expansion and Treg stability and function. Because IRX4204 is in clinical trials for cancer treatment, repurposing to attenuate acute GVHD in allo-HCT is warranted and feasible.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

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CNS relapse in DLBCL: a calculable risk?

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In this issue of *Blood*, Ollila et al[1] address a challenging problem: Can the risk for central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) be predicted better on a molecular basis? The authors found that most tumors with CNS recurrence are well defined molecularly and fall into 2 categories. The most frequent is the hc-MCD subtype, based on MYD88L265P and CD79B mutations, which molecularly resembles primary central nervous system lymphoma (PCNSL). Its association with some extranodal disease sites suggests that the molecular underpinning is the major factor driving the increased risk of CNS invasion. The second subgroup encompasses high-grade tumors characterized by double-hit biology or TP53 mutations, which frequently exhibit high-grade B-cell lymphoma signature on gene expression profiling.

To search for a molecular subtype that could be used to identify patients at high risk for CNS recurrence of DLBCL, the authors used a clinically validated 592-gene assay. DLBCL can be clustered into distinct molecular subgroups.[2,3] Further analyses have also revealed different molecular signatures for both extranodal DLBCL and PCNSL.[4,5] Currently, the decision on CNS prophylaxis relies on clinical risk stratification. Nevertheless, many patients have a CNS relapse despite being considered low risk for a CNS recurrence by these criteria at initial diagnosis. Thus, extending this risk stratification to include additional molecular information, as Ollila et al explored, is an interesting approach and of great clinical importance. Secondary involvement of the CNS is a dreaded complication of DLBCL and is associated with an extremely poor prognosis. In the MiNT study, the median time to secondary CNS involvement was 7.2 months; with a median survival of only 3.5 months after development of CNS involvement.[6] The so-called CNS International Prognostic Index (CNS-IPI) is a useful tool to roughly estimate the risk of CNS involvement during the course of disease.[7] Because kidney and adrenal gland involvement is significantly associated with CNS recurrence, the CNS-IPI includes these parameters in addition to the classic IPI, which is validated for systemic DLBCL. The CNS-IPI identifies 3 risk groups: low, intermediate, and high; the latter accounts for 12% of all patients analyzed in this cohort. Patients assigned to the high-risk group carry a 10.2% risk of subsequent CNS-involvement. Conversely, only about half of patients with secondary CNS involvement during the disease course, were considered CNS-IPI high risk at their initial systemic-lymphoma diagnosis. Gene expression analyses of 1418 patients of the GOYA trial showed that activated B-cell–like and unclassified cell-of-origin (COO) subtypes were associated with CNS relapse in DLBCL, irrespective of a high CNS-IPI score.[8] Currently, the addition of intravenous high-dose methotrexate (MTX) or intrathecal MTX to standard chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is recommended for patients at a high risk for secondary CNS involvement. However, this approach's effectiveness has only been evaluated in a single retrospective trial.[9] The challenge we face is to develop a prognostic score that reliably predicts CNS recurrence and that better targets the use of CNS prophylaxis. To address this challenge, the authors recommend a validated 592-gene assay, used on formalin-fixed, paraffin-embedded material, to identify a subgroup at significantly higher risk for secondary CNS involvement. In my opinion, the authors describe a promising approach that succeeds via next-generation sequencing (NGS). The LymGen classifier recently published by Wright et al[10] divides DLBCL into different clusters. On the basis of the subgroups described therein, the authors ultimately constructed a simplified hierarchical classifier (hc) with 3 subtypes:

hc-MCD, hc-P53, and hc-germinal-center B-cell-like. Of these 3 distinct subtypes, hc-MCD was detected in nearly half of CNS recurrences. Morever, hc-MCD is available in some of the commercially available NGS tests routinely used in clinical practice, which makes it an attractive marker.

This work raises the fundamental question of whether the risk of extranodal manifestation and especially of CNS manifestation can be better defined by applying molecular criteria rather than clinical and anatomical characteristics. These encouraging findings still need to be regarded with reservation because of the low case numbers. Despite this concern, this work could ultimately be highly relevant in a practical sense. CNS prophylaxis via high-dose MTX or intrathecal MTX, a complex and stressful undertaking for patients and practitioners, can be applied more selectively and, ultimately, more effectively. Combining CNS-IPI, COO, and perhaps this trial's results could potentially enhance our ability to predict CNS relapse and identify a subgroup of patients at high risk for developing CNS relapse. To test this hypothesis, a large prospective clinical study, accompanied by a corresponding translational program, would need to be conducted.

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