Allogeneic stem cell transplantation for adult acute lymphoblastic leukemia: when and how

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Allogeneic hematopoietic stem cell transplantation (HSCT) with a myeloablative conditioning regimen is considered the most potent post-remission antileukemic therapy in adult acute lymphoblastic leukemia (ALL).[1,2] However, an adequate balance should be established between its curative potential, the disadvantages (transplant-related mortality, late complications and reduced quality of life) and the improved outcome of the current chemotherapy regimens.[3-7] Large prospective trials,[8] several meta-analyses of randomized trials[9,10] and modeling studies[11] have concluded that allogeneic HSCT with myeloablative conditioning is of benefit for high-risk adult patients in first complete remission. The benefit of HSCT in patients with standard-risk features is controversial. Although the largest randomized trial in adult ALL so far showed a significant advantage of HSCT in patients with standard-risk-ALL,[8] the results of the current pediatric-inspired protocols are better than those from the

chemotherapy arm of randomization in that protocol.[12] This makes the decision of whether to use transplantation in standard-risk ALL patients difficult. On the other hand, minimal residual disease is currently integrated in the clinical risk models of adult ALL.[13] Negativity for minimal residual disease in standard-risk patients at baseline confirms the status of standard-risk, and such patients have shown promising responses to pediatric-based chemotherapy, with an extremely low probability of relapse.[14] Thus, modern protocols tend to avoid HSCT in standard-risk patients who are confirmed to be negative for minimal residual disease.[15] On the other hand, a proportion of high-risk patients (up to 40% or 50%) achieve sustained minimal residual disease negativity and this condition is associated with a relatively good prognosis,[16,17] thereby allowing HSCT to be avoided in some recent protocols.[18] In contrast, patients with minimal residual disease, whether clinically standard risk or high risk, constitute a true high-risk group and HSCT is the best post-consolidation therapy for these patients.

The increasing use of unrelated donors, cord blood, haploidentical donors and reduced intensity HSCT have increased the accessibility to HSCT. The results of HSCT from unrelated donors with myeloablative conditioning regimen are currently close to those obtained with transplants from HLA-identical sibling donors, the higher transplant-related mortality of the former being counterbalanced by the lower relapse rate.[19] The use of high-resolution HLA typing and donors with a negative cytomegalovirus status whenever possible have been the main contributors to this improvement in unrelated donor HSCT. Cord blood as a source of stem cells is being increasingly used in adult patients and some studies have shown results equivalent to those obtained with unrelated HSCT.[20-22] Haploidentical allogeneic HSCT often results in a very high transplant-related mortality, although recent improvements such as the use of new non-myeloablative conditioning and high-dose post-transplantation cyclophosphamide will make these transplants potentially useful for patients with very high-risk ALL who lack an unrelated donor.

Non-myeloablative HSCT could potentially be useful for elderly patients and for young and older high-risk ALL adults with significant comorbidity, for whom the outcome without allogeneic HSCT is very poor.[23-32] The antileukemic activity of HSCT with reduced intensity conditioning regimens depends mainly on the allogeneic graft-*versus*-leukemia effect. Several reduced intensity conditioning regimens for the treatment of patients with ALL have been reported by investigators. The paper by Ram *et al.* published in this issue of the journal reports a multicenter experience with allogeneic HSCT following non-myeloablative conditioning with fludarabine and 2 Gy total body irradiation for patients with high-risk ALL and identifies risk factors for disease relapse and mortality.[28] Although these regimens have substantially decreased the toxicity of HSCT and, as a consequence, have reduced the transplant-related mortality, relapse has remained a major problem. In fact, in all the published reports overall survival was significantly improved for patients who underwent HSCT early in the course of their disease. In contrast, survival was poor for patients transplanted beyond first complete remission in all the studies.

Allogeneic HSCT in patients with Philadelphia chromosome-positive (Ph^+) ALL deserves special consideration. Tyrosine kinase inhibitors in combination with chemotherapy are the standard therapy for Ph^+ ALL.[33,34] In young (transplantable) patients the most common approach is a tyrosine kinase inhibitor administered concurrently with standard induction and consolidation chemotherapy, usually followed by HSCT with a myeloablative conditioning regimen. The combination of imatinib and multiagent chemotherapy does not result in increased toxicity and does not unfavorably affect the transplant. In fact, it allows HSCT to be performed in a higher proportion of patients, with a significant percentage being negative for minimal residual disease. When imatinib-based induction-consolidation and myeloablative allogeneic HSCT are combined, promising 3-year overall survival rates can be expected, with these ranging from 55% to 65% in several studies.[35-37] Thus, allogeneic HSCT with myeloablative conditioning is generally considered as necessary for young adult patients with Ph^+ ALL patients in first complete remission, the best results being obtained when HSCT is performed while the patient is in molecular remission.

