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COMMENTARY

Allogeneic transplantation in primary refractory AML

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Acquisition of a morphological CR after induction chemotherapy was until recently considered a pre-requisite for allogeneic stem cell transplant (allo-SCT) in patients with AML. However, up to 30% of adults with newly diagnosed AML fail to achieve CR after two courses of intensive chemotherapy, and treatment options for this sizeable patient population have until recently been extremely limited.[1] Consequently, the accumulating evidence that allo-SCT can deliver long-term disease-free survival in a proportion of patients with primary refractory (PREF) AML represents an important advance in the treatment of high-risk AML.[2,3] The paper by Rambaldi and colleagues[4] in this edition of *Bone Marrow Transplantation* makes an important contribution to the field and raises fundamentally important questions concerning both the identification of patients with PREF AML likely to benefit from allo-SCT, and the development of strategies with the potential to reduce the risk of disease relapse following allo-SCT.

Although recognized as one of the most important causes of treatment failure in adult AML, there remains a lack of clarity concerning the definition of PREF AML.[5] While the International Working Group and the European LeukaemiaNet, both define refractory disease as persistent leukaemic blasts following one course of intensive chemotherapy (IC) in either the peripheral blood or the bone marrow in a patient alive 7 days or more following treatment,[6,7] most transplant studies, in contrast, have defined refractoriness as the failure to achieve a morphological CR after two courses of induction chemotherapy.[2,3] There is however a striking paucity of data to inform the definition of PREF AML in either setting. A recent analysis from the UK NCRI study group compared outcomes after IC with or without subsequent allo-SCT receiving at least two courses of induction chemotherapy according to the residual bone marrow blast percentage after each course.[8] This study analysed more than 8 000 patients with newly diagnosed AML and found that patients with greater than 15% residual blasts or a less than a 50% proportional reduction in blast count after course 1 demonstrated similar outcomes to patients who failed to achieve a morphological CR after two courses of induction chemotherapy. Importantly, while patients in both populations were essentially incurable if treated with IC alone (long-term survival rates less than 10%), allo-SCT demonstrated the capacity to deliver long-term survival in up to 30% of such patients. Consequently, utilization of these revised criteria permit early identification of refractoriness after one course of induction whose only curative therapy is an allograft. It will clearly be important to validate these data prospectively, particularly in patients receiving induction regimens containing high dose Ara-C.

While it is now clear that allo-SCT represents the only potentially curative treatment option in PREF AML, the majority of such patients succumb to disease relapse or non-relapse mortality and, consequently, there is an urgent requirement to identify more precisely which patients will benefit from an allograft. The GITMO data[4] published in this edition of *Bone Marrow Transplantation* are therefore of interest, since they broadly confirm the prognostic factors identified in a recent EBMT analysis.[2] Common to both studies is the observation that outcome is superior in patients who proceed to transplant after no more than two courses of IC and those with a lower burden of disease. These data underline the importance of rapid donor identification in order to minimize the number of chemotherapy cycles given prior to allo-SCT, and raise the possibility that either disease burden or some evidence of chemosensitivity may assist in identification of patients more likely to benefit from an allograft. More recently, the demonstration that relapse risk post transplant appears to be strongly correlated with the degree of measurable residual disease in patients who have achieved CR supports the prospective evaluation of the impact of disease burden on transplant outcome in patients with refractory disease.[9] The conflicting data concerning the impact of presentation karyotype on outcome coupled with the absence of studies addressing the influence of genotype, confirms the importance of prospective studies of outcome after allo-SCT, which also incorporate the impact of next generation sequencing on transplant outcome in patients with PREF AML.[10,11] As a general observation, given the likely biological distinction between PREF AML and refractory relapsed disease, coupled with the observed difference in clinical outcome of these two entities to allo-SCT, it will be important to restrict such studies to patients fulfilling a consistent and validated definition of PREF AML ensuring patients with refractory relapsed disease are excluded.

Disease relapse and non-relapse mortality represent the most important causes of treatment failure in patients allografted for PREF AML. While the emergence of more effective supportive care, notably advances in anti-fungal treatment and prophylaxis, coupled with rapid donor identification represent important approaches with the potential to continue to reduce non-relapse mortality, reducing the risk of disease recurrence remains an altogether more stubborn challenge. A number of strategies with the potential to reduce the risk of disease relapse are now emerging. The development of the sequential FLAMSA transplant regimen by the Munich group has been reported to deliver encouraging survival rates in patients with PREF AML and patients in CR1 with adverse cytogenetics although not in patients with refractory relapsed disease.[12,13] The evaluation of this regimen in an ongoing prospective randomized trial by the UK NCRI AML group will hopefully provide further data concerning the potential role of this regimen in patients with PREF AML. Alternative approaches to reducing the risk of disease relapse include the utilization of prophylactic or pre-emptive donor lymphocyte infusion (DLI). However, such an approach is associated with a significant risk of severe GvHD, particularly if DLI is administered within the first 6 months post transplant.[14,15] Given the kinetics of disease relapse in patients allografted for PREF AML, which are

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characterized by a high risk of relapse within the first year post transplant, alternative approaches permitting earlier intervention are required. The elective administration of pharmacological agents post transplant is an area of increasing promise and a number of classes of agents are under investigation. One conceptual approach is to deploy agents with inherent anti-leukaemic activity, which, it is hypothesized, may manipulate the kinetics of disease relapse, providing more time for the donor immune system to generate a GvL effect. Emerging data from patients allografted for FLT3 ITD-positive AML who received maintenance therapy post transplant with sorafenib, demonstrate a remarkably low cumulative incidence of disease relapse compared with historical controls. These data are of great interest and provide a compelling rationale for examination of this approach in an appropriately powered randomized trial.[16] An alternative approach is the utilization of drugs with the potential to augment a graft-versus-tumour response. In this context, the DNMT inhibitors azacitidine and decitabine, in addition to possessing inherent anti-tumour activity, demonstrate tolerability post transplant coupled with intriguing evidence of induction of CD8+ T cell responses directed against candidate tumour Ags, supporting their evaluation as post-transplant maintenance in prospective trials.[17,18] An alternative possibility would be to deploy drugs with a broader immunostimulatory potential, such as the checkpoint inhibitors nivolumab dervalumab (PD1 pathway inhibitors) or ipilimumab (CTLA-4 inhibitor) post transplant, although such an approach clearly has the potential to increase the risk of severe GvHD.[19]

In conclusion, the important paper from the GITMO group in this edition of *Bone Marrow Transplantation* should be viewed as a step on an important journey towards defining curative options for a population of patients for whom no effective treatment options existed. Although registry studies have demonstrated proof of principle of the benefit of allo-SCT in this challenging patient population, further progress is needed in the development of novel allograft strategies to reduce relapse. Such advances will be dependent on the development of prospective, randomized trials utilizing the principle of transplant trial networks, as developed so successfully by the US BMT CTN,[20] without which we will continue to fail this important and, until recently, ignored patient population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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