blood® commentary

MYELOID NEOPLASIA

Comment on Dimitriou et al, page 953

A road map of relapse in MDS after allo-HSCT

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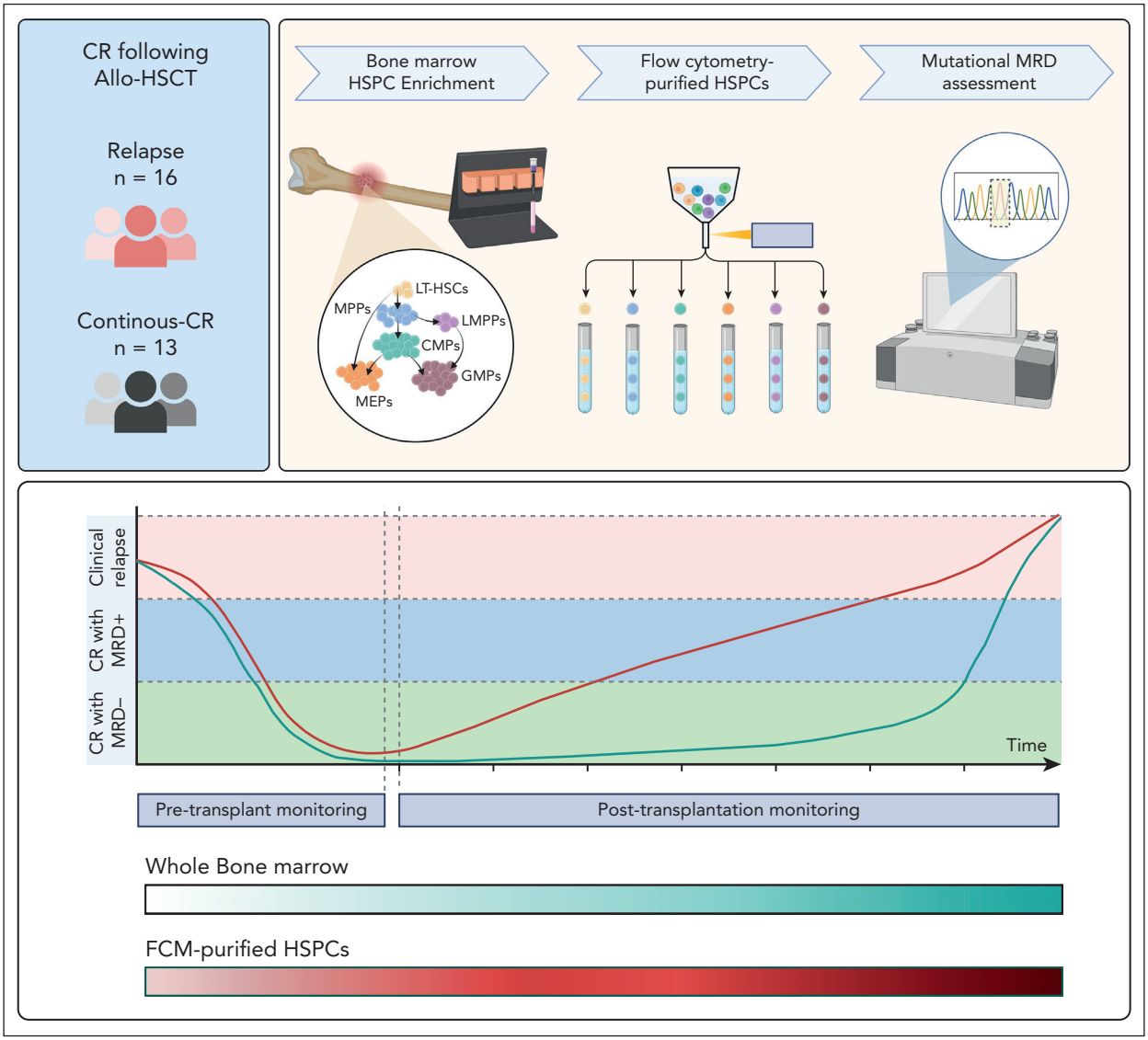
In this issue of *Blood*, Dimitriou and colleagues report that mutational screening for malignant hematopoietic stem and progenitor cells (HSPCs) that persist after allogenic hematopoietic stem cell transplantation (allo-HSCT) consistently improved the sensitivity of measurable residual disease (MRD) detection, thus allowing an earlier prediction of relapse in patients with myeloid malignancies.[1]

