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Neoteric advances in the role of hematopoietic stem cell transplantation in AML: A complete review

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Abstract
Hematopoietic stem cell transplantation (HSCT) remains an effective treatment modality for curative post-remission therapy for AML patients. Recent scientific and clinical advances in supportive care, donor selection, and conditioning regimens have decreased transplant-related mortality, an extension of HSCT to elderly patients, and improvements in survival rate. The molecular pathology of AML is studied extensively in the past decade provided with explosive information. Still, relapse remains the most important cause for failure of the treatment. It is expected that a majority of eligible patients can receive HSCT in first complete remission (CR1) by early identification of patients at a high risk of relapse. Newer conditioning regimens have been explored to improve transplant outcomes in AML. In this paper, we review recent advances in HSCT for high-intermediate and low-risk AML in CR1, for relapsed AML and the older patients, and summarize the latest approaches and provide future direction in the transplantation for patients with AML.

Keywords: Acute myeloid leukaemia, Hematopoietic stem cell transplantation

Introduction
Over the last decades, treatment of AML has improved considerably by the introduction of new diagnostic and treatment procedures [1]. The mortality and morbidity rate of AML remains significantly high even with the progress in molecular characterization of the disease, detection of low-level disease, and increasing treatment options [2]. AML treatment is usually achieved by a diverse intensive chemotherapy regimen but this approach fails to bring CR in several patients and a high risk of relapse in a substantial is population demonstrated making HSCT a potentially curative treatment option for AML [3]. For simplicity, all the transplantations using different sources of haematopoietic stem cells, cord blood, bone marrow, and peripheral blood are denoted as SCT in this review.

HSCT is a very complex and effective post-remission consolidation treatment, potentially curative, in patients with AML in which hematopoietic stem cells are infused to restore bone marrow function in leukaemia patients [4]. Hematopoietic stem cells may be obtained from the recipient (autologous-HCT) or a donor (allogeneic-HCT). They are taken from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates [5, 6]. Immunologic compatibility infused between the donor and the patient is important in the allo-HCT whereas it is not an issue in the auto-HCT [7]. HSCT offers a strong graft-versus leukaemia (GVL) effect [1]. Availability of donors has also been a concern, and with improved methods of MRD detection, timely donor availability becomes easier [8].

Worldwide, over a third of HCTs are performed as therapy for AML, which is more than any other disorder, while auto-HCT for AML accounts for less than 3% of activity. Role of molecular markers in the management of AML have been studies extensively in recent years [9]. Over the last few decades, considerable progress had been made in the HSCT with the help of major discoveries in basic science, improved diagnostic procedures, and newer therapies including the development of genetic analysis and MRD monitoring, risk stratification directed treatment, and the establishment of new approaches for haploidentical stem cell transplantation (haplo-SCT) [10, 11]. Growth in the post-therapeutics approaches in the recent years productively reduced the relapse rate of AML after allo-SCT [12].

In this review we discuss the recent advances in HSCT for AML, weighs the benefits of SCT for high-, intermediate- and low-risk AML in CR1, for relapsed AML. Discuss the advances in HSCT for the treatment of AML in older patients, and summarize the latest approaches and provide future direction in the transplantation for patients with AML. The main aim of this review is particularly to recommend indications for HSCT in CR1 and CR2, discuss the advancement in HSCT for the elderly, and the new strategies for preventing and treating relapse.

Indication of HSCT for AML in CR1

Even with all the advancements in medical treatment procedures, achieving a cure for patients with AML remains a challenge. Over 70% of patients will enter CR1 after the induction of chemotherapy [1]. Patients with a favourable risk of relapse balanced against the risk of transplant-related mortality [TRM]. Allo-SCT after myeloblastic conditioning is a curative option for AML patients in CR1. The chances of survival of patients with adverse risk disease at high risk of relapse of about 70-90% should be offered with HCT because no assurance can be given for waiting until CR2 as remission is comparatively poorer than the CR2 [13].

In terms of relapse risk, allo-SCT is accepted as the most effective anti-leukemic treatment option. However, concerns regarding allo-SCT toxicity, allo-SCT and chemotherapy are considered of equivalent benefit in terms of OS. While deciding on HSCT, patient fitness, availability of a sibling donor or an alternative donor, a clinical trial option, as well as the transplant centre experience must be taken into consideration [14].

The current consensus, reflected in treatment guidelines of the National Comprehensive Cancer Network (NCCN), is based on cytogenetic stratification into good-, intermediate-, and poor-risk AML. Patients with good-risk AML in CR1 are recommended chemotherapy, with auto-SCT considered an acceptable alternative. Patients with poor-risk AML in CR1 are recommended allo-SCT. There is no preferred therapy for patients with intermediate-risk AML in CR1: allo-SCT, consolidation chemotherapy, and auto-SCT are considered of equivalent benefit [15].

