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Can we better evaluate responses in higher-risk myelodysplastic syndromes?

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Response to treatment is the earliest measure of drug activity and the usual proxy for clinical benefit. In myelodysplastic syndromes (MDS), the International Working Group (IWG) 2000 response criteria supported the registration of azacitidine[1] and decitabine[2], and were revised in 2006[3]. A further 2018 revision covered improvement of cytopenias (hematologic improvement, HI) in lower-risk disease only, leaving IWG 2006 as the reference for higher-risk MDS (HR-MDS) for nearly two decades.

With now long-term follow-up, IWG 2006 showed two major limitations that biased response rates in opposite directions. While complete remission (CR) remained the response benchmark associated with the longest overall survival (OS), it underestimated clinical benefit: hypomethylating agents (HMA) improved survival and quality of life despite CR rates below 30%, and survival was improved in patients who only reached HI[1]. This limitation was compounded by the stringent IWG 2006 CR thresholds, particularly a hemoglobin level cutoff of ≥11 g/dL, which further restricted response classification.

Conversely, marrow CR (mCR) required no HI, and its inclusion in composite endpoints could inflate apparent response rates. This discrepancy was illustrated by later drug-development programs, in which high response rates driven by mCR in single-arm studies did not translate into a survival benefit in subsequent randomized trials[4]. Assessment timing further varied across trials, often during ongoing myelosuppressive therapy.

The IWG 2023 response criteria[5] aimed, in addition to marrow blast reduction, to better take into account HI. mCR was removed, reflecting evidence that blast reduction without HI does not confer a survival benefit[6]. New categories captured incomplete hematologic recovery: CR-L, defined by recovery of two (CRbi) or one (CRuni) blood-cell lineages; CRh, requiring partial neutrophil and platelet recovery; and CR equivalent for patients without excess marrow blasts at baseline. Accordingly, composite CR (cCR) was redefined from CR plus mCR under IWG 2006 to CR, CR equivalent, CR-L, and CRh under IWG 2023.

CR-L and CRh were introduced as provisional categories requiring prospective validation, and evidence remained limited to small cohorts. At the same time, Pleyer et al. suggested that peripheral blood CR (PB-CR) could predict survival similarly to bone marrow-based response criteria in azacitidine-treated MDS patients[7], questioning the necessity of bone marrow reassessment.

In this issue of Haematologica, Bewersdorf et al.[8] validate the IWG 2023 criteria in patients with HR-MDS treated with HMA-based therapy, using two distinct datasets: the International Consortium for MDS (icMDS) VALIDATE registry (n=1,047; 37% undergoing allogeneic transplantation) and the

randomized phase III PANTHER trial of azacitidine with or without pevonedistat (n=221; 6% transplanted)[4].

Reclassification from IWG 2006 to IWG 2023 reduced cCR from 50% to 36% in VALIDATE and from 60% to 50% in PANTHER. The change relied almost entirely on the 346 patients with mCR, and depended on concurrent HI: most retained cCR status as CRbi or CRuni, but 75 of the 209 without HI left the composite and were reclassified as nonresponders.

cCR was associated with longer OS in both datasets (VALIDATE: 23.8 versus 16.9 months; PANTHER: 22.6 versus 15.1 months). The association persisted in six-month landmark analyses and in patients receiving HMA monotherapy, and remained significant in multivariable models adjusting for age, sex, baseline white blood cell count, risk category by the revised (IPSS-R) or the molecular (IPSS-M) International Prognostic Scoring Systems, and type of HMA therapy.

Within the composite, the survival benefit was driven by CR and, to a lesser extent, by CR-L. Outcomes tended to be inferior with CRuni than with CR or CRbi, whereas CRbi and CRh were comparable to CR. Hematologic recovery therefore contributed to survival beyond blast reduction, although the extent of recovery required remained undefined. The benefit of cCR was clearest in patients who did not proceed to transplantation; among those transplanted, baseline IPSS-M risk outweighed response, as previously shown in the same database[9].

In addition to IWG 2023 validation, Bewersdorf et al. found that PB-CR, which relies on blood counts alone[7], performed as well as cCR.

Several implications are of immediate clinical relevance. First, cCR appears to be a valid proxy for outcome in patients treated with HMA and can be used to describe response in routine practice. Second, failure to achieve cCR should not delay or contraindicate allogeneic transplantation, which remains the strongest determinant of long-term outcome. Third, PB-CR may perform as well as cCR. Since marrow reassessment is performed in only about half of patients treated outside trials[7], blood counts may suffice to evaluate benefit, although this requires prospective confirmation. The same holds for clinical trials: IWG 2023 should replace IWG 2006 in response reporting, since removing mCR addresses a documented source of inflated response rates, and cCR should be an important endpoint on which trials are powered, in addition to survival.

Currently, however, the major goal in higher-risk MDS is to identify drugs that, when added to an HMA, improve OS over HMA alone, a goal that has so far remained elusive in randomized phase III trials[4,10]. Once effective combinations are identified, whether IWG 2023 response criteria, particularly cCR, and/or PB-CR, remain predictive of survival will need to be confirmed in that setting. In addition, if therapies that prolong survival after HMA failure become available, first-line trials may need to shift

from OS to earlier endpoints such as event-free or progression-free survival, which remain to be formally validated in higher-risk MDS.

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