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What is the impact of hematopoietic cell transplantation (HCT) for older adults with acute myeloid leukemia (AML)?

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Abstract

Acute myeloid leukemia (AML) patients over the age of 55 years are generally more difficult to treat than younger patients due to intrinsic drug resistance and diminished tolerance to treatment. The unfortunate result is that conventional chemotherapy is toxic and rarely curative. Recent studies suggest a better outcome for older AML patients treated with reduced-intensity conditioning (RIC) hematopoietic cell transplantation (HCT) than those treated with conventional chemotherapy. However, there are major limitations to RIC HCT. Some of these limitations may be able to be overcome, broadening the impact of allogeneic RIC HCT for older patients with AML. Ways to improve RIC HCT include making more patients eligible for RIC HCT by improving initial complete response rates using novel agents or combinations; finding a way to more rapidly identify alternative stem cell sources, such as by using donors that have already undergone HLA profiling or by using unrelated cord blood; eliminating the requirement for a complete response prior to transplant; and educating patients and physicians about the chances of survival after RIC HCT when compared to conventional chemotherapy.

Keywords

reduced-intensity conditioning; hematopoietic cell transplantation; elderly; acute myeloid leukemia; cord blood

INTRODUCTION

Acute myeloid leukemia (AML) in older adults is a very difficult disease to treat. Because of both intrinsic drug-resistance of the disease and diminished tolerance of the patient to treatment, chemotherapy is rarely curative, and less than 1 in 5 patients over age 55 or 60 (the age cut-off for older adults varies from study to study) can expect to be alive 3 years after diagnosis. Several small trials on the use of allogeneic reduced-intensity conditioning (RIC) hematopoietic cell transplantation (HCT) for AML in older adults have recently been published, reporting a 45%–74% survival rate at 3 years, an outcome seemingly better than might be expected with conventional chemotherapy. These results are obviously quite encouraging, but they also raise two important questions: how broadly can allogeneic RIC

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HCT be applied to older adults with AML, and, if the application is limited, what can be done to expand it?

ACUTE MYELOID LEUKEMIA IN THE OLDER ADULT

The nature of AML changes as the age of the patient increases. Compared to AML in younger patients, AML in patients over age 55 is more often associated with an antecedent hematological disorder (AHD), is less proliferative, presenting with a lower white count and a lower percent of marrow blasts, is more often associated with the expression of P-glycoprotein (P-gp) in the AML blasts, and is much more likely to have an unfavorable cytogenetic profile.¹ In virtually all studies, having an AHD, the presence of P-gp, and demonstration of unfavorable cytogenetics are each independently associated with a lower likelihood of achieving a complete remission and with diminished remission duration.^{2,3,4,5} In addition to a more unfavorable disease profile, older patients more often have a diminished performance status and an increased number of co-morbidities, both of which further reduce the likelihood of a favorable response to chemotherapy.^{1,6}

With conventional therapy including an anthracycline and cytarabine, complete response (CR) rates in patients over age 55 average ~ 40% in most studies. In patients aged between 55 and 70 years, the CR rate might be a bit higher, averaging around 45%, while in those over age 70, only approximately 25% of patients can be expected to achieve CR. The median duration of remission averages is 6 to 8 months in most studies, and survival at 3 years is less than 20% in virtually all studies. The survival curve from a typical study is shown in Figure 1.⁷ In the Eastern Oncology Cooperative Group trial by Rowe et al, almost no patients were over age 75, and approximately 90% had a performance status of 0 or 1, so this was not a particularly older or infirm group of AML patients. Similar results have been published by others.⁸⁻¹⁰

REDUCED INTENSITY CONDITIONING ALLOGENEIC HCT IN OLDER AML PATIENTS

Approximately 20 years ago, the first studies were published showing that patients who developed graft-versus-host disease (GVHD) following allogeneic HCT had a lower risk of leukemic relapse than those who did not. These studies suggested that an immunologic graft-versus-tumor (GVT) effect contributed to the success of allogeneic HCT. At that time, it was impossible to estimate how much of the antileukemic effect could be attributed to the high dose preparative regimen and how much to GVT because high-dose regimens were required for engraftment. With the development of more specifically immunosuppressive preparative regimens containing fludarabine and anti-T-cell antibodies (either antithymocyte globulin [ATG] or alemtuzumab) and with the discovery of the fact that more intensive post-grafting immunosuppression favors allogeneic engraftment, it has been possible to develop preparative regimens of substantially reduced intensity that still assure allogeneic engraftment. These regimens allowed for the exploration of allogeneic HCT in patients generally considered to be too old or infirm to tolerate more traditional high-dose regimens.

