Follicular Lymphoma: To Treat or Not to Treat Is No Longer the Question

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In this issue of the Journal, Al Khabori et al. (17) report the results of a meta-analysis exploring the efficacy and toxicity of HDC-ASCT compared with conventional-dose chemotherapy or chemoimmunotherapy in patients with untreated, advanced-stage follicular lymphoma. Four studies, including 941 patients with a median follow-up of 5–9 years, were identified that met the eligibility criteria; and data regarding OS, EFS, treatment-related mortality, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and secondary malignancies were abstracted (12–15). Only one of these studies included rituximab in both arms (15). There was no difference in OS between HDC-ASCT and conventionally treated patients, but EFS was statistically significantly improved following HDC-ASCT compared with conventional treatment. Treatment-related mortality and the rates of secondary solid tumor malignancies were not different between the two arms. The rate of MDS/AML was somewhat higher following HDC-ASCT compared with conventional treatment, although the difference was not statistically significant. Further attempts to improve PFS and OS have included maintenance therapy with rituximab or consolidation high-dose chemotherapy with autologous stem cell transplant (HDC-ASCT) (10–15).

In these prospective randomized controlled trials, the 4- to 7-year EFS and OS ranged from 38% to 61% and 76% to 84%, respectively, and were similar whether or not rituximab was part of the therapy in each arm. An EFS benefit despite the absence of an improvement in OS is not insignificant in a disease with a long clinical course, as time off therapy may have an important impact on personal productivity and quality of life. However, the lack of OS benefit seen following HDC-ASCT in untreated patients has often been attributed, in part, to an increased rate of secondary MDS/AML and solid tumors, which has been reported to be as high as 16%–21% at 10 years following total body irradiation–containing regimens (17,18). The lower rate of both secondary MDS/AML (4%) and solid tumors (5%) following HDC-ASCT observed in this meta-analysis may be a reflection of conditioning regimens, as two of the four studies did not include total body irradiation, or it may reflect abbreviated follow-up.

An investigation into the efficacy of HDC-ASCT in untreated follicular lymphoma is timely in light of the recent data showing the efficacy of maintenance rituximab in the ECOG1496 and PRIMA trials (10,11). The results of the studies included in this meta-analysis are similar to the 3-year PFS of 68%–75% seen in these two trials of maintenance rituximab. Given the risk of secondary MDS/AML and solid tumors following HDC-ASCT and the relatively benign toxicity profile of rituximab, many consider maintenance rituximab a preferable treatment option for patients in first remission given its comparable efficacy. However, maintenance rituximab and HDC-ASCT have not been compared directly in a randomized way to confirm their equivalence. Additionally, the long-term toxicities of maintenance rituximab have not been elucidated. An increased risk of infection because of hypogammaglobulinemia and delayed neutropenia and a small increased risk of progressive multifocal leukoencephalopathy have been documented but with short follow-up and long survivals observed in current studies, unknown late effects may appear during extended follow-up. Along similar lines, the short follow-up of rituximab maintenance does not yet allow us to know whether it will result in similar numbers of patients who are disease-free at a long interval follow-up after HDC-ASCT. Indeed, many people believe that rituximab maintenance results in disease suppression rather than disease eradication. Retrospective analysis of HDC-ASCT in untreated follicular lymphoma suggests that a PFS plateau appears at approximately 12 years, with 40% of patients being disease-free at this time (19). The benefit of such long-term disease survivorship for a subset of patients who have stopped all therapy should not be underestimated, even if OS for treatment cohorts proves similar.

These concerns aside, when HDC-ASCT has been examined in patients with relapsed chemosensitive disease, it appears to
maintain its efficacy. In the pre-rituximab era, HDC-ASCT in this setting resulted in an improved 2-year PFS of 55%–58% and a 4-year OS of 71%–77% relative to conventional chemotherapy in the prospective randomized CUP trial and was associated with a PFS plateau at 12 years of 48% in a retrospective cohort analysis (20,21). A retrospective analysis of salvage therapy at first relapse for patients on the FL2000 study suggests that the benefit of HDC-ASCT in relapsed disease persists for patients in the rituximab era, with improved 3-year OS in patients treated with transplantation compared with those who were not (92% vs 63%, respectively, \( P < .001 \)) (22). Other retrospective studies investigating salvage rituximab-containing therapy followed by HDC-ASCT in relapsed chemo-sensitive follicular lymphoma support these findings (23–25).

Given the variable natural history of this disease despite our best characterized prognostic stratification, balanced with the proven efficacy of maintenance rituximab therapy in prolonging DFS and the modest profile of known toxicities of rituximab relative to HDC-ASCT, we recommend rituximab maintenance therapy (in preference to HDC-ASCT) for patients achieving at least a partial response to first-line chemoinmunotherapy in the absence of any randomized controlled trials comparing the two. HDC-ASCT is a powerful treatment strategy for patients with follicular lymphoma, but one that does not appear to be less effective in the setting of first disease relapse than in primary treatment, and thus can be reserved for the salvage setting.

References


Notes
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