Diffuse large B-cell lymphoma of the breast: a distinct entity?

The management of squamous cell carcinoma arising in the lung is markedly different than squamous cell carcinoma of the skin, cervix, or larynx. Likewise, the optimal management of diffuse large B-cell lymphoma sometimes varies by the primary site of involvement. Knowledge of the unique clinical behavior of lymphoma arising in certain extranodal sites is necessary. Examples of this include the requirement for specialized evaluation and treatment of diffuse large B-cell lymphoma arising in the eye, brain, and testicle. It has also been questioned whether primary diffuse large B-cell lymphoma of the breast is another entity that requires management that is different than localized diffuse large B-cell lymphoma that occurs in nodal or other extranodal locations.

The report by Ryan et al. [1] from the International Extranodal Lymphoma Study Group (IELSG) in this issue of the journal attempts to answer this question. This analysis adds to the valuable information provided by other studies from the IELSG that have examined non-Hodgkin’s lymphomas occurring in other sites [2–4]. Large multi-institutional reviews of this type are designed to eliminate some of the reporting bias in other smaller series of primary breast lymphoma. Nevertheless, patients in this cohort were diagnosed over a 23-year period beginning in 1980 and this analysis is also subject to problems associated with a lack of central pathology review and standardized management. In addition, patients were treated in the ‘Pre-PET’ (positron emission tomography) and ‘Pre-rituximab’ era. Despite these limitations, this is the largest series of primary diffuse large B-cell lymphoma of the breast that has been reported and the observations from this study will assist in the management of these patients.

The first question addressed is whether the clinical behavior of primary diffuse large B-cell lymphoma of the breast is different than diffuse large B-cell lymphoma arising at other sites. Although the final answer is not known, the propensity for disease to occur and recur in the opposite breast and other extranodal sites indicates that primary diffuse large B-cell lymphoma of the breast has distinct clinicopathological characteristics. As the authors note, a similar situation occurs in testicular lymphoma. Mechanisms of lymphocyte homing to tissues such as skin and gut are well described [5]. Future studies will be required to determine whether specific adhesion molecules, chemokine receptors, or chemokines are involved in the behavior of diffuse large B-cell lymphoma in the breast. The authors also address the issue of central nervous system (CNS) relapse, which has been reported to occur at increased frequency in patients with diffuse large B-cell lymphoma of the breast. The presence of extranodal disease is a risk factor for CNS relapse in other patients with diffuse large B-cell lymphoma, and it is not surprising that this risk might also be higher in patients with lymphoma occurring in the breast [6–8]. Relapse in the CNS was noted in only 5% of patients and no CNS relapses were noted in the small fraction of patients who received prophylactic intrathecal chemotherapy. A recent series of breast lymphoma from Stanford identified a single parenchymal brain recurrence among 37 patients with breast lymphoma identified in a retrospective analysis [9]. It was concluded that routine intrathecal prophylaxis was not warranted. At our institution, no CNS relapses have been noted in 11 patients with primary breast lymphoma diagnosed from 1984 to 2004 M. L. Villanueva (unpublished data). The authors of the IELSG study conclude that routine CNS prophylaxis is not required for patients with primary diffuse large B-cell lymphoma of the breast. Nevertheless, additional study is required to determine whether some patients may benefit from this approach, such as those with other risk factors for CNS recurrence [10].

It is not surprising that outcome was related to the International Prognostic Index and that survival was improved in patients who received anthracycline-based therapy. Survival was also longer in patients who received radiation therapy in addition to chemotherapy. The survival of patients treated in this manner was similar to that of other patients with limited-stage diffuse large B-cell lymphoma from other series [11], and comparable to gastric diffuse large B-cell lymphoma, the most common extranodal site of disease [12]. It is still unknown whether patients can be treated with an abbreviated course of therapy, or whether a full 6–8 cycles are required. It is also unknown whether radiation is required for all patients. It is possible that PET imaging might help with these decisions. As noted, the impact of adding rituximab to chemotherapy has not been studied for primary breast lymphoma, although the combination of anthracycline-based chemotherapy with rituximab should be considered standard. It appears that the addition of rituximab improves the outcome of all clinical and molecular subtypes of CD20-positive diffuse large B-cell lymphoma [13–15].

Although the most common lymphoma involving the breast is diffuse large B-cell lymphoma, other histologic subtypes including marginal zone lymphoma, follicular lymphoma, mantle cell lymphoma, and Burkitt lymphoma have been described [9]. The management of these lymphomas will usually differ from the management of diffuse large B-cell lymphoma. Although we do not have all the answers, the article...
by Ryan et al. [1] provides treatment guidance for patients with this rare lymphoma presentation and it provides a framework for future studies.

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