These results raise several questions. Should we screen and monitor MDS patients for de novo/pan-AML mutations in an attempt to identify early progression prior to clinical development of secondary AML? Does it matter whether secondary-type vs de novo/pan-AML mutations occur in the founding clone or a subclone at clinical diagnosis of de novo AML? Is relapse inevitable in patients with secondary AML who have persistent secondary-type mutations in remission, and what mutations and clones emerge at relapse? Do elderly patients with clinically defined de novo AML and secondary-type mutations have worse overall survival? Do clinically defined de novo AML patients with secondary-type mutations also have persistence of mutations in remission similar to that observed in secondary AML patients? Future studies with longer follow-up will be necessary to address these questions.

Although the authors use conservative mutation-calling criteria to identify sequence variants, the use of matched normal DNA from patients in future trials would allow somatic mutations to be definitively identified. If replicated in independent cohorts, these results have clinical implications. The presence of specific gene mutations could help risk stratify clinically defined de novo AML patients and reduce the heterogeneity in treatment response that is currently observed, especially in elderly AML patients. The absence of secondary-type mutations in AML may identify a group of chemosensitive patients that have better clinical outcomes. Ultimately, serial monitoring of mutations and tumor clones in patients may be necessary to fully understand the impact that gene mutations have on the clinical heterogeneity observed in AML.

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CD30: seeing is not always believing

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Although most investigators are well aware of the incredible success of brentuximab vedotin in the treatment of patients with Hodgkin lymphoma (HL) and anaplastic large-cell lymphoma (ALCL), the study by Jacobsen and colleagues in this issue of Blood demonstrates surprising activity of this agent in patients with B-cell non-Hodgkin lymphoma (NHL).

In a planned subset analysis of a phase 2 multicenter trial of brentuximab vedotin in patients with relapsed/refractory CD30+ NHL, overall response (OR) and complete response (CR) rates of 44% and 17%, respectively, were observed in 49 patients with diffuse large B-cell lymphoma (DLBCL). Although only 20% of the enrolled DLBCL patients had a prior autologous transplant, 82% were refractory to prior therapy and 24% were transformed from low-grade NHL. OR was 44% and 50% in the patients with refractory and transformed DLBCL, respectively. This efficacy rivals that of other single agents in DLBCL, namely lenalidomide and ibritinib, where ORs of 22% to 53% have been described.4-6

Nineteen patients with B-cell NHL other than DLBCL were also enrolled. Seventy-four percent of these patients were refractory to their last therapy, and OR in this group was 26%, with responses observed in patients with gray-zone lymphoma (n = 3), primary mediastinal B-cell lymphoma (PMBCL, n = 1), and posttransplant lymphoproliferative disorder (n = 1).

Three questions arise in reviewing this study: (1) Can we predict response based on CD30 expression? (2) Why is the activity in PMBCL so low (overall response rate 17%), particularly when this disease is typically CD30+? and (3) Are certain subsets (ie, myc+, activated B-cell, or germinal-center subtype) of DLBCL more likely to respond to brentuximab vedotin than others?

With respect to question 1, patients who entered this study were required to have visible CD30 expression by immunohistochemistry (IHC) analysis in a relapse biopsy sample reviewed by a local pathologist. This tissue was also sent for central pathology review, where CD30 expression on the neoplastic cells was visually quantified, and for analysis using computer-assisted quantification of CD30 expression on all cells (malignant and nonmalignant) in a specimen. Surprisingly, no statistical correlation between response and CD30 expression by central visual IHC or by computer-assisted review was observed. Specifically, in 48 DLBCL patients, the median percent of CD30+ cells by visual central review was 25% (0, 90) in the responders vs 25% (0, 100) in the nonresponders. Twenty-one percent of the responders had <10% CD30 expression. Two patients with DLBCL with ≤1% detectable CD30 expression by central pathologist review achieved CR.