Ph^+ ALL is frequently observed in older adults and elderly patients, accounting for 40% of ALL cases. Imatinib or dasatinib combined with low or moderately intensive chemotherapy produces complete remission rates of over 90%, but many patients relapse if no additional treatment is given.[38-40] Not surprisingly, reduced intensity conditioning HSCT is beginning to gain more widespread use in fit patients. While awaiting the results of prospective studies, published retrospective reports must be interpreted with caution due to the problems of selection bias and inclusion of patients beyond first complete remission.[23-32] However, when considering this approach as used in first complete remission, some positive messages emerge. First, reduced intensity conditioning HSCT can be used with an acceptable transplant-related mortality (20% to 30%) in patients who are typically older than those suitable for a myeloablative approach. Second, no particular conditioning regimen can be considered as optimal at present. Third, graft-*versus*-host disease rates are high and have been positively associated with a better disease-related outcome in some reports. In summary, non-myeloablative allogeneic HSCT approaches appear promising, offering disease-free survival rates in Ph^+ ALL that appear to be higher than those obtained with chemotherapy and imatinib alone, and are in line with what has been achieved using myeloablative approaches.[41] A comparative study of EBMT registry reports of the outcome of myeloablative *versus* reduced intensity conditioning allogeneic HSCT in patients with ALL confirms this impression.[26]

The most striking finding of the study by Ram *et al.* was the favorable overall survival of 47% at 3 years for Ph^+ ALL patients in first complete remission given imatinib after HSCT, being 73% for those Ph^+ ALL patients in first complete remission without minimal residual disease at the time of HSCT.[28] Age did not appear to limit the feasibility of the treatment protocol. Imatinib was safe in the context of non-myeloablative allogeneic HSCT and was generally well tolerated. A very important - and as yet

unanswered - question is whether tyrosine kinase inhibitors should be administered following allogeneic HSCT and under what circumstances. The Spanish PETHEMA study reported that imatinib was poorly tolerated following myeloablative allogeneic HSCT; only 62% of patients were able to start this therapy at a median of 3.9 months after allogeneic HSCT and many patients had to discontinue the drug or take reduced doses.[42] An ongoing trial by the German GMALL group randomized post-transplant patients to receive either up-front imatinib to begin at 3 months after allogeneic HSCT whenever possible or imatinib therapy triggered by the presence of minimal residual disease.[43] This study also found that imatinib was poorly tolerated when given early after allogeneic HSCT. By contrast, most patients who started imatinib following the detection of *BCR-ABL* had a prompt suppression of *BCR-ABL* and to date there is no difference in outcome between the groups. A small, non-randomized, single center study showed a trend towards an improved outcome in patients who could be treated with imatinib in the pre-and post-transplant periods following cyclophosphamide and HSCT with myeloablative conditioning.[44] There is insufficient evidence to conclude that imatinib should be given to all patients following allogeneic HSCT. However, if it is planned to give imatinib or other tyrosine kinase inhibitors only following the detection of *BCR-ABL*, frequent quantitative *BCR-ABL* monitoring is essential. The addition of other drugs (interferon, methotrexate, mercaptopurine, among others) concurrently with tyrosine kinase inhibitors is also under investigation. The use of monoclonal antibodies, such as rituximab or the recently developed bi-specific T-cell engager blinatumomab, may be an interesting approach to be explored in future studies.[45]

Finally, in patients who fail to achieve complete remission or in those who relapse, the complete remission rate ranges from 40% to 45% and the overall survival is less than 10%.[46-48] Allogeneic HSCT is the best curative chance in patients achieving a second complete remission and should be performed immediately once the second complete remission has been achieved. However, the major problem for these patients is the limited accessibility to HSCT in *bona fide* complete remission status and in good condition. The survival rate after sibling or unrelated donor HSCT is approximately 25%, being lower for patients transplanted during subsequent complete remissions or refractory disease.

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