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Indications for Hematopoietic Cell Transplantation in Acute Leukemia

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INTRODUCTION

Chemotherapy, autologous hematopoietic cell transplantation (HCT), and allogeneic HCT are the 3 major forms of therapy available to the patient with acute leukemia. A major challenge facing the physician caring for the patient with acute leukemia is selecting the right approach at the right time. Recent progress in the development of diagnostic techniques that provide valuable prognostic information, as well as advances in each of the 3 major forms of therapy, have resulted in substantial changes in recommendations about who should be transplanted, when the transplant should be performed, and which form of transplantation is preferable. The following 3 sections provide a brief review of this general topic for pediatric acute leukemia, adult lymphoblastic leukemia (ALL), and adult acute myelogenous leukemia (AML).

INDICATIONS FOR TRANSPLANTATION IN CHILDHOOD LEUKEMIA

Introduction

More than 80% of children with ALL are now cured with chemotherapy without need for transplantation. This remarkable progress is the result of serial large-scale randomized clinical trials incorporating improvements in risk group assignment, administration of risk-adjusted therapy, and intensified therapy for children with high-risk disease [1]. Despite these advances, significant numbers of children still die of relapsed or refractory ALL, as ALL is the most frequent malignancy of childhood, and transplantation offers an important alternative modality of treatment for those children. Significant progress has also been made in the treatment of childhood AML, although chemotherapy regimens have not been as successful as in childhood ALL [2-4]. Sibling donor transplantation remains an essential component of the treatment of childhood AML, but similar to AML in adults, recent chemotherapy outcomes now support the limitation of the use of transplantation in first remission to children with intermediate or high-risk disease. Unrelated donor transplantation is an important component of treatment of relapsed AML, but is limited by the challenge of achieving a second remission, particularly in children with early relapse. Improved HLA typing techniques and strategies for donor selection mean that results approaching those seen with matched sibling donors can be achieved with well-matched unrelated donor (MUD) stem cells, leading to greater interest in identifying a role for unrelated donor stem cell sources for high risk AML cases in first complete remission (CR1) [5,6].

Transplantation for Children with (ALL)

Transplant for ALL in first remission. Many case series of HCT for ALL in CR1 have been published over the years. Overall, the majority of studies show at least a moderate reduction in relapse rate with transplantation compared with chemotherapy, but with increased treatment-related mortality (TRM). Variability in the data from different studies reflects differences in the definitions used for high-risk ALL meriting transplantation in CR1. Many of the criteria used in the past to define high risk (eg, T cell ALL and mediastinal mass, high white cell count [WCC], t[4;11]) are no longer associated with markedly inferior outcomes with modern chemotherapy, and would not currently be considered an indication for HCT in CR1. In the United States, Philadelphia chromosome-positive ALL (Ph+ ALL), low hypodiploidy, and the small number of cases with primary

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induction failure are the only subtypes of ALL considered sufficiently high risk to merit consideration of transplantation in CR1 using current Children's Oncology Group (COG) chemotherapy, and each of these indications is discussed subsequently [1]. Infants with ALL provide particular challenges, commonly presenting with biologically adverse features, altered drug pharmacokinetics, and vulnerability to infection. The role of transplant in CR1 for infant ALL is controversial, and is also discussed below.

Ph+ ALL. The low frequency (<4% of cases of childhood ALL) of Ph+ ALL has limited the identification of risk factors and optimal therapy. To try to circumvent this limitation, Arico′ et al [7] analyzed pooled data from 326 children and young adults treated for Ph+ ALL by 10 study groups. The analysis showed that HCT from a matched sibling donor was superior to other types of transplantation, and to intensive chemotherapy alone in prolonging initial complete remission. These data support the common clinical practice of offering HCT in first remission to children with Ph+ ALL and a matched sibling donor. However, for the majority of children without a matched sibling donor, there is less clear consensus on optimum management. Studies reporting outcome of unrelated donor HCT in these patients, so far show mixed results [7-9]. Some recent reports have shown encouraging results for the use of alternate donor transplant for Ph+ ALL in CR1 [10,11]. Continued investigation of the role of unrelated donor HCT in first remission for the children in this poorer prognosis group is justified. More insight into prognostic factors will also allow better stratification of patients to help improve outcomes. Based on current available data [7,10] unrelated donor transplant should certainly be considered for children with National Cancer Institute (NCI) high-risk characteristics. In contrast, children with NCI good-risk characteristics and no well-matched sibling or unrelated donor may achieve acceptable results with chemotherapy [7].

