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The elegant study by Golan et al opens up numerous questions in this emerging field of intercellular communication. Interestingly, other HSC niche cells (such as endothelial cells) also appear to uptake mitochondria from HSCs, albeit with different kinetics and independently of Cx43 (which mainly favors a tight contact and possibly metabolic coupling between BM-MSCs and HSCs). Because mitochondrial exchange can take place through tunneling nanotubes or exosomes,[5,6] future studies will determine the contribution of different niche cells to protection from chemotherapy or irradiation (eg, by buffering excessive ROS levels) and subsequent hematopoietic recovery.

Notably, only BM-MSCs (and not other stromal cells or endothelial cells) show a dramatic mitochondrial loss after TBI, but why and how BM-MSCs adapt their metabolism to compensate for reduced mitochondrial function after TBI is unclear. Increased glycolysis does not appear to provide the energy needed. Therefore, it would be interesting to test whether the damaged mitochondria are used by BM-MSCs for energy production through mitophagy, perhaps explaining the reduced mitochondrial volume in BM-MSCs caused by TBI. Similarly, it seems appealing to investigate whether and how mitophagy or mitochondrial unfolded protein response following mitochondrial stress trigger mitochondrial donation from HSCs.

Another study has shown that ROS-induced phosphatidylinositol 3-kinase activation drives Cx43-dependent mitochondrial transfer from stromal cells to HSCs in response to infection.[7] Therefore, it would be interesting to investigate the role of sensors of infection (ie, Toll-like receptors), ROS, and the metabolic coupling between HSCs and MSCs as drivers of directed organelle exchange. Importantly, mitochondrial donation from MSCs does not only regulate HSCs but also T cells, thereby inducing a regulatory T cell program and restricting the inflammatory response (as an additional mechanism of MSC-induced immunomodulation).[8] Because regulatory T cells reduce postirradiation BM injury and facilitate HSC engraftment after transplantation,[9] collectively these studies highlight the potential relevance of mitochondrial exchange in the setting of clinical HSCT.

It might be important to consider bidirectional mitochondrial exchange in the context of HSCT for leukemia treatment because the opposite mitochondrial migratory route, from BM-MSCs to acute myeloid leukemia (AML) cells, helps protect AML cells from the effect of chemotherapy.[5,6,10] However, how AML cells avoid the damage caused by the excessive ROS production from these mitochondria has remained elusive. The reason appears to be a dual protection mechanism by MSCs, enabling increased bioenergetic capacity and antioxidant defense against excessive ROS.[10] Therefore, different mitochondrial exchange mechanisms should be probably considered during therapy to (1) increase the eradication of chemoresistant leukemic cells and (2) boost hematopoietic recovery following HSCT (see figure).

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

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CLINICAL TRIALS AND OBSERVATIONS

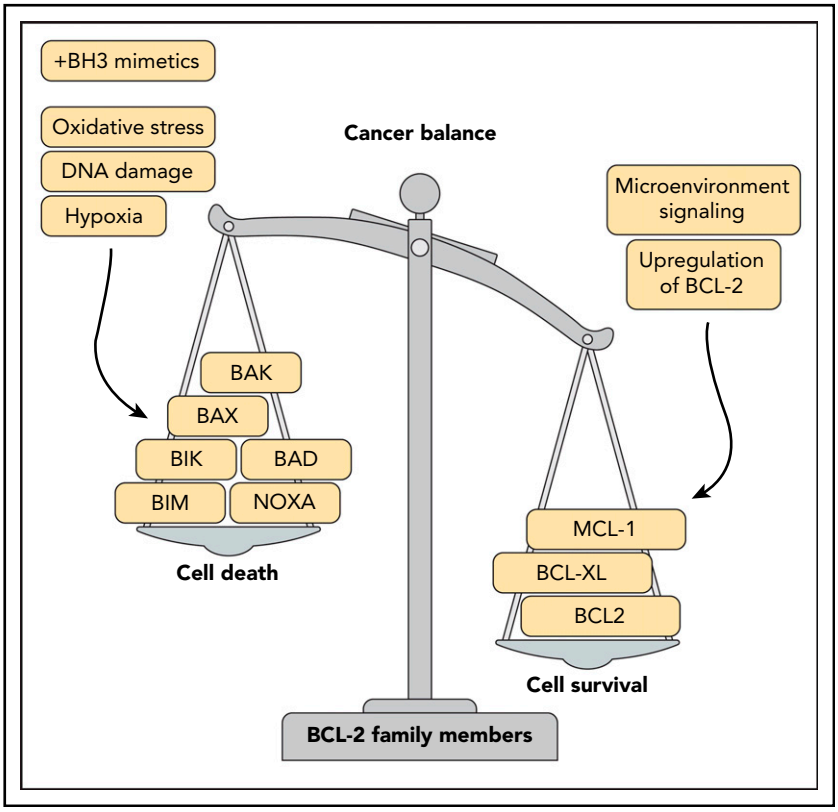
Comment on Zinzani et al, page 2628

BCL-2 inhibition in follicular lymphoma: can we tip the scales?

