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CLINICAL TRIALS AND OBSERVATIONS

Comment on Kim et al, page 2754

Checkpoint inhibition in ENKTL: Kno_le_ge G_ps

Radowan Elnair and Matthew A. Lunning | University of Nebraska Medical Center

In this issue of *Blood*, Kim et al report the results of a phase 2 trial of avelumab, a programmed death-ligand 1 (PD-L1) inhibitor, in the treatment of relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma (ENKTL), adding to our understanding of the activity of such agents in uncommon subtypes of non-Hodgkin lymphoma (NHL).[1] The use of immunotherapy in ENKTL has attracted attention, given the limited salvage options in the relapsed or refractory setting and an overall dismal outcome.

Previous reports have demonstrated single-agent activity of the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab in ENKTL, with an overall response rate as high as 43%.[2,3] Our understanding of the role of immunotherapy in NHL is evolving, but knowledge gaps exist about the ideal candidates for such therapy, predictors of response, and the best response assessment modalities. The study by Kim et al has closed several of these gaps, but many remain.

In their previous work on immune subtyping of ENKTL,[4] the authors demonstrated a correlation between outcomes with pembrolizumab in the treatment of relapsed or refractory ENKTL and the extent of PD-L1 expression as described by a PD-L1 score. The score represents a percentage of total PD-L1–positive cells, including tumor-associated macrophages among tumor cells, and a score of >10 was considered high.

The authors explored whether targeting PD-L1 may be a better therapeutic approach for ENKTL. The study recruited patients previously treated with at least 1 line of therapy, but the majority of patients (67%) had received 2 lines of therapy or more, which is reflective of a population of patients with an aggressive disease biology. The overall response rate was 38%, with a complete response (CR) rate of 24%. A high PD-L1 expression status per the score used was significantly more common among responders and was seen in all patients achieving a CR. Among those achieving a CR, the responses were durable (>10 months).

An intriguing finding was that despite a short median progression-free survival (2.7 months), at a median follow up of 15.7 months, the median overall survival was not reached. This is a notable finding in a disease with such a poor prognosis and a heavily pretreated population, which suggests that PD-L1 blockade may have a priming or sensitizing effect for subsequent lines of therapy. It also brings into question whether some of those patients were inadvertently designated as having progression events according to the available criteria, whereas in reality, some of those events may have represented pseudoprogression.

In addition, using only a high PD-L1 expression status, per the score used, seems to fill a gap as a potential predictor of deriving benefit from such therapy. The performance of the score in comparison with the conventional use of PD-L1 immunohistochemical (IHC) staining of tumor cells is yet to be addressed, and proof of reproducibility would be encouraging for broader application of the score.

There were no grade 4 adverse events, but 1 patient in this report showed signs of disease progression immediately after the first dose of avelumab, a phenomenon reported with PD-1/PD-L1 inhibitors in different malignancies, perhaps most extensively studied in the population of patients with non–small-cell lung cancer.[5]

In a mouse model of T-cell lymphoma, the absence of PD-1 in peripheral T cells triggered the development of an aggressive lymphoma that exhibited the same features as a human T cell lymphoma.[6] Clinically, this phenomenon has also been reported in the first 3 patients treated on a phase 2 study of nivolumab therapy (a PD-1 inhibitor) in patients with adult T-cell lymphoma/leukemia (ATLL), resulting in discontinuation of the trial. All those patients progressed rapidly after a single infusion.[7] The subsequent work by Rauch et al[8] investigating those 3 patients suggested a possible tumor-suppressive role for PD-1 in patients with ATLL, and that the aggressive vs indolent behavior of ATLL may be a reflection of the immune response of those subsets of patients rather than an intrinsic feature of the ATLL cells. Most cases of ENKTL are derived from NK cells but some cases may have a clonal T-cell origin,[9] and the impact of the cells of origin and the tumor immune microenvironment on the type of response to immunotherapy is another gap that needs to be filled.