The tyrosine kinase inhibitor imatinib has been shown to have activity in childhood Ph+ ALL, and current clinical trials are studying whether chemotherapy outcomes can be improved by including imatinib with intensive chemotherapy. It remains important to follow these studies carefully, as imatinib, or other newer tyrosine kinase inhibitors, may improve survival with chemotherapy sufficiently to allow use of transplantation only in second remission (CR2). In addition to incorporation into chemotherapy regimens, investigators have shown that imatinib is well tolerated when given prophylactically posttransplantation, although current follow-up is too short to determine whether outcomes are improved.

Hypodiploid ALL. Children with severe hypodiploidy (<45 chromosomes) have poor outcomes (<40% survival) with chemotherapy [12]. Most recently, Nachman et al [13] reported 139 patients with ALL and hypodiploidy (<45 chromosomes) and confirmed poor survival in children with <44 chromosomes. However, compared with patients with <44 chromosomes, patients with 44 chromosomes had a significantly better survival (69%), suggesting that this group may not merit HCT in first remission. Twenty-nine children with hypodiploid ALL transplanted in first or second remission with a matched sibling donor between 1990 and 2001 have been reported to the International Bone Marrow Transplant Registry. Three-year survival was 65% (95% confidence interval [CI] 45%-80%), supporting the use of early HCT in this small subgroup (M. Eapen, personal communication, 2002).

Primary induction failure. A small subset (<2%) of children with ALL fail to achieve remission after 28 days of induction chemotherapy, and if they do achieve remission, only 40% will survive, suggesting that early transplantation might be of benefit. No large case series are available to accurately assess outcomes after HCT in these patients, and this is an important question for future study. It cannot be assumed that HCT will necessarily cure this small group of children with a particularly resistant initial disease.

Infant ALL. Molecular rearrangements that involve the *MLL* gene occur in a high proportion of leukemias arising in infants <1 year of age, most frequently a t(4;11)(q21;q23) translocation. Prognosis in MLL-rearranged ALL in infants is generally poor with current chemotherapy, with generally <20% 5-year event-free survival (EFS) [14-16]. Because of the poor response to chemotherapy, infants with MLL-rearranged ALL are often considered as candidates for early transplantation. The Seattle group analyzed results of 40 infants who received an HCT between 1982 and 2003 [17]. Three-year disease-free survival (DFS) was 73% in 14 patients transplanted in CR1, suggesting early (in CR1) HCT might benefit these children, as reported by others. In contrast, Interfant-99 enrolled 482 infants with ALL from 22 countries between 1999 and 2005 [18], and reported that MLL gene rearrangement, very high WCC (>300 $\times 10^9$/L), age <6 months, and a poor response to the prednisone prophase were independently associated with inferior outcomes. However, the 4-year DFS did not differ significantly between high-risk patients treated with chemotherapy alone (37.4%) versus chemotherapy plus HCT (50.2%) when adjusted for time to transplantation ($P = .19$). There is a clear need for further prospective studies to define the role of HCT in infants at high risk for treatment failure. Such studies will need to be multi-institutional and possibly multinational, as infant leukemia is rare. Studies should include evaluation of the late consequences of therapy in survivors, as morbidity can be significant in young children.

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Transplant for ALL in second remission. The majority of children with ALL are considered candidates for transplantation only if they relapse after receiving chemotherapy. The appropriate use of HCT or chemotherapy alone for children with relapsed ALL remains a controversial topic. A number of cooperative groups, including COG, have attempted to compare outcomes of transplant and chemotherapy in randomized studies and have been unsuccessful, largely because of lack of acceptance of randomization by either or both physicians and parents. In the absence of randomized data, the best available comparison comes from registry analyses. Eapen et al [19] compared 188 patients enrolled in Pediatric Oncology Group chemotherapy trials and 186 children who received HLA-matched sibling transplants between 1991 and 1997. For children with early first relapse (<36 months from diagnosis), risk of a second relapse was significantly lower after transplant with a total-body irradiation (TBI) regimen (relative risk [RR], 0.49; 95% CI 0.33-0.71, $P < .001$) than chemotherapy treatment, and leukemia-free survival (LFS) was improved. In contrast, transplant in CR2 did not offer an advantage over chemotherapy for children with a late relapse (≥36 months; $P = .78$).

The Italian Bone Marrow Transplant group reported on 57 children who received allogeneic transplant for ALL in CR2 and compared them to 230 patients who received chemotherapy following their relapse [20]. In agreement with the findings of the Center for International Blood and Marrow Transplant Research (CIBMTR) study, these authors demonstrated that patients who had an early first relapse (<30 months) had significantly longer DFS following transplant than treatment with chemotherapy, but this advantage was lost in patients with a later relapse (>30 months following diagnosis).

