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Sobering realities of surviving Hodgkin Lymphoma

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CLINICAL TRIALS

Comment on Castellino et al, page 1806

Sobering realities of surviving Hodgkin Lymphoma

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In this issue of *Blood*, Castellino and colleagues investigate morbidity and mortality in a cohort of long-term survivors of Hodgkin lymphoma (HL) from the Childhood Cancer Survivor Study. They observe frequent and serious late sequelae of therapy occurring even after 20 years of follow-up; their findings highlight the need to consider long-term implications when selecting therapeutic strategies for young patients with curable lymphomas.

The unprecedented advancement and success in the treatment of childhood and adolescent hematologic malignancies over the past decades is tempered by the fact that many survivors develop secondary life-threatening complications. The extent of the spectrum of secondary malignancies and cardiac toxicities has only recently been realized. The predominant culprit of these complications has been radiation therapy.[1-3] Long-term survivors of HL are a group of people who are particularly devastated by late effects of therapy due to a "perfect storm"-type combination of factors: (1) HL is predominantly a disease of adolescents and young adults; (2) high cure rates mean that survivors can live for many decades after therapy; and (3) nodular sclerosis, the most common subtype, preferentially afflicts young women and frequently with mediastinal involvement, which has historically been treated with radiation therapy. Therefore, this interaction of disease characteristics with historical management strategies has led to the extremely high rates of solid tumors—particularly breast cancer—and ischemic heart disease in this population of survivors.

Castellino and colleagues herein report on morbidity and mortality in 2742 survivors of HL from the Childhood Cancer Survivor Study.[4] Although some other groups have specifically investigated HL survivorship, this is the largest available cohort and, thus, is an important and invaluable resource for studying and realizing the late effects of therapy in this population. In addition, this cohort is mature in that all patients were treated before 1986. Despite excellent survival rates in the early years after therapy, the authors observe that beyond 10 years, there is significant excess mortality from secondary malignancies and cardiovascular disease with no plateau despite longer follow-up. Furthermore, at 20 years after initial treatment for HL, the excess death risk from cardiovascular disease rivals that from solid tumors.

As discussed and highlighted by the authors, although women with breast cancer do not appear to have an excess risk of mortality, the scale of breast cancer morbidity in these survivors is remarkable (cumulative incidence at 30 years after diagnosis is 18.3%) and should not be underemphasized. In fact, breast cancer, cardiovascular disease, and thyroid cancer were the principal morbidities identified in this report and as 94% of patients received supra-diaphragmatic radiation, it is probable that radiation therapy was causative in most cases. Although Castellino and colleagues identify a radiation dose > 30 Gy as a risk factor for overall mortality, it is important to realize that lower doses of radiation were linked to morbidity and are not benign in terms of long-term sequelae. In addition, a recent survivorship report evaluated the long-term outcome of pediatric patients with HL who received low-dose radiation and demonstrated that secondary tumors occurred with similar frequency and latency as in studies where HL patients received high-dose radiation.[5]

Although we have made significant advances in the treatment of HL over the past 20 years and have moved on from using high-dose extended-field radiation, much progress remains to be made. The lessons of this report are clear—it is critical to consider the long-term toxicity of treatment when selecting therapy for newly diagnosed patients. Moreover, it is important to continue to develop and evaluate novel targeted therapies that maintain high cure rates while obviating the need for combination radiation and chemotherapy that may cause these unacceptable long-term effects. Immune-based therapies using monoclonal antibodies and tumor-specific T cells are examples of targeted approaches already being evaluated in clinical trials for patients with HL, which offer the promise of tumor-specific killing while sparing bystander organs.[6,7] Hence, a vision for the future of HL therapy could be that targeted therapies are combined and used upfront with carefully selected regimens so that sobering reports such as this one will be tales of the past.

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Comment on Jabbour et al, page 1822

Predicting response in CML

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Predicting response in chronic myeloid leukemia (CML) patients who are offered tyrosine kinase inhibitor (TKI) second-line therapy is vitally important. For younger patients, allogeneic transplantation is still a therapeutic option Thus, physicians need new models to predict the outcome of their patients.

