Current role of allogeneic stem cell transplantation in follicular lymphoma

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Follicular lymphoma (FL) is the second most common histotype of non-Hodgkin's lymphoma; its clinical course is generally indolent with patients having a median survival ranging from 4 to 8 years depending on prognostic factors.[1] The recent International Prognostic Index for FL (FLIPI) identified three risk groups with significantly different overall survival rates (from 71% to 35% at 10 years).[2]

Autologous stem cell transplantation (SCT) is considered the treatment of choice for young patients with relapsed disease. Autologous SCT has also been evaluated in prospective trials as first-line treatment for high risk patients at diagnosis, but the results are not yet conclusive. Several factors have been shown to influence the outcome after autologous SCT: disease status before transplant and the detection of residual tumor cells in the stem cell graft can influence progression-free survival.[3,4] Of importance, in the setting of autologous SCT the incidence of therapy-related myelodysplasias or leukemias can reach 15-20% at 10 years for patients conditioned with total body irradiation-containing regimens.[5]

Allogeneic SCT has usually been employed in patients with relapsed or refractory disease with the aim of providing both a tumor-free graft and the postulated graft-versus-lymphoma (GVL) effect. In support of the latter, the first retrospective studies comparing progression-free survival curves of patients undergoing autologous or allogeneic SCT showed a statistically significant difference in favor of allografted patients. Most retrospective studies on this issue showed that patients treated with allogeneic SCT were usually affected by more advanced or refractory disease, thus suggesting the existence of immune-mediated anti-tumor activity.[6-8] The additional evidence of clinical and molecular responses after the withdrawal of immunosuppressive therapy or donor lymphocyte infusions further supported the idea of an underlying GVL effect.[9,10] However, the main obstacle to a wide application of myeloablative allogeneic SCT, as a salvage strategy, was the high incidence of transplant-related mortality (TRM) that offset the benefit of the GVL effect in terms of overall survival.[11,12]

In this scenario, allogeneic SCT with reduced intensity conditioning (RIC) became an appealing option for relapsed/refractory FL patients for two main reasons: first, most of the patients affected by FL are old and heavily pre-treated; second, FL usually has an indolent course allowing the development of the GVL effect after transplantation.

In 1997, RIC allogeneic SCT in indolent lymphomas was pioneered at the MD Anderson Cancer Center where it was found that a conditioning regimen containing fludarabine and cyclophosphamide could provide a stable engraftment of donor cells with a low TRM rate.[13] The 2-year overall survival of 80% was impressive and led to further studies of RIC allogeneic SCT in these patients.[14] Subsequent studies showed that FL has the most favorable outcome among lymphoprolyferative disorders.[15-17] In a cohort of patients enrolled in a multicenter Italian trial, the 3-year overall survival of patients with FL was 69%, similar to the survival rate reported by Vigouroux *et al*. in this issue of the journal.[18]

The optimal conditioning regimen has not been defined yet: fludarabine-based chemotherapy seems suitable because it combines both immunosuppression and anti-tumor activity. One more matter of controversy is the role played by T-cell depletion procedures since graft-versus-host disease (GVHD) still remains the main cause of TRM after RIC allogeneic SCT, as shown in Vigouroux's study. Alemtuzumab has been used as an *in vivo* T-cell depleting agent in several conditioning regimens.[16,17] So far, published data have shown that patients with similarly treated low-grade non-Hodgkin's lymphoma undergoing T-cell depleted transplants have (compared to similarly treated patients with aggressive non-Hodgkin's lymphoma) a superior event-free survival and a lower relapse rate compared to patients with aggressive histologies.[15,17] Nevertheless, Morris *et al*. demonstrated that disease status [complete remission (CR) versus partial remission (PR)] was correlated with overall survival after alemtuzumab-containing regimens.[16] This observation is in contrast with the data published in this issue showing that patients in CR and PR had similar outcomes. We might conclude that T-cell depletion does not affect disease progression in FL patients in CR before transplant and that it can contribute to significant decreases in GVHD-related toxicity and mortality. In this view T-cell-depleted regimens become a suitable option for FL patients at high risk of GVHD such as those with mismatched or unrelated donors. Furthermore, the reduced incidence of GVHD could allow a more extensive use of donor lymphocyte infusions, which have been shown to induce responses and molecular remissions in about 50% of patients.[19]

Another critical issue is the use of monoclonal antibodies for anti-tumor purposes. The inclusion of anti-CD20 monoclonal antibody in autologous SCT protocols has improved both disease control before transplantation and the proportion of polymerase-chain reaction (PCR)-negative cell harvests, without affecting engraftment and TRM.[20] In RIC allo-SCT, rituximab has been used in order to combine its anti-tumor activity with a supposed anti-GVHD effect. The first observation of a reduced incidence of GVHD was provided by the MD

Anderson group in chronic lymphocytic leukemia, although the number of patients was limited and the cohort was quite heterogenous.[21] Recent data published by Khouri *et al*. in abstract form indicated that a rituximab-containing regimen before either autologous or allogeneic SCT induced comparable overall and disease-free survival rates at a median follow-up of 34 months even though the allografted patients had worse prognostic factors.[22] Although these results are intriguing, and the use of rituximab deserves to be exploited in the setting of allogeneic SCT, it seems implausible to consider RIC allogeneic SCT as an alternative approach to autologous SCT in high risk patients at diagnosis or in first relapse. We must bear in mind that a longer follow-up is required to evaluate the impact of late toxicity related to chronic GVHD, on survival. In fact, Vigouroux *et al*. reported a quite high 3-year TRM in 73 relapsed and refractory patients with a median follow-up of 37 months; notably TRM was 9% at 100 days and 32% at 1 year. In multivariate analysis chemoresistance and acute GVHD were significantly correlated with TRM. Although, these data must be considered with some caution because the study was retrospective, the TRM rate is relevant. It was correlated to disease status, although it should be pointed out that the group of chemorefractory patients, among whom TRM was highest, was transplanted more frequently with grafts from unrelated donors and after more than three lines of chemotherapy.

Based on these data, we can argue for the use of allografting earlier in the clinical course of FL patiens for several reasons. First, it is well known that chemosensitivity decreases with the number of relapses and chemorefractory patients have a poorer outcome even after an allogeneic SCT. Second, TRM has been shown to be related to patients' age and previously failed autologous SCT.[17,23] Third, although data from prospective phase III trials are lacking, the outcome of allografted patients compared favorably with that of patients undergoing autologous SCT with PCR-positive grafts, suggesting that at least in these patients RIC allogeneic SCT may be considered a valuable option.[24]

Finally, another question arises in the era of RIC: what is the current role of conventional allogeneic SCT in FL? Long-term disease-free survivors have been reported after conventional allogeneic SCT.[25] In addition, recent retrospective analyses have shown similar rates of TRM, overall survival and progression-free survival, although there was a trend towards an increased risk of recurrence after RIC allogeneic SCT.[26] Only a well-designed, phase III trial will resolve the issue of *conventional versus RIC*, but in the meanwhile we should at least decide when allogeneic SCT should be used in the history of FL patients. So far, the only consolidated indication seems to be after autologous SCT has failed.

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