The German pediatric cooperative groups (BFM and COALL) reported 51 children with ALL in CR2, receiving matched sibling donor transplant [21]. Comparison of HCT results with outcomes in children treated with chemotherapy for a bone marrow relapse showed that patients with an initial remission longer than 18 months had comparable survival, whether treated with chemotherapy or bone marrow transplant. Patients with an early relapse (CR1 <18 months) or a relapse of T-ALL had a minimal chance of surviving following chemotherapy, and survival rates were significantly improved by allogeneic HCT.

This data indicates that HCT from a matched family donor is usually the best option for a child with early relapse of ALL. Data are currently insufficient to determine definitively whether similar benefit can be achieved with alternative donor HCT, although in may centers, results comparable to those seen with sibling donors can be achieved with an 8-allele MUD, supporting such an approach. The majority of studies indicate that children with later relapse (generally a CR1 of ≥36 months) can achieve similar survival with chemotherapy or with transplant from a sibling donor, so treatment options for these children should be discussed carefully with the family.

Transplantation for Children with AML

Transplantation for AML in first remission. Matched sibling donor transplant for AML has been regarded as the optimal postremission therapy for children with AML for many years. Recent data, however, show that children with favorable cytogenetics have outcomes equivalent to those achieved with sibling donor transplant and common practice, and the current COG study now recommend sibling donor transplant in CR1 for children with intermediate or high-risk cytogenetics, with chemotherapy treatment only for those with favorable cytogenetics (t[8;21]; inv16, t[15;17]). This practice accords with adult recommendations [22].

Certain subtypes of AML have a notably poor prognosis with chemotherapy, and transplantation using sibling donors or unrelated donor stem cell sources has the potential to improve those outcomes. A major limitation to proving or disproving benefit of transplantation is the small numbers of cases, even in large national trials. Monosomy 7 or deletion of the long arm of chromosome 7 (del[7q]) are uncommon in childhood AML, occurring in only 4% to 5% of cases. Outcomes have been poor in the majority of cases, as confirmed in a recent international analysis of cases pooled from many studies to generate a samples size large enough to assess risk factors [23]. The data showed a low likelihood of remission induction in the monosomy 7 cases (61%) compared with del(7q) (89%). Transplant did not improve survival in 77 cases that did achieve remission, but did improve survival in 17 children transplanted without CR in whom 31% survived compared with 0% survival in children who did not achieve CR and were not transplanted.

Leukemias with FLT3/ITD have a poor prognosis with chemotherapy treatment. It remains controversial whether outcomes can be improved with allogeneic transplantation, and whether this approach holds more promise than treatment with specific kinase inhibitors. A large number of reports have examined whether killer immunoglobulin-like receptor (KIR) mismatch can improve disease control in the most aggressive leukemias, with many positive and many negative studies. A prospective clinical study in the COG will seek to address this question in children with refractory, very poor prognosis, or relapsed disease.

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Late Effects of Transplantation in Children

Late effects of transplantation in children. Children with leukemia are vulnerable to late adverse consequences of therapy, as they are treated at a time when growth and development are incomplete, and because they have a potential life expectancy of over 70 years, during which late effects may become apparent. The "cost of cure" using different treatment modalities might become an important element in therapeutic choices when differences in survival with chemotherapy and transplant are not very different. The use of myeloablative chemotherapy and radiation certainly has late consequences in children, affecting growth, endocrine function, risk of secondary cancers, and in some cases, cognition. Concern about late toxicities is greatest for those treated as infants. A recent report described health outcomes in 17 children transplanted for ALL or AML when younger than 3 years of age, between 3.25 and 22.33 years prior to evaluation in this study [24]. Eleven of the 17 children had received TBI prior to transplantation. Neuropsychologic testing showed average IQ with attention deficits or other weaknesses in most children. Frequent abnormalities identified included growth hormone deficiency (59%), hypothyroidism (35%), osteochondromas (24%), decreased bone mineral density (24%), and dyslipidemias (59%). Despite these findings on focused testing, most subjects were doing well without major ongoing medical issues. These findings of good functional outcomes many years after transplant, even in the youngest children, are in agreement with the report of Leahey et al [25], who compared late outcomes of transplant with those seen after chemotherapy for children with AML. In this report, growth, renal, and cardiac function were all similar between the 2 groups, and the only significant difference identified was that transplanted children were more likely to need estrogen replacement. Taken together, these data support treatment selection based on likely survival, without undue concern for late effects, even in the youngest children.

INDICATIONS FOR HCT IN ADULTS WITH ALL

Introduction

The cure rate of ALL in adults remains unsatisfactory. The remarkable progress in childhood ALL [1] over the past 3 decades has not been replicated in adult ALL with approximately 2/3 of patients under 60 expected to succumb to their disease and more than 90% of patients over 60 years.

Based on the success in childhood ALL, therapy of adults has been modeled on a similar therapeutic template, consisting of induction, intensification and prolonged maintenance therapy.

