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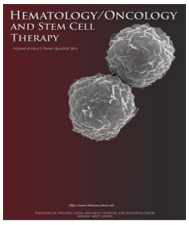

Hematopoietic cell transplantation in hematological malignancies: Hematopoietic cell transplantation in acute myeloid leukemia

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Abstract
Increasing numbers of patients are receiving allogeneic hematopoietic cell transplantation (HCT) for acute myeloid leukemia (AML). Scientific and clinical advances in supportive care, donor selection, and conditioning regimens have resulted in lower transplant-related mortality, extension of care to a wider population of patients, and improvements in survival. Recent era has witnessed an explosive information about the molecular pathophysiology of AML. By early identification of patients at a high risk of relapse, it is expected that a majority of eligible patients will receive HCT in first complete remission. Novel conditioning regimens have been explored to improve transplant outcomes in AML. Currently, a stem cell source can be found for virtually all patients who have an indication to receive HCT. The area of investigation will likely continue to be of interest in terms of optimizing transplant outcomes.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is an effective post-remission consolidation treatment, potentially curative, in patients with acute myeloid leukemia (AML) [1]. Since the first report of a successful bone marrow transplant in 1957, there has been steadily increasing numbers of patients receiving HCT for AML [2]. Worldwide, over a third of HCTs are performed as therapy for AML, more than any other diagnosis, while autologous HCT for AML accounts for less than 3% of activity [3].

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Recent years have witnessed an important role of molecular markers in the management of AML [1,4–6]. In the context of transplant practice, this information adds in to long established challenges about how best to determine their role in selecting patients for HCT. HCT is curative for many patients with AML and assessment of the potential benefit to an individual patient needs to start at diagnosis of AML so that HCT outcome is not compromised by undue delay. This assessment should integrate disease risk, patient comorbidity, and the wishes of the patient to pursue HCT.

HCT in first remission

In general, patients with favorable risk disease will not benefit from HCT in first complete remission (CR1) due to their relatively low risk of relapse balanced against the risk of transplant-related mortality (TRM) [1,7]. Such patients would be candidates for HCT in a second complete remission (CR2) if that were achieved after relapse [1,8]. However, patients aged over 60 may have poorer outcome in general and might benefit from HCT earlier in the course of their disease [1,7,8].

Patients with adverse risk disease with high risks of relapse of about 70–90% should be offered HCT in an effort to improve their chances of survival [8]. Waiting until a second remission is detrimental as a second CR is by no means assured, and outcomes of HCT in CR2 are generally poorer than those of CR1 [1,9,10].

Decisions about HCT in intermediate-risk AML were less clear-cut in the past and nowadays most patients are considered for HCT in CR1. Patient fitness, availability of a sibling donor or an alternative donor, and the availability of a clinical trial as well as the transplant center experience must be considered when making a decision about HCT.

Prognostic scores such as the Hematopoietic Cell Transplant Co-Morbidity Index [11] and the European Society for Blood and Marrow Transplantation (EBMT) score [12] may help to reach a conclusion about the validity of HCT for a given patient. An important point to consider for decision makers is that there should be a survival benefit to HCT of at least 10% for the individual patient compared with standard chemotherapy [7]. The impact of measurable/minimal residual disease (MRD) data may ultimately be the main driver for HCT in CR1 [7,13,14].

HCT in primary refractory disease

Many patients with refractory disease will not be able to receive HCT because they are unable to achieve some sort of remission/response after chemotherapy as a result of resistant or rapidly progressive disease. The outcome of such patients is not well described, despite expansion in the range of novel therapies (plus clinical trial options) available to patients who do not respond to induction/re-induction therapy, and the increasing availability of HCT [15,16]. Approximately 8–30% of selected patients who fail to respond to induction therapy may be salvaged by early HCT [15,16], although very few large series data are available.

Sequential chemotherapy as part of the reduced-intensity conditioning (RIC) regimen may avoid the need for multiple courses of induction/re-induction chemotherapy cycles to achieve remission prior to transplant [17,18]. The traditional preparative ablative regimens for eligible patients with AML include cyclophosphamide combined with total body irradiation (TBI) or the combination of busulfan and cyclophosphamide. The recently published EBMT-Acute Leukemia Working Party (ALWP) registry study showed that patients with refractory AML have similar outcomes after receiving cyclophosphamide plus intravenous busulfan or cyclophosphamide plus TBI. About a third of patients with primary refractory AML achieved long-term survival with intravenous busulfan plus cyclophosphamide or cyclophosphamide plus TBI conditioning regimen (Fig. 1) [16].

HCT in second remission

Relapse occurs in about half of patients with nonpromyelocytic AML depending on underlying risk factors [1,7,18,19]. Five-year survival for patients after first relapse is about 10–30% [19,20]. Advances in the understanding of the biology of the AML stem cell may eventually permit earlier and more accurate identification of patients destined to relapse. Ultimately, HCT will continue to be used more frequently in CR1 for those who are most in need and most likely to benefit.

In the meantime, patients who relapse should be considered for HCT. Survival rates after myeloablative conditioning regimen-HCT (MAC-HCT) for AML CR2 are approximately 40–50% [1,8,18]. However, CR2 and long-term survival are often difficult to achieve and are predicted by the duration of first remission, unfavorable cytogenetics markers at diagnosis, age at diagnosis/relapse, prior therapy including HCT and FLT3-ITD positivity, or the presence of other poor prognostic molecular markers [19].

Conditioning regimen

Substantial improvement has been achieved in the last decades in HCT outcomes in AML owing to improved supportive care and transplantation techniques, and a larger number of HCT recipients are becoming long-term survivors [21].

Traditionally, high-dose intensity has been the standard approach to eradicating AML in HCT [16,22,23]. The commonly used MAC-HCT regimens employed in AML are cyclophosphamide and TBI or cyclophosphamide and busulfan or fludarabine and busulfan [16,24–26].

AML is predominantly a disease of the middle and later years and many patients are ineligible or are not considered for MAC regimen. RIC-HCT may offer a viable alternative to older patients or those with comorbidities [22]. Dose intensity is reduced in an attempt to reduce TRM while potent immunosuppression is exerted to help with the engraftment and graft-versus-leukemia effect. RIC has been widely introduced over the past 15 years and is now widely used for AML patients, particularly in older or heavily pretreated patients and in those with medical comorbidities.

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