Nathan Fowler | MD Anderson Cancer Center

In this issue of *Blood*, Zinzani et al[1] report the results of the open-label phase 2 CONTRALTO study, which evaluated the additional benefit of adding the BCL-2 inhibitor, venetoclax (VEN), to common treatment backbones, such as rituximab and bendamustine plus rituximab, in patients with relapsed/refractory follicular lymphoma (FL).

Historically, various cytotoxic regimens coupled with a monoclonal antibody have been the mainstay of both frontline and relapsed therapy in FL. Recently, as understanding of pathogenic drivers of the malignant B cell evolved, alternative



The BCL-2 family is a key player in the balance between cell survival and cell death. Family members such as BCL-2, BCLXL, and MCL-1 are well known to be dysregulated in cancer, leading to a prosurvival advantage. Although attempts to inhibit specific BCL-2 member proteins have been partially successful, evolution of protein targets through upregulation/mutation, and signaling from the TME may ultimately lead to cell survival/progression.

therapeutic strategies have been tested. Clinical trials utilizing agents targeting the tumor microenvironment (TME; lenalidomide) as well as select cell survival pathways (PI3K, BTK, SYK, EZH2) have demonstrated promising activity in relapsed disease.[2] The fine balance between cancer cell death and survival is regulated in large through mitochondrial apoptosis and is tightly controlled through dynamic interactions between BCL-2 protein family members[3] (see figure). BCL-2 proteins include antiapoptotic members such as BCL-2, MCL-1, and BCL-XL, as well as the proapoptotic BIM, BID, BIK, NOXA, BAX, and BAK. Not surprisingly, cancer cells have developed multiple prosurvival mechanisms resulting in dysregulation of multiple BCL-2 family proteins. In fact, member aberrations are found at various levels in nearly all B-cell malignancies, and the hallmark BCL-2 translocation occurs in >90% of FL.[4] Early efforts to target BCL-2 were met with variable success, often due to ineffective target affinity and specificity as well as intolerable on-/off-target side effects.

VEN is a selective oral inhibitor of BCL-2 (BH-3 mimetic) that is currently approved for use in chronic lymphocytic leukemia (CLL) and acute myeloid leukemia. In 2017, Davids et al reported a phase 1 study of VEN in a range of non-Hodgkin lymphomas, including FL, mantle cell lymphoma (MCL), and diffuse large cell lymphoma (DLBCL). Overall responses were noted in 75% of MCL, 38% of FL, and 18% of DLBCL. Interestingly, the level of BCL-2 expression was not predictive of tumor lysis or overall response, suggesting a potential role of alternative BCL-2 family members in treatment resistance and/or survival.[5] For this reason, and to target BCL-2's role in chemotherapy resistance, subsequent studies explored the additional benefit of BCL-2 inhibition when given as part of a combination regimen. de Vos and colleagues[6] treated 60 patients (32 with follicular) with VEN plus bendamustine and rituximab (BR) in a phase 1b study, reporting 75% overall response rate (ORR) with 38% CR in FL. The recommended phase 2 dose of VEN with BR was 800 mg continuously, which was associated with grade 3 neutropenia in 59% and grade 3 thrombocytopenia in 36% of patients.

In the CONTRALTO study, Zinzani and colleagues report the results of a multicohort phase 2 study of VEN combinations in relapsed/refractory FL. The trial enrolled patients to receive either ventoclax (800 mg daily) plus rituximab (n = 52) or to be randomized into a substudy (111 patients) comparing 6 cycles of BR plus VEN (800 mg daily) vs 6 cycles of BR alone (following a safety run-in). In the VEN plus rituximab arm, the ORR and CR rates were 35% and 17%, respectively. Following 6 cycles of therapy, both BR and BR plus VEN cohorts showed an 84% ORR, with 49% of BR plus VEN patients maintaining response at 1 year compared with 57% in the BR-alone arm. The addition of VEN to BR did not appear to significantly improve either complete remission rates (75% vs 69%) or progression-free survival. Furthermore, the addition of VEN to BR resulted in higher rates of neutropenia and thrombocytopenia compared with BR alone (34% vs 61% and 16% vs 57%). These and other adverse events led to higher rates of treatment discontinuation in the VEN plus BR arm (40% vs 4%). In addition, dose reductions and interruptions resulted in dramatically disproportionate drug delivery between arms. In the VEN plus BR arm, only 25%, 85%, and 67% of patients received 90% of planned VEN, rituximab, and bendamustine, compared with 98% and 97% in the BR arm.