The initial response to induction therapy in ALL is remarkably high, with 85% to 90% of adults in recent trials achieving a CR. The response to postremission chemotherapy is dependent on the prognostic factors at presentation and the presence of minimal residual disease (MRD) at the end of induction and intensification. The most important prognostic factors at presentation are adverse cytogenetics t(9;22), t(4;11), t(8;14), a complex karyotype or hypodiploidy/triploidy], age >35-40 years, and an elevated WCC [26]. The time taken to achieve a complete remission (4 weeks or more) may not be as important in adults [27]. Once in remission, 40% to 50% of young adults (<35-40 years) who do not have adverse prognostic features can be cured with a standard chemotherapeutic approach. In contrast, for adults older than 35-40 years, or those who present with adverse prognostic features, the cure rate with standard therapy is only in the order of 15%-20%, depending on the particular subtypes.

HCT

In contrast to AML, historically there has been a reluctance to use an allogeneic transplantation for ALL in first remission, based on the success in childhood ALL using only chemotherapy, as well as reliance on retrospective registry data [28]; despite the fact that the clinical importance of graft-versus-leukemia (GVL) has been recognized since 1979 and the initial reports of GVL in humans were in ALL [29].

Nevertheless, a clear role for allogeneic transplantation has been established for patients at very high risk, such as those with the Ph+ ALL, as well as other very high-risk features in CR1, and as for patients with relapsed or refractory ALL. The notion that allogeneic transplantation may also be of benefit for patients at standard risk in CR1 has evolved over the past 15 years.

CR1

The first major study of transplantation for ALL in first remission was conducted by the French LALA group, which in 1987, prospectively assigned ALL patients in CR1 who were <40 years and had an HLA-matched sibling to an allogeneic bone marrow transplant (BMT) [30]. All other patients up to age 50 years old were randomized to an autologous transplant versus chemotherapy. Of 116 eligible patients, 92 underwent an allogeneic transplant, with an overall 10-year survival OS of 46% for the BMT group versus 31% for the control group ($P = .04$). However, a subgroup analysis confirmed that the difference was only significant among high-risk patients where the OS for those undergoing an allogeneic transplantation was 44% versus 11% of the control patients ($P = .009$). A successor study conducted by the same group (LALA 94 trial) introduced a risk-adapted approach stratifying patients according to their prognostic

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features at presentation and evaluating allogeneic transplantation only for high-risk ALL patients. High-risk patients were defined as those who had B-lineage ALL with either a WCC of $>30 \times 10^9$/L or adverse cytogenetics including Ph+, t(4;11), t(1;19) or abnormalities involving 11q 23 rearrangements. Patients with T cell lineage were offered an allogeneic transplant if they did not achieve a complete remission after 1 course of induction. Any patient with CNS disease at presentation was also considered at high risk. A significantly improved DFS (45% versus 18%) at 10 years ($P = .007$) was reported for the 100 Ph-negative high-risk patients with a donor compared to the 159 patients who did not have a donor [31].

Another French study conducted by the GOELAMS group compared sibling allogeneic transplantation versus delayed autologous transplantation for similar high-risk patients. Once again, there was a significant improvement among the 41 patients undergoing an allogeneic transplantation versus the 106 control patients ($P = .0027$) [32].

At the same time a smaller institutional study from the Princess Margaret Hospital in Toronto, Canada, compared 48 ALL patients in CR1 who had a matched sibling donor versus 39 patients who did not have a donor. All patients in CR1, regardless of risk group, were offered an allogeneic transplant. For Ph-negative patients there was no improvement in the EFS or OS among those undergoing an allogeneic transplantation [33].

Compared with current major AML studies, all of these trials in ALL were relatively small and the data are often difficult to interpret, especially when broken down by even smaller subgroup analyses.

The International ALL trial, a major transatlantic collaboration between the Medical Research Council (MRC) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG) in the United States, was initiated in 1993 to prospectively define the role of allogeneic transplants, autologous transplants, and chemotherapy in all adult patients in CR1 up to age 60 years. The CR rate for all 1826 patients was 91%; it was 93% among Ph-negative patients [27].

Among 915 Ph-negative patients who achieved a complete remission and in whom a sibling donor search was initiated, the 5-year OS and EFS were significantly improved in the 388 patients who had a donor versus the 527 who did not have a donor (53% versus 45%; $P < .05$). In contrast to other previous studies, among the 218 patients with standard-risk disease who had a donor the OS was significantly improved over the 286 who did not have a donor (63% versus 51% at 5 years; $P < .05$) [34].

