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Comment on Chiron et al, page 2808

Neighborhood imbalances: overcoming MCL drug resistance

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In this issue of Blood, Chiron et al describe imbalances in mantle cell lymphoma (MCL) Bcl-2 family expression that leads to microenvironment-dependent loss of mitochondrial priming and resistance, which can be overcome by targeting CD20.1

A seminal description of the hallmarks of cancer by Hanahan and Weinberg, almost 2 decades ago, included resistance to cell death, among other factors.2 A primary focus of research in B-cell malignancies has been to understand pathogenic abnormalities leading to resistance to cell death. In MCL, these alterations include overexpression of cyclin-D1 and Bcl-2, which leads to dysregulation of cell-cycle progression and a decreased propensity for apoptosis, respectively, eventually resulting in drug resistance.3 It has been hypothesized that chemosensitivity may in large part be determined by the proximity of tumor cells to the threshold of apoptosis. Some malignant B cells may simply start closer to the threshold than others and thus are more primed for cell death than others. Mitochondrial priming has been found to predict response to chemotherapy and may even be modulated to enhance chemosensitivity.4 More simply, the therapeutic index for lymphoma therapy may be largely determined by differences in mitochondrial priming between malignant cells and normal cells.

Until recently, there has been little attention paid to therapeutic targeting of the microenvironment, and the key underpinnings of drug resistance found in protective local niches (ie, the neighborhood), where the loss of mitochondrial priming may lead to drug resistance. Mitochondria are positioned at the very center of the intrinsic pathway of apoptosis, and are exquisitely regulated by the complex interactions of Bcl-2 family members.5 These complex interactions between anti-apoptotic proteins, including Bcl-2, Bcl-XL, and others, with the BH3-only proteins such as BIM and the multidomain pro-apoptotic factors such as Bax and Bak, have proven to be key mediators of mitochondrial outer membrane permeabilization, the central event signifying an irreversible commitment to cell death.6 Yet, despite this well-defined machinery, chemotherapy sensitivity (or conversely, chemotherapy resistance) remains a highly variable proposition among non-

Hodgkin lymphomas. Stroma-exposed chronic lymphocytic leukemia (CLL) cells were previously found to have decreased mitochondrial priming4; however, the importance of the microenvironment and its protective niches in the mechanisms of MCL drug resistance has not been investigated.

In this issue of Blood, Chiron et al explore the tumor microenvironment signaling in MCL pathophysiology by establishing novel models of stromal and lymphoidlike coculture systems. Specifically, by using a limited number of human primary MCL samples in an ex vivo culture system using CD40 feeder cells and a cocktail of cytokines, the authors demonstrate that these conditions support an MCL phenotype that closely resembles the phenotype of MCL in lymphoid organs, which promotes proliferation and ex vivo survival through cell-cycle progression. These results that allow for more successful culture of MCL tumors provide a valuable example for those trying to adapt blood cancers to a more realistic ex vivo culture environment. Moreover, this ex vivo culture system now offers the possibility of a useful way to investigate MCL regimens that target stromal prosurvival signals.

The report by Chiron et al demonstrates some of the molecular biology underlying the alterations in MCL apoptotic signaling. Through a series of well-designed experiments, they demonstrate that the proliferating MCL cells have decreased mitochondrial priming and increased Bcl-XL dependence, which may lead to drug resistance. Perhaps most interestingly, the authors show that resistance can be overcome with obinutuzumab, a type II anti-CD20 antibody, which counteracted Bcl-XL through NF-κB inhibition. Conversely, the use of stromal human mesenchymal stem cells in this model did not promote proliferation, nor did the type I anti-CD20 antibody rituximab overcome resistance.

Although there have been studies targeting tumor cells outside their protective niches, there has not been a clear consensus on how to incorporate these approaches into treatments for patients with MCL. Obinutuzumab has been studied as a single agent in MCL, and more recently venetoclax, an oral Bcl-2 antagonist, has gained Food and Drug Administration approval as a therapeutic option for patients with CLL with high-risk 17p deletion. Venetoclax has also shown promising single-agent activity in relapsed MCL.7 Using their ex vivo MCL model, Chiron and colleagues showed that
single-agent venetoclax was highly cytotoxic for Bcl-2–dependent cells. The combination of obinutuzumab and venetoclax proved to be most promising, and the combination of these 2 agents has already begun to be explored in the clinic in patients with CLL.

Signaling pathways important for crosstalk between malignant MCL cells and their microenvironment have also proven to be attractive therapeutic targets. The immunomodulatory drug lenalidomide modulates the microenvironment, separate from the malignant B cells and has well-described clinical activity in mature B-cell malignancies, including MCL. Inhibitors of the B-cell receptor signaling pathways have been shown to antagonize stromal cell–derived migration, survival, and drug resistance signals. For example, inhibitors of Bruton tyrosine kinase (BTK) or phosphoinositide 3'-kinase interrupt homing of MCL through CXCR4 pathway modulation, resulting in a peripheral lymphocytosis. The approved BTK inhibitor, ibrutinib, holds particular promise in the development of novel therapies that target therapeutic options. Moreover, using the multiple methods of their investigation, Chiron et al may lead to the development of novel therapies that overcome resistance in MCL and beyond.

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REFERENCES

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PLATELETS AND THROMBOPOIESIS

Comment on Kavanagh et al, page 2824

Interferon-induced thrombotic microangiopathy

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Although drug-induced thrombotic microangiopathy (TMA) is commonly reported, evidence for a causal association is uncommonly documented. In this issue of Blood, Kavanagh et al use multiple methods to clearly establish a causal association of type I interferon with TMA.1

In the discipline of epidemiology, “cause” is a holy word, to be used only when definitive criteria for a causal association are met.2 The report by Kavanagh et al is remarkable for the multiple methods of their investigation, their definitive documentation of a causal association, and the importance of their findings for improved patient care.

As in many clinical investigations, their story began with patient observations. Among patients treated with type I interferon for multiple sclerosis, they noticed an unexpectedly high frequency of TMA associated with severe hypertension. The clinical features of TMA (microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury) often presented after years of well-tolerated interferon treatment. In some patients, anemia, hypertension, and abnormal kidney function had been recognized for months before the onset of fulminant TMA.3

In spite of the onset of TMA years after its initiation in some patients, a causal association with interferon was suspected, because no other etiologies for TMA were apparent and no other drugs had been taken. Also, patients who developed TMA had received higher weight-adjusted doses of interferon. To support this clinical evidence, a transgenic mouse model for production of type I interferon demonstrated dose-dependent microvascular abnormalities comparable to TMA. A final step was to demonstrate that microvascular abnormalities in the transgenic mice required the presence of the type I interferon receptor. The causal association of type I interferon with TMA was established.

This knowledge was then applied to patient care. A program to monitor blood pressure and kidney function in multiple sclerosis patients treated with type I interferon was established in Scotland. This has allowed early recognition of abnormalities associated with interferon-induced TMA. Interferon treatment was stopped at the first sign of toxicity, when organ damage may be reversible. Since implementation of this program, no patients have developed fulminant organ failure due to interferon-induced TMA.

This report is a model for reciprocal translational research. It began with patient observations that supported a hypothesis for the causal association of interferon with TMA. Next, both clinical and laboratory research data documented the causal association. Finally, this knowledge was applied to develop a clinical
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