Comment on Lindsley et al, page 1367

**What came first: MDS or AML?**

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In this issue of *Blood*, Lindsley et al have identified a set of 8 genes that, when mutated, appear to be highly specific for secondary acute myeloid leukemia (AML) vs de novo AML.\(^1\)

In the absence of overt bone marrow dysplasia or a prior history of a myeloid disease, it is not always clear whether a patient has de novo or secondary AML, especially for elderly patients. This is an important distinction, because patients with secondary AML arising from an antecedent myelodysplastic syndrome (MDS) have worse outcomes compared with de novo AML patients. Can gene mutations present at the time of AML diagnosis distinguish between secondary vs de novo AML and be predictive of clinical outcomes? Lindsley et al identified a set of 8 genes that appear to be highly specific for secondary AML vs de novo AML when mutated.\(^1\) Mutations in these 8 genes define a secondary AML-like disease in elderly patients who have clinically defined de novo AML that is associated with worse clinical outcomes. These findings suggest that the presence of specific gene mutations may identify a subset of de novo AML patients with poor outcomes and explain some of the clinical heterogeneity we observe in AML.

Lindsley et al evaluated sequence variants within a panel of genes in a well-annotated set of 93 patients with secondary AML who were defined by the histologic documentation of antecedent MDS or chronic myelomonocytic leukemia according to the World Health Organization criteria, at least 3 months prior to study entry. By comparing the mutation frequency of recurrently mutated genes in secondary AML cases vs 180 non-M3 de novo AML patients from The Cancer Genome Atlas cohort,\(^2\) they showed that mutations in *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR*, or *STAG2* were 95% specific for the diagnosis of secondary AML (called secondary-type mutations). They also defined a set of genes that were more frequently mutated in de novo AML, or that had similar mutation frequencies between the 2 cohorts (de novo/pan-AML mutations). Finally, patients with *TP53* mutations defined a third set of AML patients that had the worst outcomes, confirming previous studies.\(^3\) Lindsley et al found that the presence of secondary-type or de novo/pan-AML mutations were predictive of clinical outcomes.\(^1\)

Mutations that are acquired during progression from MDS to secondary AML were uniformly de novo/pan-AML mutations, and predominantly involved genes encoding transcription factors and activated signaling genes. These findings suggest that de novo/pan-AML mutations are acquired as later genetic events and disrupt myeloid maturation, ultimately contributing to the rise in blast count in secondary AML. In contrast, Lindsley et al suggest that secondary-type mutations are earlier genetic events and contribute to the dysplasia and ineffective hematopoiesis observed in MDS. In support of this possibility, de novo/pan-AML mutations were undetectable when the blast count normalized to \(<5%\) in remission samples harvested from secondary AML patients \(\sim 37\) days after standard chemotherapy induction. In the same remission samples, secondary-type mutations, as well as *DNMT3A* and *TET2* mutations, were detectable at high levels in the bone marrow in many patients, consistent with residual clonal hematopoiesis being driven by these mutations. Next, the authors evaluated an independent cohort of elderly patients with clinically defined de novo AML and found that \(\sim 35%\) contained secondary-type mutations. The presence of secondary-type mutations in this cohort predicted lower remission rates and worse event-free survival compared with patients with de novo/pan-AML mutations.

This study provides genetic evidence that clinical heterogeneity observed in AML, in particular de novo AML in elderly patients, may be due to clonal hematopoiesis that preexisted in some patients. The results suggest that up to \(\sim 30%\) of clinically defined de novo AML may have progressed from an undiagnosed antecedent MDS harboring secondary-type mutations, which are also commonly mutated in de novo MDS.\(^4\) Alternatively, AML cells with secondary-type mutations could have arisen in the setting of clonal hematopoiesis associated with aging.\(^5\) Many of the secondary-type mutations identified here are the same genes that are somatically mutated in people with clonal hematopoiesis who are predisposed to developing hematopoietic cancers, including MDS and AML.\(^6,7\) Regardless of the mechanism, it is possible that the functional properties of a cell, including chemoresistance, may be influenced by the duration of clonal hematopoiesis. It may be that cells with secondary-type mutations can persist for years without causing clinically apparent disease compared with de novo/pan-AML mutations because they do not induce maturation arrest and an accumulation of blasts that define AML.
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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REFERENCES


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Comment on Jacobsen et al, page 1394

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 ibrutinib, where ORs of 22% to 53% have been described.

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 quantitated, 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.
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