Despite the reduced relapse rate among all patients with a donor, the high TRM for high-risk older patients (39% at 2 years) abrogated the reduction in the relapse rate such that a definitive advantage could not be demonstrated for allogeneic transplants among the high-risk patients. In this large trial high risk was defined as any patient over 35 years or those with a high WCC at presentation. Surprisingly, time to complete remission was not an independently significant variable.

Based on this large trial, the standard of care is likely to move in favor of offering a sibling allogeneic transplantation to all ALL patients in CR1 under the age of 40 years. Although this trial also included patients <20 years of age, recent data suggest that teenagers, if treated on standard pediatric protocols, may have a significantly improved outcome compared with those treated on adult protocols [35-37]. Whether an allogeneic transplant can further improve the results in this group of patients remains to be determined.

The use of MUD transplants for high-risk ALL patients has not been prospectively evaluated with an appropriate control group. Nevertheless, the data from patients with the Philadelphia chromosome suggest that such transplants can be performed with considerable efficacy and toxicity that is not significantly greater than with sibling allografts [38-40]. Recent reports from the group from Perugia, Italy, suggest that a haploidentical transplant may be as efficacious as a MUD transplant for high-risk patients in CR1 [41]. Although these data need to be corroborated by others, this may be an option for patients who do not have a sibling or in whom a MUD donor cannot be identified.

A major collaborative effort between the MRC in Britain and the major cooperative groups in the United States is planned to evaluate the role of MUD transplant in Ph-negative patients who are at high risk. This would comprise patients <40 years who have either a high WCC at presentation, adverse cytogenetics, or the presence of MRD detected after induction and intensification.

The predictive value of the presence of MRD has been confirmed in several studies, both in childhood and in adult ALL [42,43]. Further studies are needed to know whether the absence of detectable MRD after induction or intensification can spare some patients the need to undergo an allogeneic transplant.

Historically, several studies have evaluated the role of autologous transplant for ALL in CR1 [44]. It is difficult to reliably assess the data because of the small number of patients in these trials and the variability of study conditions. In general, however, the reported data suggest that autologous transplant may be at least as efficacious as standard chemotherapy, and 1 study reported superiority for high-risk patients [45]. No report suggested that autologous transplantation is inferior to chemotherapy [34]. Very recently, however, the International ALL study randomized 446 patients in CR1 to either undergo a single autologous transplant

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or receive protracted consolidation/maintenance therapy. In contrast to previous reports, in this large prospective study there was a statistically superior DFS for patients undergoing chemotherapy [34]. Thus, outside of a clinical trial, autologous transplantation cannot be recommended for ALL in CR1.

Relapsed/refractory ALL. Adults with relapsed ALL have a dismal prognosis with an OS of <10% at 5 years [45]. Allogeneic transplant provides the only option of cure for such patients, irrespective of age or other prognostic factors. Patients who have not undergone an allogeneic transplant in first remission and can be successfully induced into a CR2 can be cured by an allogeneic transplant in 25% of cases [46]. It is clear that for patients who do not have a related histocompatible donor a MUD transplant should be offered. For those patients who do not achieve a second remission or those who are refractory to primary induction an allogeneic transplant is also appropriate, although the likelihood of a cure in such patients is <10%. An important issue is whether to attempt reinduction therapy or to take such a patient immediately to transplant. Although the issue is unresolved, it is likely that the toxicity from the transplant is increased through reinduction therapy and, thus, it is often reasonable to take a patient directly to the transplant if the prognostic factors are such that it is unlikely that the patient will respond to reinduction therapy.

Ph+ ALL. For the past 3 decades the single most uncontested indication for a sibling allogeneic transplant in any acute leukemia has been a young adult with Ph+ ALL. The standard of care has evolved such that these patients have been routinely offered a MUD donor transplant if a family matched donor is not available. The data from multiple groups suggest that somewhere between 35% and 50% of such adults who had undergone a transplant, from a related or unrelated donor, can be cured. The advent of imatinib mesylate for patients with Ph+ ALL has altered the standard of care for these patients [47,48]. Data from multiple groups have reported that a greater percentage of patients can get into CR with imatinib, and can do this more rapidly. Imatinib also had a major impact on the management of older patients with Ph+ ALL who could not otherwise withstand intensive therapy.

However, the emerging data to date have not unequivocally demonstrated superiority for patients undergoing an allogeneic transplant in the imatinib era compared with those successfully undergoing an allogeneic transplant in CR1 in the pre-imatinib era. More importantly, perhaps, the remaining issue that needs to be emphasized is the fact that since the advent of imatinib there has not been a study evaluating the ongoing imperative for an allogeneic transplant in Ph+ ALL [49]. If future studies establish the curability of Ph+ patients with intensive chemotherapy and imatinib, without the absolute need for an allogeneic transplant, this would lead to a complete reversal of standard indications for an allogeneic transplant in ALL.