In this issue of *Blood*, Jabbour et al propose a simple scoring system easily applicable in the clinic.[1] The analysis was based on a group of 123 patients with chronic-phase CML who failed imatinib therapy and who were switched to dasatinib or nilotinib. Their model identified 2 variables that were significantly associated with event-free survival. In a multivariate analysis, the lack of any cytogenetic response to previous imatinib therapy and Eastern Cooperative Oncology Group performance status of 1 or more at the start of second-generation TKI therapy were identified as independent adverse factors associated with poor event-free survival. The model thus subdivides patients into 3 categories: good risk (0 factor), intermediate risk (1 factor), and poor risk (factors) associated with 2-year, event-free survival of 78%, 49%, and 20%. Of note, the 2-year overall survival was also significantly associated with the risk categories. Moreover, Jabbour et al performed additional multivariate analyses using a 12-month landmark. They stated that the lack of major cytogenetic response at 12 months after the onset of the second TKI is an adverse independent factor for event-free survival. Although the definition of "event"-free survival has to be carefully considered, the general finding is in accordance with the definition of the response to the second-generation TKIs dasatinib and nilotinib as second-line therapy of patients with imatinib-resistant CML–chronic phase (CML-CP) which was proposed by the new European Leukemia Net recommendation.[2]

Less-than-major molecular response at 12 months was considered (at least provisionally) a suboptimal response and less-than-partial cytogenetic response as failure. Using this approach, the authors confirmed that a performance status of 1 or more is a poor prognosis factor for the survival. However, other clinical and/or biological parameters could still be of interest. First, prognostic scores, such as the Sokal score, which relates to the pathophysiology of the disease at diagnosis, may still be of some value even later on the course of their disease. For example, intermediate- and high-risk patients are at higher risk of molecular relapse after cessation of imatinib.[3] The Hammersmith group recently proposed a score including 3 factors associated with the achievement of responses after second TKI therapy: that is, the best cytogenetic response on imatinib, the occurrence of neutropenia, and the Sokal score at diagnosis.[4] Second, mechanisms of resistance to imatinib are not unique. Consequently, some parameters may be predictive of resistance to second generation of TKIs in specific subgroups of patients and not in others.

Early retrospective data showed a high incidence of imatinib noncompliance in CML patients which could lead to undesired clinical outcomes. The ADAGIO (adherence assessment with gleevec: indicators and outcomes) study[5] evaluated adherence to imatinib in 169 CML patients and found that during the initial 90-day period of imatinib treatment, one-third of patients were considered to be non adherent. Only 14.2% of patients were compliant with all prescribed doses of imatinib. Thus, nonadherences could be an issue with second TKI. Chronic adverse events of even grade 1 or 2 must also to be considered, essentially because these side effects may explain non adherence to treatment. In these 2 situations, predictors of response to second TKI may be somewhat different from those of patients who received imatinib using prescribed dosages.

Point mutations in the BCR-ABL kinase domain, which are frequently involved in TKI resistance, may be an important determinant in clinical decisions. Several recent reports suggested that routine mutation screening could provide valuable information regarding the selection of the optimal TKI and could also identify patients at high risk of disease progression.[6] Thus, such biologic abnormalities should be considered in parallel with the new score.

Clonal cytogenetic abnormalities and elevation in BCR-ABL transcript levels could be investigated for further models because some studies showed that elevations in BCR-ABL transcript levels might indicate a potential for BCR-ABL gene mutations and emergence of TKI resistance.[7]

Identification of biomarkers to predict resistance to TKIs is currently in progress. For example, gene array data on blast cells or the CD34-enriched cell population from chronic phase have provided interesting information.[8,9] Although a pretreatment molecular signature has been identified for imatinib-treated patients, such a signature could serve as a molecular biomarker for stratifying patients treated with any other TKI into risk group. Moreover, recent data provided evidence that BCR-ABL mutation leads to kinase activation, suggesting that this mechanism may extend beyond activation loop mutations.[10] Finally, it would be helpful if several international CML groups could select a large independent cohort of patients to validate these new scoring systems and select the one that would produce the most accurate information for the monitoring of CML patients.

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