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COMMENTS AND CONTROVERSIES

Curability of Advanced Indolent or Low-Grade Follicular Lymphomas: Time for a New Paradigm?

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As oncologists, we have for decades accepted two major paradigms that have shaped our management of non-Hodgkin lymphomas (NHLs): the current incurability of advanced indolent or low-grade NHL and the potential curability of most types of histologically aggressive NHL. Essentially all working oncologists have been raised under these precepts to the point that they have become our operational doctrine and sometimes our practicing dogma. After so many years, it is fitting to examine the basis for these two paradigms.

The first paradigm in essence tells us that advanced low-grade NHLs are incurable disorders marked by multiple relapses in which the average patient survives for 6 to 9 years. With the advent of rituximab, their average survival has been lengthened to ≥ 10 years. This paradigm is the basis for the watch-and-wait approach first promulgated by the Stanford group,[1,2] the origins of which stem from the fact that if the disease behaves indolently and is incurable, why treat it? Indeed, a few randomized trials that have attempted to look at early intervention have failed to prove superiority in survival over watch and wait.[3,4]

The second paradigm states that aggressive NHLs are potentially curable, and if a patient survives disease free beyond 2 years, he or she can be considered cured. The source of this practice standard can be traced back to a report by De Vita et al,[5] entitled "Diffuse Histiocytic Lymphoma, a Potentially Curable Disease," published in *Lancet* in 1974. It described a total of 27 patients with what used to be called diffuse histiocytic lymphoma, which is now designated diffuse large-cell lymphoma (DLCL). Of these 27 patients, 10 achieved complete remission, and of these 10, only one experienced relapse. On the basis of these nine so-called cured patients, they concluded that "survival free of disease beyond two years from the end of treatment may be considered tantamount to cure."[5(p248)]

Having summarized the basis and origins of these two paradigms, it is now appropriate to examine their legitimacy. Because these paradigms have shaped our thinking throughout decades, these issues are not of merely academic significance. If we accept that indolent NHLs are indeed incurable, then the research questions that we will ask, as well as the therapeutic goals that we will set, can be fogged by this concept of incurability. The primary goals of phase II trials can then become response rate and progression-free survival; cure can turn into a nonissue, thus leading to discovery of multiple new active agents but not to the development of an integrated curative strategy.

Before proceeding further, it becomes necessary to define what we mean by cure. The traditional unwritten definition of cure is that the failure-free survival (FFS) or tumor-free survival curve becomes flat beyond a certain point, indicating that patients who reach that time point in first remission can be considered cured. However, if we apply this cure criterion to DLCL, we find that it does not hold. In 1992, we published our experience with late relapses in DLCL and found that 6.8% of patients relapse beyond 2 years from completing therapy.[6] A similar experience was described by Coiffier et al[7] in a more recent study. Does this mean that DLCL is not a curable disorder? It seems likely that requiring an absolute plateau in the FFS curve is not reasonable. Thus, a better definition of cure is the one proposed by Frei et al,[8] when in 1971 they asserted that "for several cancers, it can be stated with confidence (probably greater than 95%) that patients who remain relapse free for a given time after treatment are cured. Thus in patients with localized Wilm's tumor treated with surgery and radiotherapy and in some instances, dactinomycin, tumor free survival beyond 2 years is associated with cure in over 95% of the instances."[8(p1828)] This definition does not require an absolute plateau in the FFS curve but rather refers to a confidence greater than 95% that the patient will not relapse after a certain time point. In other words, it refers to what we now know statistically as the hazard or risk ratio. Furthermore, this definition is not only time dependent but also tumor dependent. That is, what is true for Wilms tumor is not necessarily correct for low-grade follicular lymphoma. They are totally different and unrelated disorders.

This should lead us to ask if we have we been applying the right criteria for cure to NHL, especially to the indolent types. It is a well-known fact that indolent NHLs tend to relapse late in their clinical course, in contrast to aggressive NHLs. This should not come as a surprise, because indolent NHLs are characterized by a lower proliferative rate, which can explain why it takes longer for them to relapse, but the fact that they relapse late does not necessarily mean that they are incurable; it instead suggests that a different time point cutoff might be necessary to define their curability. If we analyze the data on indolent NHLs, applying the same cutoff criteria as we would for aggressive NHLs, we will arrive at the wrong conclusion. A review of the literature data focusing on studies in which management has not been based on the watch-and-wait approach, and which have included long-term follow-up data, can provide meaningful information regarding this issue. We will concentrate on those series in which