Older adults. Probably the most difficult and challenging current issue in the management of adults with ALL is to know how to manage patients over the age of 40 years with or without other adverse prognostic factors. Clearly, these patients are at high risk regardless of the presence of other recognized adverse prognostic factors. Althouh the GVL effect in CR1 is very important in significantly reducing the rate of relapse, the problem is that the nonrelapse mortality (NRM) in this age group may be as high as 40% [34]. Reduced intensity transplant conditioning (RIC) regimen in ALL is likely to reduce the toxicity in such patients. However, unlike the emerging data in AML, for ALL there are insufficient data at the present time to reliably predict the overall efficacy of this approach. This will be studied in the prospective international US Intergroup/MRC trial.

Summary

The overall efficacy of treatment of adult ALL with chemotherapy seems to have stalled over the past 15 years, with no further significant progress. At the same time, the role of HCT in ALL is becoming clearer, although much remains to be learned.

The indications for allogeneic HCT in CR1 are broadening to include all but teenagers; alternative donors are a viable option for all patients (not only Ph+) who do not have a family donor, and the enthusiasm for autologous transplants is waning. The greatest challenge and uncertainty remains in the management of older adults with ALL.

INDICATIONS FOR HCT IN ADULT AML

Introduction

AML includes a spectrum of disorders with common features but also considerable heterogeneity in biology and therapeutic responsiveness. This heterogeneity, together with the multiple forms of HCT available, demands careful evaluation and planning to best integrate HCT into the care of the individual patient.

Standard Chemotherapy

Remission induction. For more than 2 decades, standard induction chemotherapy for patients with newly diagnosed AML age <60 years has been cytarabine 100 mg/m^2 by continuous infusion for 7 days combined with an anthracycline, such as daunorubicin 45-60 mg/m^2/day for 3 days. Althouh many variations on this general theme exist, none has been shown to be clearly superior. For patients ≥60 years with an acceptable performance status, similar regimens can be used, but for those with diminished performance

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status, less intensive induction approaches may be more appropriate. With standard induction chemotherapy, CR rates average approximately 75% to 80% for adults age <60 years, and roughly 50% for adults ≥age 60 years. A number of known prognostic factors greatly influence these CR rates, as will be discussed. It is, of course, axiomatic that entry onto a well-conceived and designed clinical trial should be considered, if at all possible.

Postremission chemotherapy. If no postremission chemotherapy is given, patients will inevitable relapse, usually within 4-6 months. Most contemporary postremission chemotherapy regimens for younger patients include multiple cycles of high-dose cytarabine, with or without additional agents. In the United States, the most commonly used approach is 4 cycles of high-dose cytarabine, 3 g/m^2 every 12 hours on days 1, 3, and 5 [50]. Patients ≥60 years, particularly those with comorbidities, are less able to tolerate such aggressive chemotherapy and are more commonly treated with several cycles of moderate-dose chemotherapy [51]. With commonly used chemotherapy regimens, 35% to 40% of adults <60 years and 10% to 15% ≥60 years can expect to be alive in remission 5 years after diagnosis.

Chemotherapy for recurrent AML. The choice of chemotherapy for recurrent AML is generally influenced by patient age, health, initial therapy, and duration of first remission. Younger patients, and particularly those with a longer first remission, are usually treated with a regimen containing an anthracycline plus high-dose cytarabine. For younger patients with shorter remission durations, newer alternative agents are generally recommended. Older individuals and particularly those thought not to be candidates for further aggressive therapy can benefit from a gemtuzumab-containing regimen. The likelihood of achieving a second remission is heavily influenced by the duration of first remission, among other factors. CR2 rates as high as 75% are seen in patients relapsing after a first remission of >2 years, but remission rates of <25% are seen in those with a first remission lasting <6 months [52]. Except for occasional patients with favorable risk cytogenetics, the duration of second remission is short, averaging 4-6 months in most studies.

HCT

Indications for HCT in patients age <60 years.

First remission. In 1979, Thomas et al [53] first reported the outcome of allogeneic transplantation from matched family member donors for a small series of patients with AML in first CR. Currently, 37% of these patients remain alive in remission 27 to 28 years later. Since that original report, large numbers of patients with AML in first remission have been transplanted; the CIBMTR reports 3174 patients receiving transplants from HLA-matched siblings after high-dose preparative regimens for AML in CR1 between 1998 and 2004 with a 3-year probability of survival of 60% ± 1% [54].

