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Checkpoint inhibition in CNS lymphoma

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In this issue of Blood, Nayak et al1 report the clinical outcomes for 5 patients with relapsed or refractory primary central nervous system (CNS) lymphoma (PCNSL) and primary testicular lymphoma (PTL) with secondary central nervous system involvement who were treated with nivolumab, a programmed cell death 1 (PD-1) inhibitor.

One of the most challenging clinical scenarios to manage in patients with diffuse large B-cell lymphoma is primary or secondary CNS involvement because of the debilitating nature of the diagnosis and the toxicities of the currently available therapies. Traditional treatment of CNS lymphoma includes high-dose methotrexate–based induction followed by a variety of consolidation strategies, including radiation and autologous stem cell transplant. High-dose methotrexate is difficult to administer, requiring both intensive monitoring and access to the necessary supportive care that is not readily available in all settings. The treatment approach for patients with advanced age, poor performance status, or impaired organ function is generally palliative. In the case of PTL, concurrent CNS and systemic involvement presents even greater clinical challenges. Treatment is also associated with the potential for significant acute chemotherapy-associated toxicity and long-term neurotoxicity. Even with intensive therapy, the prognosis of primary and secondary CNS lymphoma remains poor.2,3

Recently, novel targeted approaches have shown promise in primary and secondary CNS lymphoma. Phase 1 and 2 studies of ibrutinib, a Bruton tyrosine kinase inhibitor, have demonstrated overall response rates ranging from 56% to 75%,4,5 and ibrutinib has also been successfully incorporated into a combination chemotherapy regimen.6 Lenalidomide, an immunomodulatory agent, has also demonstrated preliminary efficacy in combination with rituximab in CNS lymphoma.7,8

The shared genetic characteristics of PCNSL and PTL have been previously described by the authors’ and support exploration of other novel targeted therapies in these diseases. PCNSL and PTL exhibit unique genetic alterations in comparison with systemic diffuse large B-cell lymphoma, including a high frequency of 9p24 copy gain and increased PD-1 ligand expression, as well as chromosomal translocations resulting in PD-L1/PD-L2 deregulation.9 Based on these genetic characteristics, the authors hypothesized that PD-1 blockade was a rational therapeutic approach in PCNSL and PTL.

In the current case series, the authors report their clinical experience administering nivolumab off-label to patients with relapsed or refractory CNS lymphoma who had exhausted standard therapy. Reported toxicities in this series were consistent with the expected side effect profile of nivolumab. Notably, none of the patients experienced “pseudoprogression,” an immune-mediated phenomenon resulting in a transient increase in tumor burden. All 5 patients in this series had evidence of durable responses lasting >1 year, with 3 patients remaining without evidence of progression, exceeding expected survival in this setting.

PCNSL and PTL frequently affect older patients and oftentimes result in compromised performance status, as illustrated in this series. In a disease where standard therapy can be associated with prohibitive short- and long-term risk, this case series has significant clinical implications. These preliminary data, along with the genetic features that result in immune evasion through 9p24.1/PD-L1/PD-L2 copy-number alterations and translocations,9 support evaluation of PD-1 blockade in PCNSL and PTL in the setting of a clinical trial. A phase 2 study of nivolumab is currently underway (NCT02857426). In the future, combinations of novel targeted therapies both in the relapsed setting and incorporated into front-line regimens may potentially alter the historically poor prognosis of PCNSL and secondary CNS involvement of PTL.

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REFERENCES


4. Choquet S, Houillier C, Bijou F, et al. ibrutinib monotherapy in relapse or refractory primary CNS lymphoma (PCNSL) and primary vitre-retinal lymphoma (PVRL): result of the interim analysis of the iLOC phase II

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Comment on Siwaponanan et al, page 3087

Rusty neutrophils in β-thalassemia: no traction!

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In this issue of Blood, Siwaponanan et al provide a potential novel mechanism for the increased infections observed in patients with β-thalassemia. The authors find that neutrophils in 6-month-old β-thalassemic mice (Hbbth3/4+) and in patients have overall lower baseline levels of the ets-family transcription factor PU.1, and in mice lack upregulated Pu.1 expression in response to bacterial infection. This aberrant Pu.1 expression in mouse Hbbth3/4+ neutrophils is accompanied by defects in chemotaxis, phagocytosis, and production of reactive oxygen species (ROS).

It has long been recognized that patients with β-thalassemia suffer from increased infection.2,3 Granulocyte dysfunction has been described among other predisposing factors that include splenectomy, iron overload, and treatment with deferoxamine. But the underlying molecular cause(s) of neutrophil dysfunction in β-thalassemic patients has yet to be elucidated. To determine whether neutrophil dysfunction is directly linked to the β-thalassemic genetic disorder, Siwaponanan et al closely examine distinct neutrophil populations in the bone marrow (BM), spleen, and peripheral blood in Hbbth3/4+ mice based on the commonly used criteria of cell surface Ly6G vs Ly6C expression (eg, Ly6Ghigh/Ly6C+). Although they find that BM-derived neutrophils in Hbbth3/4+ mice do not differ from their wild-type (WT) counterparts, peripheral blood and spleen neutrophils exhibit nuclear hypolobulation and deficient chemotaxis in response to CXCL2 due to reduced expression of CXCR2, the receptor for CXCL2. Splenic neutrophils in Hbbth3/4+ mice also express lower levels of the integrin CD11b, explaining at least in part their reduced phagocytic capacity. Finally, splenic neutrophils from Hbbth3/4+ mice display reduced ROS production secondary to reduced expression of all essential components of the NAD phosphate-oxidase machinery.

Terminal neutrophil differentiation and maturation is a tightly controlled process directed by several key transcription factors, including C/EBPa, Pu.1, and C/EBPe. Given the broad defects observed in neutrophils from Hbbth3/4+ mice, Siwaponanan et al explore whether these defects may be due to aberrant maturation caused at the level of transcriptional control. They focus on the ets transcription factor that regulates monocytic-granulocytic lineage choice and maturation, Pu.1. Pu.1 is one of the master regulators in hematopoiesis; in conjunction with a versatile array of key transcription factors, Pu.1 directs several lineage choices, including those between the myeloid and lymphoid lineages and between monocytes and granulocytes. But is Pu.1 the only factor that controls lineage choice and neutrophil maturation that is affected by β-thalassemia and iron overload? Both Pu.1 and the neutrophil-specific factor C/EBPe cooperate with additional regulators (eg, Gabp) to control neutrophil-expressed genes such as CD11b and granulocyte-colony stimulating factor, among others; might they or additional factors such as Sp1 or retinoid receptors also be involved in the observed defects? How would iron overload uniquely affect neutrophil maturation without affecting lineage choice? Are other cells of the innate immune system affected, in particular macrophages that take up the majority of the iron and are also regulated by Pu.1?

Iron chelation has come a long way. Although parenteral administration of deferoxamine was the sole option only a few years ago, various oral chelators are now available, making prevention of significant iron overload a possibility.
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