Myelodysplastic syndromes (MDSs) arise from a rare population of disease-initiating hematopoietic stem cells (HSCs). MDS HSCs, which can persist and expand during conventional therapy, are the major effectors of disease progression and relapse.[2] Aside from allo-HSCT, no curative treatments for MDS have emerged over the past decade,[3] which underscores an urgent need to improve preventive strategies, including current approaches for the early detection of relapse. In particular, the lack of highly sensitive methods capable of predicting relapse in the early posttransplant phase has significantly inhibited the clinical implementation of new exploratory treatments for patients with MDS whose disease relapses after allo-HSCT. The detection of MRD during complete remission (CR) is an important predictor of survival in patients with acute myeloid leukemia (AML).[4] However, MRD assessment is not yet a routine part of the management of patients with MDS.

MDSs are propagated by the expansion of HSC clones carrying preexisting or newly acquired recurrent mutations. Given that the progression of MDS to AML and the relapse of MDS after allo-HSCT are mainly caused by clones harboring persistent founder mutations,[5] targeted screening for these recurrent disease-initiating mutations could facilitate the earlier detection of MDS relapse after allo-HSCT. Indeed, in a retrospective study, the detection of oncogenic mutations in bone marrow (BM) after allo-HSCT was associated with a higher risk of disease progression.[6] However, the same study showed that 20% of patients without detectable MRD after allo-HSCT ultimately had disease progression and that 30% of patients with detectable MRD after allo-HSCT did not have disease progression. These results challenge the sensitivity of our approaches to detecting MRD, thus underlining current limitations in predicting relapse after allo-HSCT. Other technologies commonly used to assess MRD in MDS BM cells, such as flow cytometry for aberrant cell surface antigens, have not been extensively validated to detect MRD in MDS after allo-HSCT.[7] Current efforts to improve MRD assessment in MDS are focused on detecting MRD in the $CD34^+$ HSPC compartment, which drives MDS progression and relapse.[8]

Dimitriou et al compared the sensitivity of MRD detection using flow cytometry–purified HSPCs with that of MRD detection using unfractionated mononuclear cells. The authors analyzed 25 samples from 15 patients who initially had CR after allo-HSCT and then had disease relapse. Among these samples, MRD was observed in all flow cytometry–sorted HSPCs but only 9 of the 16 available BM samples. MRD detection in HSPCs consistently preceded that in mononuclear cells across multiple sequential samples, with an average lead time of 10 months, which translated into a 97-fold higher sensitivity of MRD detection. Interestingly, HSCs, multipotent progenitors, lymphoid-primed multipotent progenitors, and granulocyte-monocyte progenitors were more frequently clonally involved than other BM populations and had the highest variant allele frequencies (VAFs) among the different HSPC populations analyzed. Sequential samples collected during CR typically showed increasing clonal burden, with higher VAFs in HSPCs, which were correlated with shorter time to relapse (see figure).

However, owing to the limited number of samples used in their study, the authors could not evaluate the implication of detecting MRD in HSPCs from patients whose disease did not progress after allo-HSCT. The detection of MRD after allo-HSCT in patients whose disease ultimately does not relapse is common, which limits our ability to determine whether and when preemptive treatments for relapse should be initiated in patients who become MRD^+ after allo-HSCT but still have CR. Therefore, prospective studies involving a larger cohort of patients than that analyzed by Dimitriou et al are urgently needed to evaluate whether MRD detection in HSPCs predicts disease relapse more reliably than MRD detection in unfractionated BM cells. Taking into consideration the type of genomically defined MDS-specific



MRD detection in flow cytometry (FCM)-purified HSPCs enriched from the BM of patients in CR after allo-HSCT precedes that in whole BM cells and more reliably predicts disease relapse. CMP, cytidine 5′-monophosphate; GMP, granulocyte monocyte progenitors; LMPP, lymphomyeloid primed progenitors; LT-HSC, long-term hematopoietic stem cells; MEP, megakaryocyte-erythroid progenitors; MPP, multipotent progenitors. The figure was created with BioRender.com.

subtypes, the presence or absence of higher-risk genomic alterations, the type of allo-HSCT treatment, and other clinical variables may also improve our capability to assess the risk of progression.