A question of great practical importance is whether patients with AML and a matched sibling should be transplanted while in first remission or have transplant delayed for use as salvage therapy. A large number of trials have attempted to address this question by studying a cohort of patients using a "genetic randomization" in which patients with matched siblings are allocated to allogeneic transplantation, whereas those without serve as the chemotherapy controls. A recent metaanalysis, which included all such studies conducted between 1995 and 2003 that were written in English, included an intent-to-treat analysis and provided survival data, identified 5 studies involving 3100 subjects [55]. For the entire cohort, there was a statistically significant survival advantage associated with the use of allogeneic transplantation. The benefit was greatest for patents with unfavorable cytogenetics, and lost for those with favorable risk cytogenetics. Although this and similar studies provide interesting information, they fall short of the mark of answering the precise question for the patient with a matched sibling, because such patients have an option of salvage transplantation from their matched sibling, whereas the "controls" in the genetic randomized studies do not. With this caveat, the conclusion from the meta-analysis is that there seems to be a survival advantage for transplantation from a matched sibling for patients with AML in CR1 with poor- or intermediate-risk cytogenetics.

Recent data suggest that the intermediate-risk category of AML might be divisible into subgroups with poorer and more favorable prognoses. Schlenk et al [56] recently reported that most patients with AML with normal cytogenetics will have mutations in various genes including NPM1 in 53%, FLT3-ITD in 31%, FLT-TKD in 11%, CEBPA in 14%, and NRAS in 13%. In a prospective study in which patients with AML in CR1 with normal cytogenetics were allocated to an allogeneic transplant if they had a matched sibling and/or to chemotherapy if no donor was available, a survival advantage for allogeneic transplantation was found, except in those with NPM1+/FLT3ITD− AML [56].

For patients without matched family member donors, the utility of autologous transplantation compared to chemotherapy has been the subject of a number of prospective randomized trials. A recent metaanalysis considered all such studies that focused on adult patients, were analyzed on an intent-to-treat basis, and included greater than 75 patients in each arm [57]. Six trials involving 4410 patients were included. The combined results of these 6 trials indicated that autologous transplantation modestly

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improved EFS, but did not improve OS. The trials included in the metaanalysis were heterogeneous with regard to treatment strategies, preparative regimens and stem cell sources. Among the 6 studies, those that showed the least evidence of benefit employed autologous transplantation early after remission induction without much preceding consolidation therapy, whereas those that applied transplantation after several cycles of intensive consolidation seemed to show a greater suggestion of benefit.

MUD transplantation offers another approach to the treatment of AML in CR1. The CIBMTR reported 41% ± 2% 3-year survival among 1066 adult recipients of unrelated transplants [54]. Registry data may be influenced by a number of factors, including, on 1 hand, a likelihood that physicians only send higher risk patients for unrelated transplants in CR1, but on the other hand, that patients must remain in remission for some months to actually be transplanted. The sole prospective study so far reported is the German 01/99 trial in which high-risk patients, as defined by cytogenetics or having >5% blasts remaining in marrow on day 15 of induction, were allocated to allogeneic transplantation if a matched sibling or MUD could be found, or to autologous transplantation if no donor was available [58]. At 4 years, survival was 68% among recipients of matched siblings transplants, 56% among unrelated donor transplant recipients, and 23% after autografting ($P = .01$).

Untreated first relapse or second remission. Except for rare patients with favorable risk cytogenetics and a long CR1, few patients with AML who relapse after initial chemotherapy can be cured with salvage chemotherapy. Thus, transplantation should be considered for most patients who chose not to be transplanted in first CR and subsequently relapse. For such patients, an initial question is whether to proceed directly to transplant or to first attempt reinduction using chemotherapy. Often the answer is dictated by the lack of an immediately available stem cell source or access to a transplant facility. But in other cases, a matched sibling or family member has already been identified or autologous stem cells have been stored while in first remission making transplantation in untreated first relapse a possibility. To date, there have been only a limited number of studies describing the outcome of matched sibling allogeneic transplantation for AML in untreated first relapse. Studies from the FHCRC report 3-year DFS of 28% among 126 patients [59]. A very similar result was reported by Brown et al [60] from St. Louis. Data from the CIBMTR suggest a 47 ± 2% 5-year survival for patients over age 20 years receiving matched sibling allogeneic transplantation for AML in second remission [54]. Although at first glance 47% appears superior to 28%, it should be remembered that the likelihood of successful reinduction using chemotherapy is <50%. Thus, if 50% of patients with recurrent AML achieve second remission, and 50% of those are cured with allogeneic transplantation, the overall salvage rate is about 25%, a figure not superior to the 28% seen with allogeneic transplantation in untreated first relapse. Of course, considerable selection bias exists in both the patients who make it through reinduction therapy and actually get to transplant, as well as those who are stable enough to make it to transplant without an urgent need for reinduction chemotherapy.