The inability of the study to demonstrate a clear benefit of VEN addition to BR may in part be secondary to poor drug exposure, especially in the chemoimmunotherapy backbone, and future trials could benefit from exploring alternate dosing and schedules. However, the addition of VEN to rituximab monotherapy also demonstrated only marginal improvement over previously published studies with rituximab alone in similar populations. These results lie in stark contrast to recent studies in CLL demonstrating profound activity of VEN both as a single agent and in combination with anti-CD20 therapy.[7]

The reasons behind FL's puzzling lack of response to BCL-2 inhibition remains an area of ongoing study. FL is characterized by intratumoral heterogeneity of BCL-2 expression and an increasingly recognized dependence on BCL-Xl. It is also possible that although t(14;18) is required for

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lymphogenesis, clonal evolution and subsequent genetic aberrations lead to redundancy, reducing the lymphoma's dependence on BCL-2 for survival and maintenance.[8] The TME also plays a key role in FL survival and evolution.[9] Competing prosurvival signals arising from the TME could potentially further negate select inhibition of BCL-2 family members and contribute to VEN resistance.

Unfortunately, CONTRALTO adds to an ever-growing list of randomized trials in FL that have failed to show a significant benefit of novel agents to various clinical outcomes when substituted or added to traditional chemotherapy backbones (especially overall survival!). These experiences highlight not only the complexity of clinical trial design but also the biologic heterogeneity of FL. As such, there is a growing need for predictive biomarkers to help select appropriate populations for subsequent prospective studies, ultimately resulting in a higher chance of trial success, and more importantly, to better patient outcomes.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Ghosh et al, page 2638

CD27-CD70 defects: a wolf in wolf's clothing?

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Signaling through the CD27/CD70 pathway is critical for Epstein-Barr virus (EBV) immune surveillance, and, in this issue of *Blood*, Ghosh et al report on symptoms and treatment of an international cohort of patients with defects in CD27 or its ligand, CD70.[1]

CD27 is expressed on a variety of T lymphocytes including naive and central memory T lymphocytes, as well as germinal center and memory B lymphocytes and plasma cells. The expression of its ligand, CD70, is restricted to activated lymphoid and myeloid cells. The CD27-CD70 axis delivers costimulatory signals to enhance T-lymphocyte activation, survival, proliferation, and differentiation; maintain antigen-specific $CD4^+$ and $CD8^+$ T lymphocytes; and promote memory B-lymphocyte differentiation and plasma cell survival. Thus, the CD27/CD70 axis can activate innate and adaptive immunity, has an important role in maintaining immune tolerance, and has a critical role in EBV immune surveillance.

For an increasingly recognized number of primary immune deficiencies, EBV is an important pathogen, associated with the pathogenesis of lymphoma, lymphoproliferative disorders, and/or hemophagocytic lymphohistiocytosis (HLH).[2] Patients with defects in CD27 characteristically display susceptibility to EBV-associated lymphoproliferative disorders and lymphomas. Many also report fever, oral ulceration, and other infections.[3] More recently, patients with defects in CD70 have been reported, with similar features including lymphoma, recurrent fevers, lymphoproliferation, persistent EBV viremia, hypogammaglobulinemia, recurrent respiratory infection, and autoimmunity.[4,5] Now, Ghosh et al report the clinical features, treatment, and outcome of 49 patients (33 with CD27 defects, 16 with CD70 defects), one-half of whom were previously unreported.

A number of features are notable from this report. First, the presentation is pleiomorphic (see figure panel A). Although over 90% of patients were EBV^+ at diagnosis, most presented with lymphoproliferation (71%), lymphoma (43%), and, in CD27-deficient patients only, HLH (27%). Lymphoma developed in 43% of patients before the age of 10 years. However, neither malignancy nor lymphoproliferation was inevitably the presenting feature. Autoinflammatory features were present in 43% of patients, including Behcet symptoms, uveitis, arthritis, and periodic fever. Non-EBV-related infections were also common, predominantly due to other herpesviruses, but upper and lower respiratory tract infections were also described in more than one-half of the patients. Almost 40% of patients had documented hypogammaglobulinemia. There was intrafamilial symptom variation, and some individuals were asymptomatic. In terms of treatment, given the spectrum of clinical phenotypes, a variety of approaches were documented. Patients with hypogammaglobulinemia were treated with immunoglobulin replacement and antibiotic prophylaxis, those with HLH received either the HLH-1994 or -2004 protocol, whereas those with malignancies received the appropriate disease-specific protocol. Treatment details for autoinflammatory diseases were not provided. Nineteen patients underwent allogeneic hematopoietic stem

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