Role of Interferon-Alfa in NHL: Still Controversial?

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By Bertrand Coiffier, MD, PhD [2]

Drs. Haase-Statz and Smalley review the role of interferon-alfa (Intron A, Roferon-A) in the treatment of lymphomas. As they point out in the introduction to their article, lymphoma is a very heterogeneous disease with more than 10 different entities and a large variety of clinical presentations. Currently, therefore, the treatment of lymphoma patients is not uniform, but rather, depends on the entity in question and the presence or absence of adverse prognostic parameters, such as those described in the International Prognostic Index.[1]

Is There a Standard Therapy for Any Type of Lymphoma?
Interferon has been tested in only some types of lymphomas, mostly follicular lymphoma and cutaneous T-cell lymphomas, and randomized studies have been conducted only in patients with follicular lymphoma. However, although the role of interferon has not been fully determined, neither has the type of treatment for all these entities been firmly established. Many regimens have been used during the 25 years since the possibility of curing lymphoma patients with chemotherapy was first suggested,[2] but very few of these regimens or strategies have become a standard for any lymphoma entity. A standard is defined as the reference to which any other treatment must be compared and the therapy associated with the longest survival, if not a cure, in a large proportion of patients. The only standard regimens identified to date for the treatment of lymphoma patients are: (1) CHOP regimen (cyclophosphamide, 750 mg/m²; doxorubicin, 50 mg/m²; Oncovin, 1.4 mg/m²; and prednisone, 40 mg/m²/d × 5 days) for patients with diffuse large B-cell lymphoma and a good or intermediate International Prognostic Index[3]; (2) autologous transplantation for those with relapsing aggressive lymphoma[4]; and (3) CHOP plus radiotherapy for those with localized aggressive lymphoma.[5]

Can Interferon Be Considered a Standard Therapy for Any Type of Lymphoma?
In patients with follicular lymphoma, several randomized studies have compared the addition of interferon to chemotherapy-naïve patients or have compared interferon vs no further treatment in responding patients. As Haase-Statz and Smalley point out, several, but not all, of these studies showed a benefit in terms of time to progression or overall survival among patients who received interferon. Because of the diversity of the settings in which interferon has been tested and because of the discrepant results, interferon may not be considered a standard treatment to which newer options must be compared in follicular lymphoma. The fact that the mechanism (or mechanisms) of action of interferon in lymphoma was never really understood may have contributed to the lack of definitive results. However, the combination of chemotherapy plus interferon yielded the best results ever obtained in patients with follicular lymphoma.[6-8]

Treatment with monoclonal antibodies, either conjugated or unconjugated,[9,10] has produced a response rate of over 50%, particularly in follicular lymphoma, but these agents have never been tested in any randomized study, and, thus, they certainly cannot be considered as a standard. However, the number of regimens or trials planned with monoclonal antibodies outpaces those conducted with interferon; undoubtedly, this is due to the simple mechanisms of action of these drugs and their good safety profile.

Nearly all of the studies that have shown a benefit of interferon in terms of time to progression or survival have accrued only patients with adverse prognostic parameters, have treated these patients with a doxorubicin-containing regimen or a regimen including mitoxantrone (Novantrone), and have used higher dose of interferon for a longer duration.[11] Conversely, all of the randomized studies that failed to demonstrate a benefit have accrued only follicular lymphoma patients, whatever the tumor burden and the need for treatment, and all have used lower doses of interferon for a shorter
duration. This last point may be fundamental, because we know that, in chronic myeloid leukemia, interferon has to be given for at least 3 years in order to improve survival. The median follow-up is longer in the studies that showed a benefit. Similarly, the Eastern Cooperative Oncology Group (ECOG) trial that recently reported an overall survival benefit of interferon also had a longer median follow-up.[8] Moreover, patients without adverse prognostic parameters may have a good survival no matter what treatment they receive, even if it is delayed, and their accrual into a trial may dilute the visible benefit or delay its observation for several years. Thus, interferon administered concurrently with or following chemotherapy may be recommended as the current standard for follicular lymphoma patients with a high-tumor burden. However, most patients so treated will still relapse, and other modalities must be tested in randomized studies, such as the addition of rituximab (Rituxan) or high-dose therapy with autologous transplantation.

References:


