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LYMPHOID NEOPLASIA

Comment on Kim et al, page 2548

Is the CNS-PINK the new CNS risk model in ENKTL?

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In this issue of *Blood*, Kim and colleagues sought to develop a much needed clinical predictor of central nervous system (CNS) relapse in extranodal natural killer (NK)/T-cell lymphoma (ENKTL).[1] Because CNS relapse in lymphomas is an uncommon but often devastating event, recent efforts have focused on the identification of high-risk patients to consider for CNS diagnostic tests and upfront treatment modifications.

CNS relapse occurs almost exclusively in aggressive lymphomas, including Burkitt lymphoma, which is associated with a very high risk. In addition, "double-hit" high-grade B-cell lymphomas, in particular, those that harbor *MYC/BCL2* (± *BCL6*) rearrangements and those with high-grade morphology, are also associated with an elevated CNS relapse risk. Apart from these specific subtypes, additional risk factors associated with CNS relapse have been most extensively explored in diffuse large B-cell lymphoma (DLBCL). Advanced stage disease, extensive extranodal (EN) involvement, and specific anatomic localizations, such as testicular involvement, have been consistently associated with CNS relapse. In the largest study to date, Schmitz et al developed and validated the "CNS-IPI" (international prognostic index) risk model in DLBCL, which incorporates the standard IPI factors, as well as kidney or adrenal gland involvement, to stratify patients into 3 risk groups: low risk (0 to 1 factor); intermediate risk (2 to 3 factors), and high risk (≥4 factors), with the latter having a risk of CNS recurrence of ≥10%.[2] Although the CNS-IPI is a robust model, some factors are not captured. Furthermore, more objective molecular markers, such as cell of origin and dual expresser phenotype, have refined the risk model; however, they may not be readily available in routine clinical practice.[3,4]

Few studies have addressed the incidence and outcome of CNS relapse in peripheral T-cell lymphomas, most combining diverse subtypes. Frequencies range between 2.1% and 8.8%, with higher rates observed in those with >1 EN sites.[5-7] A previous study by Kim et al described an overall frequency of 5.8% in ENKTL,[8] but to date, large-scale studies have been lacking.

In the current study, 399 patients with newly diagnosed ENKTL were assembled and served as the "training set." All cases were Epstein-Barr virus positive by local review, and treatment integrated a non–anthracycline-based regimen.[1] A separate "validation" cohort consisted of 253 ENKTL Japanese patients.[9]

The overall risk of CNS relapse was ~7% across both cohorts, and the survival post-CNS relapse was only ~3 months. The median time to CNS relapse was 10.1 months, highlighting that occult disease was likely present at diagnosis.

Factors representing high tumor burden were associated with CNS relapse, most of which are captured by the prognostic index of natural killer (PINK) score (age >60, Ann Arbor stage 3/4, distant lymph node involvement, nonnasal type). Multivariate analysis revealed that EN ≥ 2 (hazard ratio [HR] 4.628 [1.974 to 10.852], $P < .0001$) and intermediate/high PINK score (1/2 or more factors) (HR = 2.677 [0.936 to 7.652], $P = .066$) were associated with CNS relapse, although the latter did not reach statistical significance. Applying this, those with 0 or 1 factors (76.2% of all patients) were considered low risk and have a 2-year CNS risk of 4.1% and those with 2 factors (23.8%) were high risk with a 2-year CNS risk of 22.8%. This "CNS-PINK" model also stratified patients in the validation cohort (low-risk 2-year CNS 4.5%; high-risk 2-year CNS 13.9%, $P = .038$).

The most robust factor is the number of EN sites, likely also due to the weaker impact of some of the PINK components, including age. Beyond the CNS-IPI in DLBCL, EN > 2 was noted to have prognostic significance.[10] The current study did not evaluate different cutoffs for number of EN sites, and conceivably EN ≥ 3 may provide improved specificity. In the development of the CNS-IPI, specific EN sites were evaluated, and kidney/adrenal emerged as a powerful independent factor. A future larger study in ENKTL could similarly evaluate the impact of specific type and number of EN sites.

The authors also explored whether the integration of "intermediate dose" (≥2 g/m^2) intermediate-dose methotrexate (IDMTX) reduced the risk of CNS relapse. Appropriately, they focused on the impact in the high-risk group because there may have been inherent selection bias in the use of a treatment regimen. Interestingly,

those patients in the high-risk group who received ID-MTX had a lower risk of CNS relapse ($P = .03$), but there was no difference in the low-risk group. These findings were not replicated in the validation cohort; however, the overall CNS risk was lower. Thus, power was limited to detect a small difference. Furthermore, although the optimal prophylaxis dose is unknown, it is widely accepted that a minimum dose of 3 g/m^2 is needed to achieve adequate CSF levels and is considered "high dose." There is very limited evidence that this strategy is protective in other aggressive lymphomas, including DLBCL, and a larger study specifically in high-risk patients is awaited. Complicating the analysis is the inclusion of other cytotoxic agents that can also penetrate the CNS, such as ifosfamide and etoposide, making it difficult to determine the independent effect of ID-MTX. Taken together, the current study suggests that there may be a protective effect, but larger confirmatory studies are needed. As gemcitabine-based combinations are also used but lack CNS penetrant agents, there may be an opportunity to compare the risk of CNS relapse in larger cohorts treated with these regimens.

In summary, the CNS-PINK is the first step forward to a CNS risk model in ENKTL. Further validation studies and investigation of the protective effect of MTX and other CNS penetrant agents are eagerly awaited.

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PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Comment on Dabek et al, page 2574

Wnt to the rescue! A new role in granulopoiesis

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In this issue of *Blood*, Danek et al reveal a previously unknown role for the canonical Wnt signaling pathway in the regulation of granulocyte production in both steady-state and during emergency granulopoiesis.[1]

Neutrophilic granulocytes serve as a first line of defense against pathogens. Adequate numbers are critical for survival, as demonstrated by the severe and often fatal infection in patients with congenital or iatrogenic neutropenia.[2] Given their short half-life, neutrophils need to be constantly replenished to maintain steady-state neutrophil counts. Moreover, upon severe systemic infection, when neutrophils are being consumed, granulopoietic output is massively enhanced to meet the high demand. Consequently, an intricate and redundant regulatory network consisting of cytokines/growth factors, their cognate receptors, and downstream transcriptional programs has evolved to sustain appropriate, demand-adapted granulocyte numbers.[3]

Danek et al now identify the canonical Wnt signaling pathway as yet another important regulator of granulopoiesis. The canonical Wnt pathway signals via various secreted Wnt ligands that bind to the Frizzled receptors, leading to stabilization and accumulation of β-catenin and its translocation to the nucleus, where it ultimately acts as transcriptional coactivator by interacting with members of the T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) family of transcription factors such as TCF4.[4] The role of the canonical Wnt signaling pathway in hematopoietic stem and progenitor cell (HSPC) biology has been extensively studied, yielding conflicting results.[5] Stimulatory, inhibitory or even neutral effects have been described, and these discrepancies are likely due to use of different experimental model systems that interfere with canonical Wnt signaling at various levels of the pathway and to varying degrees.[6]

In an attempt to overcome these likely limitations, Danek et al use a novel mouse model that employs a dominant-negative form of TCF4 (dnTCF4) whereby transcriptional activity of β-catenin-TCF4 in HSPCs is impaired, whereas the non-transcriptional activities of β-catenin as well as noncanonical Wnt signaling are left intact. The authors show that mice expressing dnTCF4 have reduced peripheral blood and bone marrow (BM) neutrophils and increased immunophenotypically defined HSPC subsets with the exception of long-term hematopoietic stem cells HSCs (LT-HSCs). This accumulation of HSPCs is due to impaired