rising number of agents; however, Lowe et al have shown that BV has place in the treatment of patients with newly diagnosed disease and that relapse during therapy can be substantially overcome with its use. It remains to be seen how BV will be incorporated into future strategies that are less acutely toxic and more effective. The prospect of combining BV with other targeted therapy and reducing or eliminating conventional chemotherapy is one that can be explored based on the results of this study. Stumme et al have presented a single case report of the combination of crizotinib and BV combined in relapsed ALCL, with good efficacy and without limiting toxicity; however, this combination did not prevent central nervous system relapse,[10] and so it seems likely that some form of conventional chemotherapy will continue to be needed, and further studies will be required to define the place of BV. For now, at least, there is additional, effective help on the frontline of therapy for children newly diagnosed with ALK$^+$ ALCL.

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LYMPHOID NEOPLASIA

Comment on Gupta et al, page 3604

Sensitivity to venetoclax: the B-side of myeloma?

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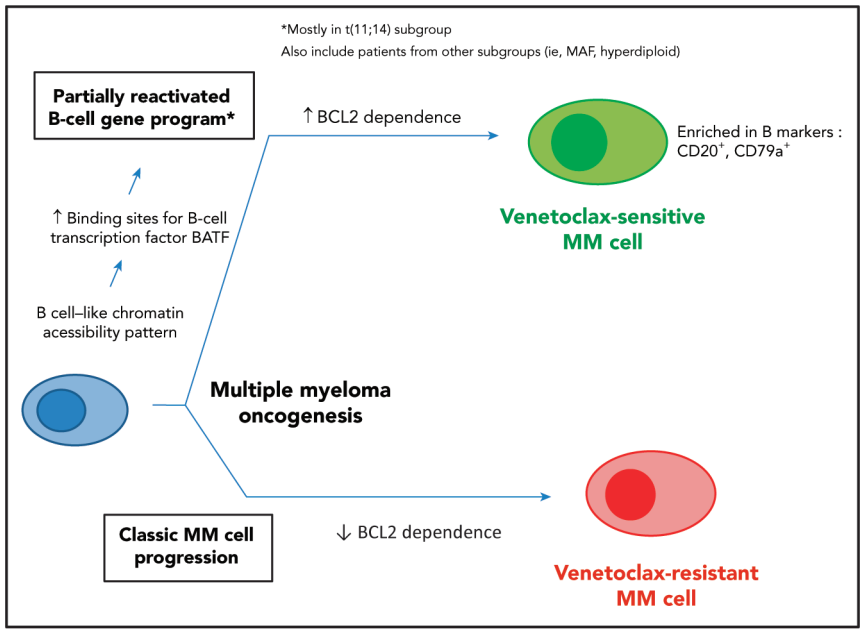
In this issue of *Blood*, Gupta et al[1] demonstrated that venetoclax sensitivity in multiple myeloma (MM) is associated with B-cell gene expression. This study brings a new approach to improve identification of patients with MM most likely to respond to BCL2 targeted therapy.

The oral BH3 mimetic venetoclax induces apoptosis by displacing proapoptotic proteins from the antiapoptotic protein BCL2.[2] Venetoclax is the first targeted therapy with clinical efficacy demonstrated in a specific cytogenetic subset of patients with MM. Preclinical studies demonstrated that sensitivity to venetoclax was restricted to MM cells harboring the t(11;14) translocation, a cytogenetic abnormality found in 15% to 20% of patients with MM.[3] Phase 1 to 3 clinical trials in relapsed MM confirmed the efficacy of venetoclax in t(11;14) patients, whereas few patients from other cytogenetic subgroups obtain substantial benefit from the drug.[4-6] Biomarker analysis from these clinical trials also showed the prognostic value of high BCL2 expression, which is associated with higher response rate and longer progression-free survival.

To date, we still need to improve the identification of patients with MM most likely to respond to venetoclax. First, although most patients sensitive to BCL2 targeting harbor the t(11;14), only 40% to 60% of patients from this subgroup actually respond to this approach.[4,5] Moreover, BCL2 expression is not yet a standardized test and thus not available for routine use.

In the present study, Gupta et al demonstrate that MM cells sensitive to venetoclax are enriched for specific B-cell genes, including CD20 and CD79A. This partially reactivated B-cell program is related to a specific chromatin accessibility pattern leading to an increased binding of transcription factor involved in B-cell development (ie, basic leucine zipper ATF-like transcription factor [BATF]). This aberrant B-cell reprogramming may contribute to BCL2 dependence, which is normally downregulated during plasma cell differentiation (see figure). By using a flow cytometry score including B markers (ie, CD20, CD79A), the authors correctly



Partially reactivated B-cell program in myeloma cells as proposed model for venetoclax sensitivity. Gupta et al demonstrated that myeloma cells sensitive to venetoclax are enriched for B-cell genes, including CD20 and CD79A. This partially reactivated B-cell program is related to a B cell–like chromatin accessibility pattern favoring an increased binding of transcription factor involved in B-cell development such as BATF. Whereas most patients with B cell–like phenotype belong to the t(11;14) subgroup, this aberrant B-cell phenotype could be identified in patients from other molecular subgroups (ie, hyperdiploid and musculoaponeurotic fibrosarcoma [MAF]).

predicted sensitivity to venetoclax in a series of MM cell lines and primary samples.

Previous flow cytometry and gene expression profile analysis revealed that CD20 expression in MM is mostly observed in patients with t(11;14).[7,8] However, in the study from Gupta et al, a subset of venetoclax-sensitive samples was identified by flow with positive B markers without t(11;14), including patients from the hyperdiploid molecular subgroup. CD20 expression was also shown in a subset of patients from the MAF subgroup.[8]

From a practical point of view, the use of flow cytometry using readily available reagents to predict sensitivity to venetoclax in patients with MM is very attractive. The mandatory next step will be to confirm the predictive value of B markers in a prospective study of patients treated with venetoclax. If confirmed, the determination of this B-cell phenotype using flow cytometry may help to identify patients that could benefit from venetoclax beyond the presence of t(11;14).

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