There are very little data about the use of autologous transplantation in untreated first relapse. A single study reported 8 of 38 patients (21%) alive in remission several years after autografting in untreated first relapse [61]. A much broader experience exists for autografting for AML in CR2, where the CIBMTR reports a 5-year survival of 40% ± 3% [54]. Patients with AML in CR2 also have an option for unrelated donor transplantation. The CIBMTR data base reports 5-year survivals of 42% ± 2% for unrelated donor transplants for AML in CR2 [54]. There are no prospective randomized trials comparing the 2 approaches. There are, however, both single institution and registry comparisons using matched-pair analyses or proportional hazards regression in an attempt to make adjustments for prognostic variables [62]. These studies show, not surprisingly, decreased relapse rates with unrelated donor transplants but decreased NRM with autologous transplantation. These risks tend to balance, and thus neither approach shows a clear advantage in these retrospective studies. Common sense would argue that the increased disease control seen with unrelated transplantation would favor this approach in younger patients and those with shorter first remissions, whereas autologous transplantation might be considered in older patients with longer first remissions.

Refractory relapse. Lack of a consistent definition of "refractory relapse" complicates any discussion of the topic. A simple and relatively unambiguous definition includes only those patients who once achieved a complete response, have since relapsed, and have failed to achieve a subsequent CR or CRp with the last reinduction attempt. The chance that such patients will benefit long term from an alternative chemotherapy regimen was <1% in the M.D. Anderson experience [63]. The results with transplantation are likewise poor, with only 10% of such patients achieving 3-year DFS with matched sibling transplants, and 7% using MUD transplants [64,65]. Among those transplanted in refractory relapse, results are marginally better for patients with a lower leukemic burden at the time of transplant, an observation that has led to the practice of administering intensive chemotherapy to clear circulating leukemic blasts prior to initiating the transplant preparative regimen. Whether such an approach really improves the ultimate outcome of

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transplantation is unknown. Less stringent definitions of "refractory relapse" exist; for example, Hiddemann et al defined refractory relapse to include patients who relapse within 12 months of first remission and those in second and subsequent relapse, regardless of whether they had received any attempts at reinduction. Not surprisingly, transplant studies using this or similar definitions of refractory relapse report modestly better outcomes than those restricted to patients who failed their last reinduction attempt.

Primary induction failure. In general, patients with primary induction failure (defined as failure to achieve an initial CR after at least 2 cycles of treatment) have almost no hope for long-term survival using alternative chemotherapy strategies, yet several studies have reported long-term DFS in approximately 20% of such patients if transplanted from a matched sibling [66,67]. Because of the time required to find an MUD, very little data exist about unrelated transplants for primary induction failure, but the limited data available demonstrate that cure is possible in 10% to 20% of patients. The potential of allogeneic transplantation to save the lives of some patients who fail to achieve a first remission emphasizes the importance of typing patient and family members shortly after AML is diagnosed so that valuable time is not lost in identifying donors should remission induction attempts fail.

Indications for HCT in patient age 60 years or greater. Autologous transplantation can be carried out in patients age 60 years or greater with relative safety, assuming the patient is otherwise reasonably fit. However, there have been no prospective randomized trials comparing autologous transplantation to chemotherapy for patients in this age group with AML of any particular stage, and most guidelines, including those of the National Comprehensive Cancer Network (NCCN) do not recommend autologous transplantation as a standard option for patients age 60 years or greater with AML in CR1.

Few studies of allogeneic transplantation for AML in patients age 60 years or greater have been carried out because of the perception that the use of high-dose preparative regimens coupled with complications because of allogenicity would prove overwhelmingly toxic. With the popularization of RIC preparative regimens, there has been renewed interest in the application of allogeneic transplantation for this patient population. A phase II trial using a preparative regimen of fludarabine and low-dose TBI in 122 patients, median age 58, with AML reported a 2-year DFS of 44% for recipients of matched sibling transplant for AML in CR1 and 63% after matched unrelated transplantation [68]. The only prospective donor versus no donor study so far published suggested an advantage for allogeneic transplantation, with 4-year DFS of 54% in those with donors versus 30% in those treated with chemotherapy [69].

SUMMARY

Based on available data, all adults with AML under age 60 years with matched siblings should be considered for allogeneic transplantation in first remission, except for those with favorable risk cytogenetics and possibly those whose disease has normal cytogenetics and is FLT3/ITD negative and NPM1 positive. Patients with matched siblings not transplanted in first remission should be followed closely so that transplantation in early first relapse can be considered. Those without matched siblings should receive a MUD transplant in first CR if they have higher risk disease. All others should receive standard chemotherapy and consider a matched unrelated transplant or autologous transplant, should they relapse. RIC allogeneic transplantation using either a matched family member or a MUD can be considered for patients age 60 years or greater with AML in second or subsequent remission, or AML in first remission with intermediate or high risk disease.

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