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CLINICAL TRIALS AND OBSERVATIONS

Comment on Sauter et al, page 1805

Improving on R-ICE in relapsed DLBCL

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In this issue of *Blood*, Sauter et al report the results of a multicenter phase 1 study of rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) in combination with ibrutinib in relapsed/refractory diffuse large B-cell lymphoma.[1] This combination was well tolerated and resulted in high response rates.

Therapies to improve survival among patients with relapsed and refractory (R/R) diffuse large B-cell lymphoma (DLBCL) are greatly needed, notwithstanding the newly approved chimeric antigen receptor T cell for second relapse of DLBCL.[2] DLBCL is the most common lymphoma in the Western world. Only 60% of patients are cured with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone–like chemoimmunotherapy.[3] Patients with R/R DLBCL who are transplant-eligible have an approximately 50% chance of responding to salvage therapy and receiving an autologous stem cell transplant (ASCT). Overall only 40% of these patients are long-term survivors.[4,5] Since the comparative studies of Gisselbrecht et al[4] and Crump et al,[5] which established R-ICE and rituximab, gemcitabine, dexamethasone, and cisplatinum (R-GDP), respectively, as acceptable salvage therapies prior to ASCT, there have been no further significant improvements in this curative approach. Also, the great progress in our understanding of molecular drivers of DLBCL and its resistance to chemoimmunotherapy in both frontline and relapse settings has yielded few biomarker-driven therapeutic improvements. However, the report in this issue of *Blood* provides some promising, though very early phase data of a biomarker-driven salvage regimen for relapsed and refractory DLBCL.

Herein, Sauter and colleagues report on a 21-patient, phase 1 study combining ibrutinib with R-ICE in patients with R/R DLBCL, primary mediastinal B-cell lymphoma (PMBCL), and Richter's transformation (RT). The trial is a classic 3 + 3 design, with 3 dose levels for ibrutinib added to the standard doses of R-ICE, which is given for up to 3 cycles. Ibrutinib is tested at 420 mg, 560 mg, and 840 mg orally, daily for days 1 to 21. No dose-limiting toxicities were reported at any dose level. In particular, no patients required dose delays beyond 1 week. Fifteen patients were enrolled in the dose-expansion phase at the 840-mg dose of ibrutinib. Overall, the regimen was tolerable, with rates of infection and febrile neutropenia similar to those observed with R-ICE.[4] Adverse events of concern with ibrutinib were few: only 1 patient had atrial fibrillation and was removed from the study early; there were no significant bleeding complications; and both the cardiac complications and infections were not specific to ibrutinib. The absence of added toxicity, in part, relates to the short exposure to ibrutinib. Lastly, stem cell collection was successful in 14 of 15 patients in whom it was attempted.

The most important result of this trial is the tolerability of ibrutinib in combination with R-ICE, something not to be taken lightly given the prohibitive dose-limiting toxicities of ibrutinib in combination with R-GDP[6] and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP).[7]

The second important finding is the high rate of response of 90% (complete response [CR] = 11, partial response = 7) in a cohort comprising 17 patients with primary refractory disease. These are patients who fare the poorest with salvage regimens.[4] Lastly, the results are notable for the higher rate of response in the non–germinal center (non-GC) versus GC DLBCL, in which all evaluable non-GC patients had a complete response by positron emission tomography–computed tomography in comparison with 1 of 3 GC patients. This stark split is reassuringly consistent with the difference in single-agent activity of ibrutinib noted for non-GC versus GC DLBCL reported time and again.

As the authors state, a complete metabolic remission pre-ASCT is associated with greater long-term survival after transplant.[8] However, does this hold true if the rate of CR is increased because of the addition of a nonchemotherapeutic/targeted agent? The quality of the response to salvage chemotherapy may simply be a reflection of the sensitivity of the tumor to chemotherapy or may provide a state of minimal residual disease allowing the transplant to be more effective. If the latter is true, then the addition of ibrutinib during salvage only should improve survival of transplant patients with R/R DLBCL. However, it is possible that the targeted agent is needed throughout and even beyond the salvage and transplant period to provide the maximal benefit, as was seen with the advantage in overall survival obtained from maintenance rituximab post-ASCT in mantle cell lymphoma.[9] Studies examining the addition of targeted agents, such as ibrutinib, venetoclax, immunotherapies, and others, in transplant-eligible R/R DLBCL will have to consider this possibility.

