EDITORIAL

Myeloablation for Lymphoma — Question Answered?

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The value of early myeloablative treatment of aggressive lymphoma in adults has been the subject of argument for many years. Before the addition of rituximab to the four-drug regimen known as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), a meta-analysis of randomized trials showed similar survival among patients undergoing up-front autologous stem-cell transplantation and those undergoing standard chemotherapy.[1] At that time, outside clinical trials, high-dose chemotherapy with autologous stem-cell support was recommended only for patients with primary refractory or relapsed aggressive lymphoma. The widespread use of CHOP plus rituximab (R-CHOP) chemotherapy has considerably improved overall survival rates among patients with diffuse large-B-cell lymphoma; however, the survival rate among patients in an International Prognostic Index (IPI) risk category of high-intermediate or high remains about 60%. Thus, early myeloablative treatment in these patients with the highest risk of relapse is worth investigating. In this issue of the *Journal*, Stiff et al.[2] report the findings of an 8-year study of high-intermediate-risk and high-risk patients who began treatment before R-CHOP became standard induction therapy, so that fewer than half the 370 adults younger than 66 years of age eligible for inclusion in their study cohort received it.

Stiff et al. randomly assigned 253 patients who had a response to induction therapy either to continued chemotherapy (control group) or to autologous stem-cell transplantation after an additional round of induction chemotherapy plus a preparative regimen of total-body irradiation or high-dose chemotherapy (transplantation group). They found that progression-free survival in the control group was similar to that in the transplantation group for the 165 high-intermediate-risk patients; however, for the 88 high-risk patients, survival was significantly shorter in the control group. The results of their study certainly bring hope for high-risk patients, but they merit discussion as to whether they can be applied broadly, in view of what we have learned in the years since this study was initiated.

At least three other randomized trials have not shown an obvious benefit of early myeloablative treatment, but their study designs differed from that of Stiff et al. (i.e., the other studies involved only patients with diffuse large-B-cell lymphoma treated with rituximab, and regimens used to treat the chemotherapy-only groups were more dose intense).[3-5] The value of this treatment for aggressive, diffuse large-B-cell lymphoma therefore remains unresolved. It is clear only that such treatment is feasible — but at the price of greater toxicity than that associated with the current standard treatment.

Going forward, it should be possible to better select patients for enrollment in trials of early myeloablative therapy, and the selection should not be based simply on the IPI risk category. We must identify patients at highest risk for nonresponse to standard treatment (about 15% of patients) and those at highest risk for relapse (about 25% of patients), so that they can be given alternative treatments; we must also give patients without these risk factors an excellent chance of cure with easier-to-administer and less toxic chemotherapeutic agents. Several means can be envisioned; for example, choosing patients according to cell of origin of the lymphoma —

germinal center or activated B cell — because lymphomas of the activated-B-cell phenotype are associated with a poor prognosis.[6] However, this approach requires microarray-based gene-expression profiling, which is not routinely available in clinical practice, and the simplified immunohistochemistry-based algorithms that have been proposed as surrogate markers of gene expression have poor reproducibility. Another possibility is to select lymphomas characterized by deregulation of the *MYC* proto-oncogene in association with overexpression of BCL2 (so-called double-hit lymphomas), which are associated with extremely poor prognoses with standard treatment. These lymphomas can be easily identified by immunohistochemical analysis of tumor samples and may account for 20% of cases of diffuse large-B-cell lymphoma, regardless of IPI risk category.[7] Finally, it has been well documented that patients with negative results of positron-emission tomographic scanning performed after a few cycles of R-CHOP have an excellent prognosis with standard treatment.[8] Therefore, myeloablative treatment, even for patients in a high IPI risk category, may be unnecessary for the subset of patients with an excellent early response to R-CHOP treatment.

An improved understanding of the biologic complexity of diffuse large-B-cell lymphoma has revealed the diverse range of oncogenic driver mutations and signaling pathways that are essential for the growth and survival of malignant cells.[9] Many of these signaling pathways can be targeted by small-molecule inhibitors, and early reports hint at promising results. The targeting of immune checkpoints used by tumors to actively evade immune destruction could also prove useful, as has been shown in the treatment of chemoresistant solid tumors.[10] It remains to be proved that these targeting agents will challenge myeloablative therapies for the aforementioned patients with a poor prognosis, and obtaining proof will necessitate clinical trials in which patients should be encouraged to participate. Until these questions are answered, early myeloablative therapy, a 20th-century therapeutic innovation, remains an option for patients carefully selected with the use of 21st-century risk criteria.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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