A number of reports have now been published describing the outcome of RIC HCT for AML. Hegenbart et al described the results in 122 older patients treated with the "Seattle" preparative regimen of fludarabine (90 mg/m²) combined with low-dose total body irradiation (TBI) (2 Gy) followed by cyclosporine and mycophenolate mofetil as GVHD prophylaxis.¹¹ Survival at 3 years with this regimen was 46% for the 51 patients transplanted in first remission (CR1), 42% for the 39 patients transplanted in second remission (CR2), and approximately 18% for those transplanted with more active disease (Figure 2). Somewhat better results were seen in recipients of unrelated-donor transplants

compared recipients of matched, related-donor transplants. Transplant-related mortality was 22% for all patients.

Shimoni et al reported results using a somewhat more intensive regimen of fludarabine (150 mg/m²) plus busulfan (6.4 mg/kg) followed by cyclosporine plus methotrexate for GVHD prophylaxis (recipients of unrelated transplants also received ATG as part of conditioning).¹² A total of 41 patients were reported. Among 14 patients with active disease at the time of transplant, none survived disease-free, but among 27 in first remission at the time of transplant, 74% were reported to be disease-free at 3 years.

Sayer et al published a retrospective study of the results of the Cooperative German Transplant Study Group and reported an event-free survival of 52% at 24 months among 25 patients transplanted in first remission, most of whom were treated with a fludarabine-busulfan preparative regimen.¹³ Among 34 patients transplanted in second remission, the event-free survival was 40%, but among 54 patients transplanted for more advanced disease, less than 20% were alive and disease-free at 2 years.

Wong et al,¹⁴ Bertz et al,¹⁵ and others have published similar outcomes. These reports are important in demonstrating that allogeneic HCT using RIC is possible in older patients with AML and that, in selected patients, outcomes are encouraging. But these reports deal only with patients referred specifically for transplantation and do not address the questions of what percent of older patients with AML might be candidates for this procedure or what outcomes would be achieved if HCT were applied to the broader population. Mohty et al began to approach these issues in a study that attempted to address whether transplantation yielded results superior to what might be expected with chemotherapy.¹⁶ In that study, they identified 95 patients with AML in first remission and who had known siblings. Thirty-five had an HLA-matched sibling and were considered the “donor” group, while in 60 patients, the siblings were not a match. Twenty-five of the 35 in the donor group actually proceeded to transplant using a reduced intensity regimen of fludarabine, busulfan, and ATG. Using an intent-to-treat analysis, leukemia-free survival at 4 years was superior in the donor group (54% vs 30%). While this study comes a bit closer to estimating the possible impact of RIC HCT on older patients with AML, it does not directly address the issue because of the retrospective nature of the study and the fact that it only dealt with a select group of patients already in CR who had an available sibling.

The sole study that has prospectively addressed the issue of the broad applicability of RIC HCT was reported by Estey et al, who conducted a trial in which all AML or high-risk myelodysplasia (blasts >10%) patients admitted to the University of Texas MD Anderson Cancer Center were entered on a trial with the plan for them to be seen by the transplant service.¹⁷ If transplantation was thought to be plausible, a search for an appropriate donor was to be conducted and the patient was to proceed to transplantation. A total of 259 patients entered the study. CR was achieved in 99 patients (38%). Of those 99, 53 were referred to the transplant service and 46 were not. The reasons for not referring these 46 patients were not clear and may have reflected patient age, underlying health, or a bias of the physician and/or patient against transplant. Among the 53 patients referred for transplantation, a matched sibling was identified in 21 cases, and a matched, unrelated donor was found for an additional 5 patients; thus a donor was found for 49% of those referred for transplantation. Fourteen patients actually underwent transplantation, 13 from a matched sibling and 1 from an unrelated donor. Among those that underwent HCT, the results were encouraging, with a 57% disease-free survival (DFS) at 4 years (Figure 3). After accounting for age, cytogenetics, AHD status, and lead time bias, there was a >99% probability that the outcome after RIC was superior to that seen in patients not transplanted. However, the 14 patients who underwent transplantation represent only 26% of those seen by the transplant service,

only 14% of all those who achieved a CR, and only 5% of the original 259 entered onto study.