By computer-assisted CD30 quantification, all responding patients had quantifiable CD30 expression, and the median percentage of CD30 found using the computer-assisted technique was 58.5%, 37.4%, and 20.7% in the CR, CR + partial response, and nonresponding patients, respectively. This trend to higher CD30 expression levels in the responding patients by using the computer quantification method rather than by pathologist inspection may reflect an accounting for CD30 expression in all cells.
rather than just the malignant cells. Therefore, it is unclear whether CD30 expression in the malignant cells is necessary for brentuximab vedotin’s activity in NHL or whether some minimum level of background staining must be present. The authors postulate that in the setting of CD30 positivity of the inflammatory infiltrate, a bystander effect may be responsible for brentuximab vedotin’s activity in patients where limited CD30 is visually detected on the malignant cell. Specifically, this bystander effect occurs with the release of monomethyl auristatin E into the surrounding tissue upon binding of the anti-CD30 antibody, killing the adjacent malignant cells.

As a result of the provocative findings of CRs observed in patients with very low CD30 expression, Bartlett and colleagues amended this phase 2 clinical trial to permit enrollment of an additional 50 patients with DLBCL with undetectable CD30 by IHC and reported these results at the American Society of Hematology 2014 meeting. At the time of the meeting, 13 responses (OR 31%, 4 CR) in 42 evaluable patients had been observed. Although the OR is lower than that observed in patients with IHC-detectable CD30, this study demonstrates activity of brentuximab in CD30− patients and is indicative that more sensitive techniques (computer-assisted CD30 visualization or CD30 mRNA detection by gene expression profiling) may have a future role in identifying patients who could benefit from brentuximab-based therapy.

In regards to the second question, the authors acknowledge that only 1 of 6 responses in patients with PMBCL is unexpectedly low, patients and is indicative that more sensitive techniques (computer-assisted CD30 visualization or CD30 mRNA detection by gene expression profiling) may have a future role in identifying patients who could benefit from brentuximab-based therapy.

Finally, addressing the third question, the study by Jacobsen et al did not assess cell of origin, myc, or bcl-2 expression in the DLBCL patients. Therefore, it is unclear whether response is associated with a specific DLBCL subtype as is observed with lenalidomide and ibrutinib, where OR is higher in the activated B-cell subtype. However, in a recent study by Hu et al, 461 cases of de novo DLBCL (PMBCL was excluded) were assessed for CD30 expression, and 14% were found to have CD30 expression of at least 20%. Of these 65 cases, 38, 26, and 1 were germinal-center, activated B cell, and unclassifiable, respectively, by gene expression profiling. None of the CD30+ cases had a detectable myc translocation by fluorescence in situ hybridization, although 38, 26, and 15 patients were found to have myc, bcl-2, or both myc and bcl-2 overexpression by IHC analysis. Moreover, CD30− patients had a superior overall survival and progression-free survival, with 5-year overall survival and progression-free survival of 79% and 73%, respectively, in the CD30+ group compared with 59% and 57% for the CD30− cases. The favorable outcome of the CD30− patients was observed regardless of cell of origin. The studies by Hu et al and others demonstrate that we still have a lot to learn about how best to use these prognostic markers in the care of patients with DLBCL and that multiple prognostic markers may affect patient outcomes in DLBCL beyond myc, bcl-2, and cell of origin.

In conclusion, this trial and the previously referenced trials of lenalidomide and ibrutinib are among the first studies to usher in an era of target-directed rather than histology-directed therapy in B-cell NHL. On the basis of this study, I believe our use of brentuximab vedotin should expand from patients with relapsed/refractory HL and ALCL to patients with relapsed CD30− DLBCL. However, correlative studies will need to be analyzed from the undetectable CD30 DLBCL trial to determine which patients without visible CD30 by IHC respond to this agent. Recent studies have confirmed the safety of brentuximab vedotin in combination with chemotherapy including rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (RCHOP). A phase 2 study of RCHOP with brentuximab vedotin in patients with newly diagnosed DLBCL is ongoing (NCT01925612), and preliminary data in 12 response-evaluable patients demonstrate an overall response rate of 92%, with 58% of those CR, although long-term follow-up and correlation of response with CD30 expression by IHC or mRNA, myc and bcl-2 expression, and cell of origin will be necessary to determine whether this agent should be incorporated into front-line DLBCL regimens.

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