Predictors of central nervous system involvement in diffuse large B-cell lymphoma: a divining rod is wanted

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In the last decades, our knowledge on the management of diffuse large B-cell lymphomas (DLBCL) has expanded remarkably. Nevertheless, some important questions, like the impact of dose dense chemotherapy, the role of consolidation radiotherapy, the selection of the best candidates for new target drugs, the optimal management for patients with high International Prognostic Index (IPI) scores and the prevention of central nervous system (CNS) relapse, remain unanswered. CNS dissemination is a rare but fatal event in DLBCL. It is more common in highly aggressive lymphomas, such as Burkitt's and lymphoblastic lymphomas, but DLBCL patients with intermediate-high IPI and advanced disease and/or affected by some forms of extranodal lymphomas are usually retained at high risk of CNS dissemination. However, predicting variables and scores have low sensitivity, identifying only ≈25% of high-risk patients[1,2]. In these studies, CNS prophylaxis is variably indicated, following unclear definition of high-risk patients and using often ineffective strategies. Moreover, studies are invariably undersized since the CNS relapse rate in DLBCL is near 5-6%; this small number of events would require thousands of cases to draw reliable conclusions, especially to accurately assess the risk of CNS in DLBCL arising primarily in different extranodal sites. Last but not least, available predictive scores were established in the pre-rituximab era, which is a relevant interpretation bias as this antibody has changed the natural history of DLBCL and seems to be associated with a reduction of CNS recurrence risk[3,4].

In this issue of the Revista Brasileira de Hematologia e Hemoterapia, da Rocha et al. report their efforts to identify reliable variables predicting CNS recurrence in a retrospective series of 133 patients with DLBCL diagnosed between 2001 and 2008[5]. Accordingly, male gender, previous use of intrathecal chemotherapy and refractory response to the initial treatment were independent risk factors for CNS infiltration. The authors should be commended for the effort to analyze all this bulk of data to identify risk predictors. The intrinsic value of this study is evident if we compare these observations with prior studies in this field. Patients' characteristics, CNS relapse rates, and survival figures are very similar to those previously reported. At the same time, this study exhibits most of the major limitations of the previous articles, which are directly related to the small numbers of events (CNS relapses) and investigated patients. In particular, denominators of some subgroups are really small; for instance, only five patients had involvement of extranodal sites associated with increased CNS risk, such as paranasal sinus and the testes, and only nine patients had multiple extranodal involvement, a well-known risk factor. Conclusions on a series with these figures should be taken with caution. Actually, general readers may wrongly understand that, for example, DLBCL patients with paranasal sinus involvement should not be considered as at high risk of CNS dissemination and, thus, should be managed without CNS prophylaxis. Another example of interpretation bias in this study is the inclusion of refractory response to the initial treatment and intrathecal chemotherapy in the multivariate analysis. Actually, treating physicians would wish to know the risk factors at baseline assessment and not after treatment failure. This is an important issue considering that CNS dissemination is an early event in DLBCL patients, and that prophylaxis, if indicated, should be delivered as soon as possible; thus, to define a due patient as having increased risk of CNS involvement after the lymphoma progresses has a limited informative value. In addition, this choice may have clouded the predictive value of advanced stage, high serum lactate dehydrogenase level and a high IPI score, all variables strongly related to refractory disease and to increased risk of CNS dissemination in prior studies. Likewise, as recognized by the authors themselves, intrathecal chemotherapy was used mostly in patients judged as having a high-risk lymphoma, with a consequent selection bias resulting also from the fact that it is insufficient as a prophylactic strategy[3,4].

It is frustrating to have to discuss again about predictors of CNS dissemination in the most common lymphoma category. Reported studies exhibit invalidating methodological

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pitfalls that seem to be unsolvable. Undersized investigated series with evident intrinsic, selection biases are opposed to a small number of events. The key question is still what should we do to improve the sensitivity of prognostic variables and scores? As proposed by da Rocha et al.[5], this must be done through the study of grouped risk factors and a more sensitive assessment of hidden disease in the CNS. To reduce study populations to a specific lymphoma category, or to a single extranodal lymphoma, treated with a uniform strategy, excluding any form of CNS prophylaxis, and prospective data collection may be suitable strategies to improve the reliability of conclusions. In addition, we have to renounce to the idea of identifying high-risk patients by using only clinical parameters. The investigation of molecular markers related to CNS dissemination is an advisable approach. Future studies should analyze the predictive value of molecules involved in lymphocyte activation, adhesion and trafficking towards the CNS. Some molecules with these capabilities have already been reported, but the establishment of many others will require important investments and collaborative efforts to perform morphological and molecular studies associated with functional *in vitro* and *in vivo* tests. Only in this way, we will assemble the divining rod that will allow us to perceive a drop of water in the arid desert of DLBCL.

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