The study by Estey et al certainly has its shortcomings. By the author's own admission, some of the physicians participating in the trial were reluctant to encourage patients to proceed to a matched, related transplant, and particularly a matched, unrelated transplant. The authors attempted to estimate the maximum number of patients who could have gone to transplant, assuming all patients were sent for a transplant consult and donor searches were conducted more vigorously, and concluded that, at best, 50% of those entering CR1 would have gone to transplant, or 19% of the patients overall.

BROADENING THE IMPACT OF ALLOGENEIC RIC HCT FOR OLDER PATIENTS WITH AML

The apparent improved survival seen with allogeneic RIC HCT for older patients with AML provides a compelling argument for identification of those factors that limit the impact of this approach and consideration of methods to overcome these limitations.

Improve complete response rates

An initial factor limiting the application of RIC HCT for AML is the low CR rates seen with conventional chemotherapy. As noted above, CR rates for older patients with AML have remained at the 40%–45% range for several decades. Most prior studies centered on variations of the use of an anthracycline and cytarabine, including alterations in dose, addition of a third or fourth agent, use of hematopoietic growth factors, or attempts to reverse the effects of p-gp. Unfortunately, none of these approaches has reproducibly improved CR rates. In a recent study, Nand et al have combined the hypomethylating agent 5-azacytidine with reduced-dose gemtuzumab ozogamicin.¹⁸ They report a CR rate of >70% in a group of AML patients with an average age >70 years. This regimen is currently being tested in a larger phase II study by the Southwest Oncology Group (SWOG) (S0703). Other novel approaches include combinations of demethylating agents with histone deacetylase inhibitors and the use of protease inhibitors in combination with conventional therapy.

Eliminate the requirement for a complete response prior to transplant

While reduced intensity conditioning provides an opportunity to apply allogeneic HCT to an older population, the diminished immediate antitumor effects of RIC make it generally unsuitable for patients with active leukemia. The low disease-free and overall survival rates in patients with active disease noted in the studies above have led to an appropriate reluctance to recommend RIC for patients not in remission. The ability of current RIC regimens to obtain an allogeneic graft with minimal toxicity may, however, provide a platform onto which more specific antileukemia therapies might be added. For example, several investigators have shown that it is possible using monoclonal antibodies to specifically target radioisotopes to the marrow and other sites of leukemia, a form of therapy termed radioimmunotherapy (RAIT). At the Fred Hutchinson Cancer Research Center, we have explored the use of an ¹³¹I-labeled anti-CD45 antibody, and have shown that this reagent is capable of delivering between 2- and 3-fold more radiation to marrow and spleen than to liver, the normal organ receiving the highest radiation dose, and approximately 10-fold more radiation to the marrow than to the whole body. In a phase 1/2 trial, ¹³¹I-labeled anti-CD45 antibody has been added to the usual Seattle regimen of 90 mg/m² fludarabine plus 200 cGy TBI.¹⁹ While the degree of myelosuppression is far greater with this newer regimen, other organ toxicities do not appear to be different, and the overall risk of non-relapse mortality does not appear to be higher. This trial included patients too old or infirm to be treated with a myeloablative transplant regimen, but with disease too advanced

to be treated with our usual RIC approach. Among the small number of patients treated at the maximum tolerated dose of RAIT (24 Gy to liver), the survival at 2 years is 54%. If these results persist, this or similar approaches may provide a method for treating older AML patients who achieve less than a complete response with initial therapy.

Identify alternative stem cell sources more rapidly

It generally requires, on average, about 3 months to identify an unrelated donor and proceed to transplantation. The average duration of complete remission in many studies of conventional chemotherapy for AML in older patients is only around 6 months. Thus, if initial typing is not obtained until after a complete remission is achieved, as many as 50% of patients may relapse before they can be transplanted. Currently, patients who relapse before the transplant can be conducted are either denied transplantation or reinduction is attempted with an acknowledged very low probability of reestablishing remission.