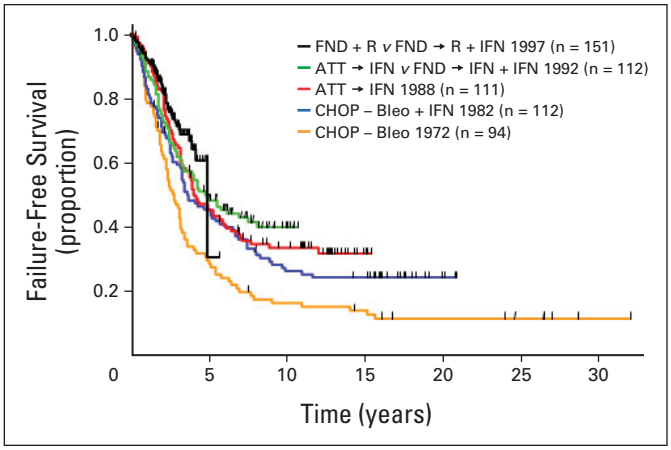

Fig 1. Failure-free survival according to treatment regimen. The overall *P* value for all curves is < .001. ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, and with mitoxantrone, vincristine, prednisone, and procarbazine, with interferon-alfa (IFN) maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin; FND, fludarabine, mitoxantrone, and dexamethasone; R, rituximab. Data adapted.[12]

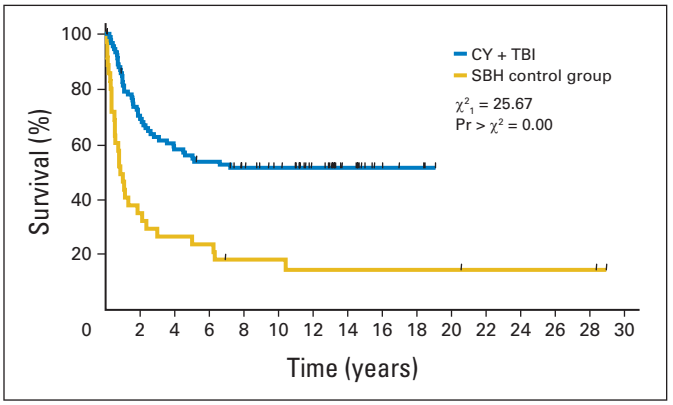

Fig 3. Freedom from progression for patients with follicular lymphoma treated with high-dose cyclophosphamide (CY) and total-body irradiation (TBI) followed by autologous stem-cell transplantation in second remission compared with results of a historical control group. SBH, St Bartholomew's Hospital. Data adapted.[14]

follow-up includes data beyond 10 years. Allogeneic bone marrow transplantation, including reduced-intensity conditioning regimens, has shown its potential for cure in follicular lymphomas. This is most likely related to the graft-versus-lymphoma immune phenomenon. That subject has been reviewed elsewhere[9-11] and will not be discussed in this commentary.

Liu et al[12] published the MD Anderson experience with first-line treatment of stage IV indolent follicular NHLs, those considered the least curable of all, which covered a 25-year period during which various research protocols were used. Figure 1 shows that the initial part of the FFS slope is rather steep, but then it changes into a more gentle slope. This change in slope occurs approximately at 8 years, particularly in the more recent studies, such as the 1988 and 1992 studies, which used more effective therapy. In those patients whose prognostic features are more favorable, such as those with Follicular Lymphoma International Prognostic Index scores < 3, the change in slope seems even more pronounced. However, we need to take into account that the median follow-up for the 1992 cohort in this study is 8.2 years, and even though most patients with long-term follow-up had restaging computed tomography scans performed every 6 to 12 months, not all of them did. The Stanford group has also published long-term follow-up data using front-line high-dose chemotherapy consolidation with autologous stem-cell transplantation in a limited number of patients who were in first complete remission.[13] Interestingly, their data also show a clear plateau in event-free survival shortly after 5 years (Fig 2). We should bear in mind, however, that the median follow-up in this report is 6.5 years, and only 24 patients remain at risk for relapse.