The phenomena of pseudoprogression and hyperprogression continue to complicate treatment with PD-1 and PD-L1 inhibitors, which highlights the need for reassessment of response assessment criteria to be explored in clinical trials of immunotherapy in ENKTL and other subtypes of NHL. An insightful precedent was the development of the iRECIST criteria for

use in oncology clinical trials of immunotherapy to avoid stopping immunotherapy too early in those patients deriving benefit despite imaging that generates concern for progression. Unfortunately, as planned, this study did not meet its planned number of CRs per a Simon 2-stage design, which leaves another gap on whether an enriched population with high PD-L1 expression per the used score would have achieved similar responses and durability. The recurring reports of hyperprogression in the studies of the uncommon forms of NHL with relatively small sample size calls for further investigation into underlying mechanisms of such responses. The risk-benefit balance is critical in this scenario and would have an impact on timing for using such therapy (earlier vs later lines of therapy) because only a small percentage of patients are expected to be salvageable if they develop hyperprogression with these agents.

In summary, this report adds to the body of evidence for the activity of checkpoint (PD-1 and now PD-L1) inhibitors in ENKTL and serves as a useful reminder of the spectrum of responses of such agents, reconsideration of clinical trial design with particular agents, and the continued pursuit of filling our knowledge gaps in uncommon diseases.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Weisel et al, page 2774

Novel players: tissue-resident memory B cells

Natalia Savelyeva[1] and Christian H. Ottensmeier[2] | [1]University of Southampton; [2]University of Liverpool

The paper by Weisel and colleagues in this issue of *Blood* identifies a novel subset of human memory B cells (MBCs), tissue-resident memory B (BRM) cells, with a unique gene expression signature and a function distinct from conventional CD27$^+$ MBCs.[1]

The conventional approach to understanding the biology of the human memory B-cell compartment has focused on studying peripheral blood and secondary lymphoid tissues, largely focusing on tonsil and spleen.[2-4] Previous studies using gut-associated lymphoid tissues (GALTs) led to increased understanding of MBC subsets and deeper understanding of B-cell biology in lymphoid tissues, but gut tissue itself was not evaluated.[5]

Not until now has a comprehensive analysis of B-cell lineages across multiple lymphoid and nonlymphoid tissues been performed. Shlomchik et al have carried out a deep phenotypic analysis of tissues that became available from multiple healthy donors. They enumerated the broader B-cell subsets using conventional B-cell markers, including CD38, CD27, and immunoglobulin isotype, to identify immature, antigen-naive, and antigen-experienced memory B-cell and antibody-secreting subsets. This carefully conducted comparison provides a unique source of data on the distribution of multiple B-cell lineages in the human body. A further focus on understanding the heterogeneity among MBC populations using CD45RB and CD69 as an early activation marker linked to residency in nonlymphoid tissues identified a double-positive CD45RB$^+$ CD69$^+$ MBC population among CD27$^+$ B cells. This was enriched in the gut and present in secondary lymphoid tissues, in smaller proportions, but was strikingly absent in the blood or bone marrow. In fact, most MBCs in the gut were CD45RB$^+$ CD69$^+$, prompting the proposal that these markers identify gut BRM cells. Remarkably, single-positive, double-positive, and negative subsets were also distinctive in their functionality with the double-positive subset highly effective in generating antibody upon stimulation. These findings indicate that tissue-located B cells are distinctive and not in homeostasis with the more commonly studied circulating B cells.

RNAseq analysis comparing the 4 MBC subsets selected on the expression of CD45RB and CD69, and carefully isolated from ileum avoiding GALTs and compared with splenic MBCs, revealed a unique subset of genes exclusively expressed in the double-positive MBCs in the intestine. Indicative of B-cell effector function, the CD45RB$^+$CD69$^+$ BRM cell subset had increased expression of gene signatures consistent with B-cell differentiation into antibody-secreting plasmablasts and plasma cells.