CLINICAL TRIALS AND OBSERVATIONS

Comment on Borchmann et al, page 2121

To treat or not to treat, that is the NLPHL question

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By summarizing the Memorial Sloan Kettering Cancer Center (MSKCC) long-term treatment results for patients with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) managed with active surveillance instead of immediate intervention,¹ Borchmann et al, in this issue of Blood, prompt us to rethink the traditional treatment approach. Although therapeutic guidelines for the treatment of classic Hodgkin lymphoma (cHL) rest firmly on carefully conducted prospective clinical trials, those for NLPHL are almost entirely based on expert opinion and retrospective analyses.²,³ In the absence of randomized trial data, we can easily slip into reliance on doing again what seems to have worked before, solely because that is what we have always done. When the disease is rare, symptoms uncommon, and disease progression typically indolent and seldom fatal, it can be particularly difficult to systematically analyze alternative treatment approaches.

Borchmann et al examined the records of 163 adult patients with newly diagnosed NLPHL followed at MSKCC since 1974. By requiring modern immunophenotypic diagnostic criteria, they ensured accurate exclusion of other lymphoid cancers, such as T-cell/histiocyte-rich B-cell lymphoma and lymphocyte-rich cHL. As expected for NLPHL, most patients were men (63%), were asymptomatic (96%), and had stage I or II disease (74%), whereas extranodal and mediastinal involvement (7% and 14%, respectively) were quite uncommon. Treatment was traditional for 126 (77%) patients (radiotherapy alone, 46%; systemic therapy ± radiation, 31%), but, provocatively, 37 (23%) patients were managed with active surveillance, reserving intervention until threatening or symptomatic disease developed (see figure). These 37 patients fared just as well as those treated with active intervention. Both groups had excellent overall survival, estimated to exceed 95% at 10 years. Only 1 patient out of the entire 163 is known to have died due to progressive lymphoma.

Appropriately, because untreated patients were expected to experience first progression of disease earlier than those treated at the time of diagnosis, the investigators used the time to second progression (progression-free survival 2 [PFS2]) to compare the therapeutic approaches and found no difference (5-year PFS2 95% vs 97%, respectively). Only 10 (27%) of the active surveillance patients developed progressive disease; only 1 (3%) had a second progression, and none died. Even secondary outcomes show that the active surveillance patients did well. NLPHL carries a known risk of transformation to large B-cell lymphoma⁴ and an increased risk of other second neoplasms, presumably related to treatment.⁵ Both negative secondary outcomes occurred less frequently in the patients on active surveillance (transformation, 5.4% vs 7.9%; second cancer, 5.4% vs 7.9%, respectively). Overall, no outcome measure was worse in those on active surveillance.

Retrospective comparisons can only be suggestive, not definitive, and must be carefully examined for potential biases. It is reassuring that Borchmann and his coauthors minimized this risk. Diagnosis rested on modern immunophenotyping in 95% of the cases. The active surveillance patients did not differ from the treated patients in terms of sex distribution, extranodal disease, mediastinal involvement, presence of bulky disease (>5 cm largest mass), laboratory findings, or international prognostic score. Moderately more active surveillance patients had advanced stage disease and older age, both of which might have biased outcome against, not in favor of, that group. Documentation of relapse of NLPHL requires biopsy proof because these patients frequently develop other causes of recurrent lymphadenopathy, including progressively transformed germinal centers and follicular hyperplasia.⁷ Almost all relapses (89%) were biopsy proven. When comparing groups of patients who have been diagnosed and managed in different treatment eras, we must be concerned about the impact of stage migration or improvements in therapies or supportive care. Usefully, the authors conducted a sensitivity analysis confined to patients diagnosed since 1999 and found no change in their major observations. Overall, no obvious bias appears to be present in favor of the patients on active surveillance.

Although overall survival was not inferior in the observed patients compared with those who were treated at diagnosis, they might have experienced some other negative outcome, such as an inferior response to eventual therapy or more frequent transformation to large B-cell lymphoma. It is reassuring that treatment effectiveness was not diminished in the patients on active surveillance. Only 10 (27%) patients required treatment due to disease progression, and excellent disease control was achieved. Only 1 patient subsequently experienced a second relapse. Effective disease control was achieved without intensification of treatment (local radiation, n = 4; single agent rituximab, n = 2; or no intervention, n = 1) and only required...
chemoimmunotherapy in 3 patients. Transformation developed in the active surveillance group no more frequently than in the active intervention group. Recommending deferral of intervention when a patient is found to have a potentially fatal but straightforwardly treatable disease must be done very carefully. We must be reassured that eventual outcomes are not inferior compared with those seen after immediate intervention both in terms of survival and in the quality of that survival. Borchmann et al’s observations suggest that patients on active surveillance of asymptomatic, low tumor burden NLPHL do not suffer any disadvantage compared with those receiving intervention at diagnosis in terms of long-term disease control, responsiveness to subsequent treatment, overall survival, or freedom from transformation to large B-cell lymphoma. Indeed, almost three-fourths of their observed patients avoided the cost, inconvenience, and long-term toxicity of cancer treatment. However, such patients must be chosen very carefully. They should have no disease-related symptoms or mass lesions threatening organ compromise. They should be psychologically comfortable with treatment deferral, and they must be committed to long-term follow-up with clinicians experienced in the management of lymphoid cancer. Finally, this approach, reliance on active surveillance for NLPHL, should be regarded as provisional, and only continued if validated by other groups adopting a similar approach.

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REFERENCES

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Karschnia et al, page 2212

CAR-T–cell neurotoxicity: hope is on the horizon

Omar Ahmed | Humanigen

In this issue of Blood, Karschner et al spotlight the “Achilles heel” of chimeric antigen receptor (CAR) T-cell therapy and call for prospective clinical trials to evaluate strategies to manage and potentially prevent CAR T cell–induced neurotoxicity (NT).1

Although the emergence of CAR T-cell therapy has dramatically improved response rates for patients with relapsed or refractory B-cell hematologic malignancies, its utility is hampered by the potential for significant side effects, including severe...
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