apparent result of a delayed intervention looks favorable for two reasons – exclusion of early relapse patients from the intervention group and their inclusion in the nonintervention group. An example is the initial comparison of BMT vs. chemotherapy for continuing remission of ALL in second hematological remission in the POG study 8303 [27]. A marginal superiority was noted for BMT with regard to remission duration. However, remission duration was measured from remission induction for the chemotherapy patients and from time of BMT, 3–28 weeks later, for BMT patients. Thus, early relapse patients reduced the apparent failure rate of BMT and increased the apparent failure rate of chemotherapy without BMT.

Conclusions

In determining the value of alternative therapeutic interventions in childhood acute leukemia, two questions need to be answered. Which treatment results in the higher cure rate, and what is the relative cost/benefit ratio of the treatments? At present there is no demonstration of superior survival of children treated with allogeneic BMT for ANLL in first remission, ALL with "unfavorable prognostic factors" in first remission, or ALL in second remission. There is also no demonstration of superior survival with bone marrow autografts. At the same time, the immediate toxicity and late sequelae of these procedures are clearly greater than with modern chemotherapy, especially current successful protocols that avoid or minimize use of radiation therapy, anthracyclines, and alkylating agents [28].

For these reasons BMT and autograft procedures in children with acute leukemia need to be reserved for experimental investigations in those leukemias and preleukemias that are clearly demonstrated to be usually fatal with current chemotherapy regimes. Secondly, the investigations should be collaborative and prospective with randomization for BMT immediately prior to myeloablation, optimal graft procedures and chemotherapy regimes, and comparable specialized medical care. Just as important, there must be complete accounting and description of the health and growth of survivors as well as meticulous data analysis and reporting.

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