There are several ways that alternative stem cell sources might be identified more rapidly. The number of patients in the unrelated donor pool with molecular typing already available has been steadily increasing. If a suitably matched donor with molecular typing already available exists, a transplant can usually be conducted within 6 weeks of initiating the search. An argument can be made that it might be preferable to proceed immediately with a 7 of 8 human leukocyte antigen (HLA)-matched donor with available molecular typing rather than delay the transplant and search for an unknown 8 of 8 HLA-matched donor. This is particularly true if the mismatch is at HLA-B or -C, which appear to be better tolerated than mismatches at HLA-A or -DR.²⁰

Unrelated cord blood (UCB) provides another source of immediately available stem cells. The initial experience of UCB transplantation in children showed a clear association between cell dose (measured either as total nucleated cells or CD34+ cells) and survival. Limited cell dose was likely the major contributing factor to the poor results seen with initial trials of cord blood transplantation in adults. More recent results of UCB in adults using high-dose conditioning are showing improved outcomes, likely because of the appreciation that transplants should be restricted to those settings where an adequate cell dose is available. Two retrospective studies show outcomes with UCB transplants in adults that approach those obtained with matched unrelated donors.^{21,22} These reports are limited to younger adults receiving high-dose conditioning. In an effort to overcome the limitation of low cell dose found in single cord blood units, limited phase II studies of double cord transplants have been published, demonstrating that this approach may lessen the risks of graft rejection and high early mortality previously associated with the use of single cords with lower cell dose. Experience with the use of reduced-intensity conditioning UCB transplantation is only now beginning to emerge.²³ The data so far available suggest that grafts can be obtained in the large majority of cases using regimens of fludarabine, cyclophosphamide, and low-dose TBI. Longer-term follow-up of treated patients is needed.

Educate patients and physicians

The impact of RIC HCT for older patients will remain very limited as long as patients and physicians are reluctant to consider the procedure. A prior SWOG study of this approach was closed early because of poor accrual, and a subsequent study of the Cancer and Leukemia Group B (CALGB) has struggled as well. While all of the reasons noted above (requirement of a CR, low CR rates, lack of rapidly available donors) contribute, the SWOG and CALGB studies were relatively small phase II trials with very modest accrual goals for a relatively common disease. Thus, there is an obvious reluctance to refer patients for this procedure. Perhaps patients and physicians overestimate the benefits of conventional chemotherapy for older adults. Do patients really understand that the large majority of older

AML patients treated with conventional chemotherapy will not live 1 year from diagnosis and only about 1 in 10 will live 3 years? And likely many nontransplant physicians overestimate the acute toxicities of RIC regimens. While some patients will develop life-threatening or fatal GVHD and others will develop fatal infections, early toxicities are generally well-tolerated. In most centers, the nonrelapse mortality during the first 3 months after transplant is 10% or less, and the overall nonrelapse mortality is approximately 20%. While these figures are regrettably high, most would not view them as unacceptable if the procedure offers an increase in cure rates from less than 10% to over 50%. Of some concern is the long-term quality of life of older survivors of RIC HCT. While the available data about quality of life after allogeneic HCT is encouraging, these studies have largely been focused on younger patients. More detailed information about the quality of life of older survivors of RIC HCT might help encourage patients and physicians to consider this approach.

CONCLUSION

Recent studies seem to suggest a better outcome for older AML patients treated with RIC HCT than those treated with conventional chemotherapy. However, there are still limitations to RIC HCT, but there are several methods to overcome these limitations and hence broaden the impact of allogeneic RIC HCT for older patients with AML. These methods include improving the complete response rates by using novel agents or combinations; finding a way to more rapidly identify alternative stem cell sources, such as by using donors that have already undergone HLA profiling or using unrelated cord blood; eliminating the requirement for a complete response prior to transplant; and educating patients and physicians about improved chances of survival after RIC HCT when compared to conventional chemotherapy. Further research into the quality of life of older survivors of allogeneic HCT is needed.

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Figure 1. Overall survival among 348 patients aged older than 55 years with previously untreated AML entered onto a recent ECOG trial.⁷

Figure 2. Survival of 122 patients with AML in CR1, CR2, or with more advanced disease treated with reduced-intensity conditioning using the Seattle regimen.¹¹

Figure 3.

Relapse-free survival among 97 patients with AML or high-risk myelodysplastic syndrome who achieved CR1, including those who did not have a consult for possible transplant, those who had a consult but no donor, those who had a donor but didn't receive a transplant, and those who received a transplant.¹⁷