Interestingly, the authors showed that in patients who had CR after allo-HSCT, distinct patterns of HSPC clonality were correlated with the MDS cellular architecture. Indeed, whereas HSC clonality was predominant in lower- and intermediate-risk MDS, more differentiated progenitor cell clonality was predominant in higher-risk MDS.[9] Thus, further characterization of these relapse-driving HSPCs could elucidate how these cells selectively evade pretransplant conditioning regimens and posttransplant graft-versus-leukemia effects and lead to the discovery of novel therapeutic approaches to prevent recurrence after allo-HSCT.

Our understanding of the clinical implications of detecting MRD in MDS continues to evolve as new technologies, such as single-cell sequencing, are introduced.[10] However, formal guidelines for the clinical application of these technologies to detect MRD in patients with MDS have not yet been defined. Larger prospective studies are needed to assess the impact of different approaches for MRD detection toward the development of a more robust and reliable predictive model for early intervention. Although intervening in the early stages of disease recurrence after allo-HSCT is important, overtreating patients who may not later experience relapse should be avoided to decrease the risk of secondary therapy-related cancers.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Ghesquières et al, page 983

Aging Kairos: treating older Hodgkin patients

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In this issue of *Blood*, Ghesquières et al[1] conclude that the prednisone, vinblastine, doxorubicin, and bendamustine (PVAB) regimen, which lacks any novel drugs, could be a valuable nonbleomycin regimen for older patients with classical Hodgkin lymphoma (cHL). They also note that the outcome of older patients with chemotherapy-treated cHL remains dismal, regardless of the chemotherapy regimen used, and needs improvement.

Older patients with cHL do not share the favorable prognosis of their younger counterparts. They often suffer from more comorbidities and have a lower tolerance to toxic chemotherapy. There is no chemotherapy gold standard demonstrated by large randomized trials to guide the treatment decisions in this group. The Kairos principle (coined by Volker Diehl; Kairos had hair in the front but was bald at the back of his head), to hit hard early to grab the chance of cure, seems valid for young patients, given the evidence for dose-dense therapies like escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). Unfortunately, older patients do not tolerate that approach. Hence, less intensive regimens, like the regimen studied here, PVAB, are used (see figure).

The inferior prognosis for older patients with cHL is partly explained by comorbidities and frailness.[2] The biological characteristics of the disease are also different in older compared with younger patients. Older patients more commonly have mixed cellularity histology, advanced disease stage, and more frequent Epstein-Barr virus positivity. Anthracycline-based therapy remains important in curative treatment, but more intensive regimens like BEACOPP often result in intolerable toxicity and even death.[3] Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is commonly used in clinical practice, but bleomycin-induced lung toxicity is a major problem for older patients.[4-6] Also, granulocyte colony-stimulating factor is not recommended after ABVD, due to the risk of bleomycin toxicity. Omission of bleomycin (AVD) has been tried and seems to be a feasible strategy, but cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) seems inferior.[7] PD-1 inhibitors and the antibody drug conjugate brentuximab vedotin are promising additions to standard therapy but both the optimal timing and combination of agents are still being explored.[8,9] The latest contribution is combining brentuximab vedotin with dacarbazine or nivolumab for the slightly different group of patients not eligible for chemotherapy.[10]

The patients in the Ghesquières study were all aged >60 years and diagnosed with advanced stage disease. The 89 included patients had a median age of 68 years. They received treatment with 6 cycles of the chemotherapy combination PVAB. Complete metabolic remission after treatment was 77.5%. Four-year progression-free survival (PFS) and overall survival (OS) were 50% and 69%, respectively. Patients aged >69 years were evaluated according to the geriatric cumulative illness rating scale (CIRS-G) and, interestingly, a mini nutritional assessment. Unfortunately, the relatively small sample size limits the power of the study. However, compared with other prospective studies of this age group, 89 patients is a respectable number. Performing a study of older patients with cHL is, in itself, quite an achievement. Despite this limitation, as older patients with cHL have worse PFS and OS than young patients, the statistics in the study are convincing.

The PVAB regimen contains no novel agents such as PD-1 inhibitors or antibody drug conjugates. Combining the standard anthracycline doxorubicin, with the proven (yet not too toxic) agent vinblastine and bendamustine, which has known efficacy both as a single agent and in combination in the relapse setting, seems reasonable. The absence of bleomycin is positive considering the risk of lung toxicity, and all patients received granulocyte colony-stimulating factor.

This study, like other cHL studies in this age group, is a nonrandomized phase 2 study. Ideally, a randomized trial should