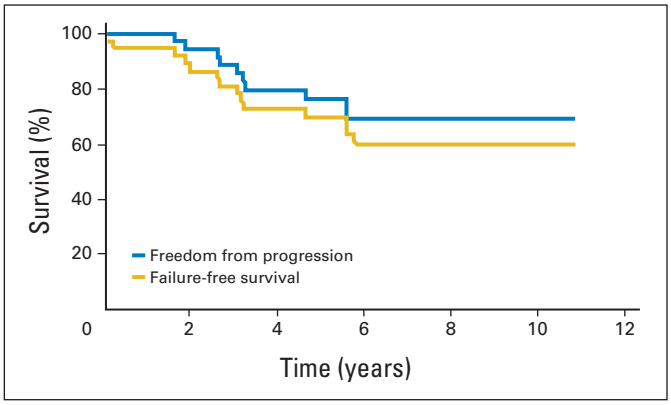

Fig 2. Freedom from progression (blue line) and failure-free survival (gold line) of patients with stage III to IV low-grade follicular lymphoma treated with high-dose chemotherapy and autologous transplantation as part of front-line therapy. Reprinted with permission.[13]

Moving on to the relapsed setting, the available literature data are also in keeping with this observation. Rohatiner et al[14] published their experience using high-dose chemotherapy with autologous stem-cell transplantation, which they contrasted with more traditional management of relapsed low-grade follicular NHL. Their follow-up is among the longest of any published series. Patients treated with high-dose chemotherapy showed a clear plateau in the FFS curve at approximately 8 years (Fig 3).

All these data tend to indicate that we have been assessing the curability of indolent NHLs using criteria that specifically apply to aggressive NHLs. In view of the different biology of these two disorders, it seems that we have been using the wrong criteria. I propose that when we evaluate the cure potential of a given treatment regimen for advanced low-grade follicular NHL, we should focus on more long-term follow-up data, particularly looking at FFS beyond 8 years. The paradigm of incurability of indolent NHLs arises from the fact that patients have either not been treated with effective chemoimmunotherapy regimens or not been observed long enough to realize that there is indeed a plateau in the FFS curve. When focusing on the curability of advanced low-grade follicular NHL, we should keep in mind that the impact of cure on survival will not be as pronounced as in DLCL, which is a more aggressive and rapidly lethal disorder.

The original paradigm applied to these disorders should evolve into a new benchmark: indolent NHL is a slow-growing disease characterized by a continuous relapse rate for the first 8 years, with a subsequent plateau in the FFS curve at 40%. This suggests that these disorders are perhaps as curable as DLCL.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Portlock C, Rosenberg S: No initial therapy for stage III and IV non-Hodgkin's lymphomas of favorable histologic types. Ann Intern Med 90:10-13, 1979

2. Brice P, Bastion Y, Lepage E, et al: Comparison in low tumor burden follicular lymphomas between an initial no treatment policy, prednimustine, or interferon alfa: A randomized study from the Groupe D'Etude des Lymphomes Folliculaires. J Clin Oncol 15:1110-1117, 1997

3. Ardeshna K, Smith P, Qian W: An Intergroup randomised trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a): A preliminary analysis. Blood 116, 2010 (abstr 6)

4. Young RC, Longo DL, Glatstein E, et al: The treatment of indolent lymphomas: Watchful waiting v aggressive combined modality treatment. Semin Hematol 25:11-16, 1988

5. DeVita VT Jr, Canellos GP, Chabner B, et al: Advanced diffuse histiocytic lymphoma, a potentially curable disease: Results with combination chemotherapy. Lancet 1:248-250, 1975

6. Cabanillas F, Velasquez WS, Hagemeister FB, et al: Clinical, biologic, and histologic features of late relapses in diffuse large cell lymphoma. Blood 79:1024-1028, 1992

7. Coiffier B, Thieblemont C, Van Den Neste E, et al: Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: A study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 116:2040-2045, 2010

8. Frei E 3rd, Gehan EA: Definition of cure for Hodgkin's disease. Cancer Res 31:1828-1833, 1971

9. Barr PM, Lazarus HM: Follicular non-Hodgkin lymphoma: Long-term results of stem-cell transplantation. Curr Opin Oncol 20:502-508, 2008

10. Khouri IF: Reduced-intensity regimens in allogeneic stem-cell transplantation for non-hodgkin lymphoma and chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 390-397, 2006

11. Thomson KJ, Morris EC, Milligan D, et al: T-cell–depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. J Clin Oncol 28:3695-3700, 2010

12. Liu Q, Fayad L, Cabanillas F, et al: Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. J Clin Oncol 24:1582-1589, 2006

13. Horning SJ, Negrin RS, Hoppe RT, et al: High-dose therapy and autologous bone marrow transplantation for follicular lymphoma in first complete or partial remission: Results of a phase II clinical trial. Blood 97:404-409, 2001

14. Rohatiner AZ, Nadler L, Davies AJ, et al: Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: Long-term follow-up. J Clin Oncol 25:2554-2559, 2007

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