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LYMPHOID NEOPLASIA

Comment on Ferreri et al, page 252

Is it time to revisit R-CHOP for primary CNS lymphoma?

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In this issue of *Blood*, Ferreri et al report preliminary results from the INGRID trial regarding the feasibility and safety of using engineered tumor necrosis factor-α for increasing blood-brain barrier permeability in patients with relapsed or refractory primary central nervous system (CNS) lymphoma.[1] The authors demonstrate that treatment with tumor necrosis factor coupled with NGR (NGR-hTNF), a drug that targets CD13 on tumor blood vessels, followed by rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is safe, selectively increases permeability of the blood-brain barrier (BBB) in the tumor regions, and is associated with radiographic responses.

Primary central nervous system lymphoma (PCNSL), a rare type of extranodal diffuse large B-cell lymphoma (DLBCL), is typically treated with methotrexate-based induction followed by consolidative whole-brain radiation therapy vs myeloablative or nonmyeloablative chemotherapy. However, survival of PCNSL patients is inferior to that of other extranodal lymphomas, and improved treatments are needed. In addition to the unique biological characteristics of lymphoma within the nervous system, resistance to therapy is also mediated by the inability to adequately deliver therapeutic agents to the cancer due to the BBB.[2] The BBB is a dynamic, complex structure of pericytes, astrocytes, and endothelial cells connected by tight junctions that regulate the biochemical composition of the brain interstitial milieu and protects the brain from toxic molecules (including xenobiotics). Because of its physicochemical properties, the BBB is relatively impermeable to many water-soluble compounds. Most cytotoxic drugs that gain access to the brain cross the BBB by passive diffusion. Aside from pharmacokinetic properties, the main factors that influence the extent to which these compounds distribute into the brain include lipid solubility, molecular mass, charge, and plasma protein binding. Specifically, small organic compounds with a molecular weight <200 that are lipid soluble, neutral at physiologic pH, and not highly bound to plasma proteins readily cross the BBB. Consequently, this limits delivery and cancer cell exposure of certain chemotherapeutic agents (including the components of R-CHOP), antibodies, and cell therapies. However, the BBB is partially disrupted in the setting of malignant neoplasms, including PCNSL. This partial disruption is the basis for the characteristic contrast leakage noted on brain computed tomography or magnetic resonance imaging studies and may demarcate a window during which there is enhanced delivery of chemotherapeutics. However, PCNSL is a diffuse disease with lymphoma cells infiltrating throughout the brain "behind" intact BBB, well beyond the contrast-enhancing borders noted on neuroimaging.[3] Moreover, there is evidence that partially disrupted BBB is reconstituted with treatment, as marked by decreased contrast enhancement on computed tomography or magnetic resonance imaging. To further complicate matters, because of concurrent involvement of the brain, cerebrospinal fluid (CSF), and the eye in up to 20% of cases, it is not only the BBB, but also the blood–CSF barrier and the blood–retinal barrier that are relevant for drug delivery in PCNSL.[4] Thus, strategies that enhance delivery of therapeutic agents beyond the BBB are critical for success.

Studies to date have demonstrated poor efficacy of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in primary CNS DLBCL despite its demonstrated efficacy in systemic DLBCL. Radiographic response rates to CHOP or cyclophosphamide, doxorubicin, vincristine, and dexamethasone in PCNSL are 19% to 59%.[5,6] However, the responses are not durable, with early progression in most patients. Moreover, single-arm studies demonstrated a median survival of only 10 to 18 months. A randomized phase 3 trial of whole-brain radiation therapy with or without CHOP demonstrated no apparent difference in survival between the 2 arms, although the trial was terminated early because of poor accrual.[7] Consequently, R-CHOP is not considered an effective induction regimen for PCNSL. Compromised delivery of the component drugs of R-CHOP beyond the BBB is likely an important factor in the failure of this regimen in PCNSL.

There have been considerable efforts to overcome the BBB and enhance drug delivery to brain tumors. Some of these strategies include direct drug administration into the brain using biodegradable polymers

and catheter-based convection enhanced delivery, or strategies to increase BBB permeability by using focused ultrasound or hyperosmotic solutions.[2] Ferreri et al use NGR-hTNF, a drug that binds to CD13, a metalloproteinase, almost exclusively expressed by tumor blood vessels, thereby selectively increasing vessel permeability (and "opening" the BBB) at the level of the tumor, and, in theory, increasing intratumoral delivery of R-CHOP.

As noted, the disruption of the BBB is heterogenous within different regions of PCNSL and additionally the BBB is intact in tumor-infiltrated, nonenhancing regions. It is critical to deliver chemotherapy across all these regions. Ferreri et al observed CD13 expression on tumor vessels in all 12 cases and low baseline values of BBB permeability in the peritumoral areas. These same peritumoral regions demonstrated increased permeability after infusion with NGR-hTNF. In theory, this increased permeability may result in increased delivery of the component drugs of R-CHOP in these regions. However, this remains unproven. As expected, drug delivery to the subarachnoid space was unchanged likely the result of lack of impact of NGR-hTNF on the blood–CSF barrier. Thus, the CSF may emerge as a sanctuary site and source of future relapse in these patients. The blood–retina barrier was not assessed in this study. The efficacy assessments are preliminary but encouraging, with complete and partial radiographic responses observed in 8/12 and 1/12 patients, respectively. However, further assessment is necessary to determine the durability of these radiographic responses.

Disruption of the BBB can be associated with increased cerebral edema as well as increased hydrostatic pressure within the tumor, which could cause seizures or other focal neurological symptoms and signs as well as diminished delivery of drugs, respectively.[2,8] However, in this small study, there was no neurotoxicity of any grade reported after 62 infusions.

Nearly all cases of PCNSL most closely resemble the activated B-cell subtype of DLBCL by gene-expression profiling. Patients with the activated B-cell subtype of DLBCL have inferior outcomes after R-CHOP vs the germinal center B-cell subtype of DLBCL.[9] Hence, increasing the delivery of R-CHOP alone across the BBB may ultimately prove less effective vs the development of novel agents and combinations that target the known oncogenic drivers of PCNSL. Moreover, whether this strategy will be effective in the 10% to 20% of PCNSL patients with concurrent brain, CSF, and eye involvement is an open question given the uncertainty around the effect on the blood–CSF and blood–retina barriers.

As noted by Ferreri et al, NGR-hTNF failed to demonstrate an improvement in survival in a randomized phase 3 trial in malignant pleural mesothelioma.[10] However, the rationale and safety data in PCNSL are compelling to continue further development of NGR-hTNF in PCNSL. Moreover, confirmation of these encouraging, but preliminary, results in the ongoing expansion phase of the INGRID trial would set the stage for reassessment of this "augmented" version of R-CHOP for PCNSL.

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MYELOID NEOPLASIA

Comment on Garg et al, page 263

Triple-mutant AML: too clever by HLF?

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In this issue of *Blood*, Garg et al report on their investigation of the molecular interaction between mutations affecting *DNMT3A* and *NPM1*, and internal tandem duplications (ITDs) of *FLT3* in acute myeloid leukemia (AML). They found that when the 3 mutations cooccur in AML, they synergize to drive increased expression of hepatic leukemia factor (*HLF*), a transcription factor, and are associated with particular characteristics such as increased leukemic stem cell (LSC) frequency and an aberrant immunophenotype (GPR56^{high}CD34^{low}), which seem to be at least in part attributable to overexpression of *HLF*. Their findings establish *HLF* overexpression as an important mediator of the adverse phenotype and propose that HLF or its downstream effectors represent potential therapeutic vulnerabilities of this poor-prognosis AML subtype.[1]