predominant clone at presentation may differ from the clone ultimately responsible for clinical relapse; further work will be needed to determine if this will be a significant factor requiring modification of the bioinformatics strategy employed in post allo-SCT monitoring.

The prognostic significance of MRD in patients with ALL undergoing SCT had previously been established [15] and the use of MRD-guided therapy has already resulted in remarkable outcomes in the treatment of children with ALL [16]. The advance, therefore, represented by this NGS approach is the ability to have a standardized, extremely sensitive MRD platform available for most cases of ALL. This should allow the truly "next generation" era of MRD to be reached; the use of highly sensitive measurement of disease burden to routinely determine treatment efficacy and make evidence-based clinical decisions, in real-time, regarding the most appropriate next therapeutic intervention for an individual patient. Risk stratification based not on historical, population-average correlates of the likely disease biology and chemo-sensitivity of the predominant leukemic clone before any treatment, but rather on the actual amount of malignant disease a patient still has left requiring treatment at key clinical decision points "moves the goal posts" and will allow true personalization of therapy.

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Pretransplantation Therapy with Hypomethylating Agents in Patients with Myelodysplastic Syndromes Receiving Reduced-Intensity Conditioning Regimens

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The only potentially curative treatment for patients with myelodysplastic syndrome (MDS) is allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the effectiveness of this approach is limited by considerable morbidity and mortality. The introduction of reduced-intensity conditioning regimens has resulted in a significant reduction in transplantation-related mortality, leading to a rapidly growing number of transplantations in elderly patients.

Despite these recent advances, the long-term survival rate is currently about 30% [1]. In MDS patients receiving reduced-intensity conditioning, disease relapse represents the leading cause of transplantation failure, especially in those with an advanced disease stage (ie, intermediate-2 and high International Prognostic Scoring System risk). The

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issue of performing cytoreductive chemotherapy before allo-HSCT in these patients to reduce the risk of disease relapse is a matter of debate. Significant concerns about chemotherapy, such as that used to treat acute myeloid leukemia, include the low response rate and the risk of long-lasting myelosuppression and organ toxicities. It should be considered, in addition, that there is no definitive evidence of a survival benefit associated with administering chemotherapy before allo-HSCT in patients with MDS [1,2]. The only randomized study, from the European Group for Blood and Marrow Transplantation, had to be stopped because of slow recruitment, whereas retrospective single-center studies showed no conclusive results, with additional selection bias as a result of the impossibility of accounting for patient drop-out (ie, patients who received induction chemotherapy but never received allo-HSCT because of death or toxicity) [2].

The availability of hypomethylating agents, including 5-azacitidine and decitabine, has changed the landscape of MDS treatment. Azacitidine results in hematologic improvements in approximately 25% to 50% of cases and complete response in 10% to 20%, with prolonged survival, compared with supportive care alone in high-risk MDS, with a good toxicity profile, compared with induction chemotherapy [3].

Although hypomethylating agents can induce hematological and cytogenetic responses, these therapies do not appear to eradicate MDS clones, and recent data suggest that even in patients ages 60 to 70 years and with intermediate-2 or high international prognostic scoring system risk, transplantation offers a survival benefit with respect to non-transplantation procedures [4]. The use of hypomethylating agents is, therefore, increasing as a bridge to more definitive therapy, as a part of a comprehensive strategy to prevent relapse after allo-HSCT in MDS patients with advanced disease. The mechanism by which hypomethylating agents exert an antitumor effect in MDS remains not completely understood. Inhibition of DNA methyltransferases results in hypomethylation and, consequently, might result in reactivation of tumor suppressor genes, terminal differentiation, and apoptosis of neoplastic cells, with reduction of tumor burden before allo-HSCT. In addition, treatment with hypomethylating agents seems to affect T cell–mediated and innate immunity.

Several studies have evaluated the role of hypomethylating agents given before transplantation, although very few were conducted prospectively. Overall, these investigations showed similar post-transplantation outcomes for patients receiving hypomethylating agents versus those receiving remission-induction chemotherapy, without significant treatment-related toxicity. Moreover, in some cases, an improved outcome was reported for patients who underwent transplantation in complete remission compared with those with active disease at the time of allo-HSCT [5,6].

In the present issue of *Biology of Blood and Marrow Transplantation*, Damaj et al. examined the impact of pre-transplantation treatment with azacitidine in 128 consecutive MDS patients who received reduced-intensity or nonmyeloablative conditioning allo-HSCT. In this series, patients with MDS who underwent upfront allo-HSCT without prior cytoreduction had similar outcomes compared with those who received azacitidine as a preconditioning treatment, in terms of overall survival and cumulative incidence of relapse and nonrelapse mortality, emphasizing the need to perform prospective protocols to delineate the role of a debulking strategy and to identify subsets of patients who may benefit from this approach. In the absence of data from prospective trials on patients with MDS who are candidates for allo-HSCT, the decision to perform a cytoreductive treatment should be made on an individual basis, accounting for clinical considerations with respect to each specific patient. As the rate of complete remission is generally higher with induction chemotherapy compared with the rate for hypomethylating agents, that strategy might still be the best option in selected medically fit patients with immediate availability of a suitable donor. On the other hand, hypomethylating agents could be considered mainly for older patients (including those with comorbidity) who are at risk of losing eligibility for a transplantation procedure as a result of treatment-related toxicity and as a bridging strategy to allo-HSCT in subjects where no donor has yet been identified. Finally, azacitidine and decitabine may be active in patients with a complex karyotype, for whom conventional chemotherapy invariably fails.

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