An important ethical point that comes to mind while reviewing this study pertains to the enrollment of transplant-eligible patients. Although this regimen proved to be safe, transplant-eligible patients

enrolled in phase 1 studies of salvage therapy may miss a chance at transplant if the experimental salvage regimen proves too toxic. Interestingly, this trial has a large proportion of patients with refractory and early-relapsed DLBCL, as well as patients with relapsed RT and PMBCL, lymphomas with low response rates to salvage therapy, suggesting that there may have been a selection bias toward patients less likely to respond to R-ICE alone. (Despite this, response rates were impressively high.)

With these questions in mind, we look forward to both the results of the phase 2 study of ibrutinib and R-ICE and to the design of future studies hoping to improve on salvage chemotherapy and transplant for patients with relapsed and refractory DLBCL.

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

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Vari et al, page 1809

Awakening exhausted NK cells in lymphomas

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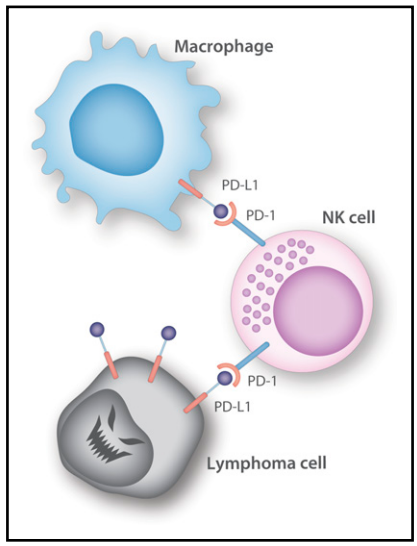
In this issue of *Blood*, Vari et al describe a novel immune evasion strategy in classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL) mediated by the expansion of an exhausted programmed cell death protein 1 (PD-1) CD3^{-ve}CD56^{bright}CD16^{-ve} natural killer (NK) cell population.[1]

PD-1 is the most clinically relevant immune checkpoint molecule to date.[2] Although it is physiologically expressed on activated T cells to prevent autoimmunity and maintain peripheral tolerance in healthy individuals, engagement of PD-1 with its ligand PD-L1 expressed on cancer cells leads to T-cell exhaustion and tumor immune evasion.[2] Monoclonal antibodies targeting PD-1 have shown significant clinical activity in solid tumors, cHL, and, to a lesser extent, in DLBCL by enhancing immune-mediated antitumor response.[3-5] Lymph nodes from cHL patients are characterized by a small percentage of malignant Reed-Sternberg (RS) cells within an extensive but ineffective inflammatory and immune-cell infiltrate. RS cells express high levels of PD-L1 because of genetic alterations in most cases.[4] Unlike cHL, lymph nodes from DLBCL patients demonstrate a diffuse proliferation of large lymphocytes with minimal immune infiltrate. PD-L1 expression is reported in ~10% to 30% of DLBCL cases, possibly explaining the differences in treatment response to PD-1 targeting antibodies between cHL and DLBCL.[6] In addition, PD-L1 expression appears to be higher in activated B-cell DLBCL and is associated with inferior overall survival.[5,6] In both cHL and DLBCL, PD-L1 is also expressed by nonmalignant cells in the tumor microenvironment.



PD-L1 expressed on monocytes/macrophages and B-cell lymphoma cells interacts with PD-1 on (CD56^{bright}CD16^{-ve}) NK cells and induces NK cells' exhaustion. Professional illustration by Somersault18:24.

Most of the published work thus far focuses on the role of immune checkpoint molecules in modulating T-cell expansion and function in B-cell lymphoma, with significantly less information available on the relevance of the PD-1/PD-L1 network in other immune cell subsets such as NK cells. NK cells play a major role in cancer immune surveillance and are conventionally classified in 2 main subsets identified as CD56^{bright}CD16^{-ve} and CD56^{dim}CD16^{+}.[7] Whereas CD56^{bright}CD16^{-ve} NK cells represents a less mature population, CD56^{dim}CD16^{+} NK cells, the major circulating subset in the peripheral blood of healthy individuals, are able to spontaneously kill