The benefit of HCT for a given patient can be determined with the help of different methods like prognostic scores such as the Hematopoietic Cell Transplant Co-Morbidity Index and the European Society for Blood and Marrow Transplantation (EBMT). Survival benefit is one of the important considerations to undergoing HCT for AML. Thus, the impact of MRD data may ultimately be the main pointer for HCT in CR1 [16].

HSCT for high- and intermediate-risk AML in CR1

HLA-matched SCT and haplo-SCT methods are the most preferred type of post-remission therapy for high-risk and intermediate AML in CR1. Haplo-SCT provides an immediate donor to patients who lack an HLA-matched donor this increased the adoption rate of haplo-SCT [17].

Recent studies suggest that with the improvements in transplantation, significant RFS and OS advantages of HLA-matched allo-SCT were noted for patients with intermediate-risk AML in CR1. However, HLA-matched SCT is affected by the availability of a MSD or MUD [18, 19]. At that time patients are recommended for allo-SCT from a matched sibling or alternative donor according to National Comprehensive Cancer Network (NCCN) guidelines [13]. In a large study focused on AML both the myeloablative and reduced intensity setting, the OS after haplo-SCT was comparable to that after MUD transplantation for AML [20]. Even though the mechanism underlying the immune tolerance induced by is still unknown the outcomes from different studies of haplo-SCT showing the successful bridging of HLA barriers, support the rationale for considering haplo-SCT as a front-line post-remission treatment option for adults with AML. When taken together both approaches are having comparable outcomes and are a valid treatment option for acute leukaemia patients lacking an HLA-matched donor with high- and intermediate-risk AML in CR1 [21]. Transplantation should not be delayed for such patients. The Acute Leukaemia Working Party of the European Society for Blood and Marrow Transplantation recommended haplo-SCT as a valid post-remission therapy for high-risk AML in the absence of a matched donor or for those in need of an urgent transplant procedure [22].

Haplo-SCT for patients without HLA-matched donors

Patients without an HLA-matched donor are advised to undergo haplo-HCT [22]. Though differences in the outcomes between an MSD and alternative donor are decreased to the improvement in selection criteria and strategies to control alloreactive reactions, relapse is found to be a major problem. Initially, haplo-SCT was performed using the T-cell depleted grafts but it had unacceptable transplant-related mortality caused by delayed immune recovery and other life-threatening infections [23]. Outcomes of haplo-SCT significantly increased with the introduction of post-transplant cyclophosphamide (PTCy) and significantly lowering the incidence of GVHD, NRM, and better overall survival. A recent study data suggest haplo-SCT does not compromise transplant outcomes in the absence of an MSD when transplant is urgently needed and a MUD may take too long to be found for the patient. Application of intensified conditioning regimen by addition of anti- thymoglobulin (ATG) and infusion of conventional T cells and regulatory T cells after T cell-depleted grafts and selective αβ T-cell depletion has been found to increase the outcome [24]. Different protocols are applied in different countries in different cases and they are in continuous development to address the limitations. In Asia, the GIAC (Beijing) protocol is the most commonly applied to both haplo-SCT and HLA-matched transplants. Umbilical cord blood is another alternative source for allo-HSCT [25]. Haplo-SCT have lower initial costs and require less technical expertise, while HCT-matched transplant may result in faster recovery, with the near absence of chronic GVHD; further studies are important in this field to improve the outcomes of HSCT [26].

Indication of HSCT for AML in CR2

Relapse occurs in about half of patients with non-promyelocytic AML depending on underlying risk factors [27]. There have been no large prospective studies, either truly randomized or based on donor availability, that have compared outcomes of further chemotherapy with allogeneic HCT for patients with AML in CR2. Retrospective studies have analyzed variables anticipating endurance among adults with recurrent AML. Five-year survival rate for patients after first relapse is around 10–30% [28]. Advances in the comprehension of the science of the AML stem cell may eventually permit prior and more precise identification of patients bound to relapse. Ultimately, HCT will keep on being utilized more frequently in CR1 patients who are most in need and most likely to benefit. Meanwhile, patients who relapse ought to be considered for HCT. Survival rates after myeloablative conditioning regimen-HCT (MAC-HCT) for AML CR2 are approximately 40–50% [29]. However, CR2 and long-term survival are often difficult to achieve and are predicted by the duration of first remission, unfavourable 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 [30]. Breems *et al* developed a prognostic index that predicted

outcome after relapse based on four factors: length of first remission, age at relapse, cytogenetic risk factor at diagnosis, and whether or not the patient had received a transplant in CR1. Patients are then divided into lower-, intermediate-, and higher-risk groups, and in all three groups, those patients who were treated with HSCT fared better than those treated with alternative therapies [31]. However, with improved ability to monitor MRD, it may become possible to monitor patients with disease in remission, and, based on persistence or re-emergence of MRD, proceed to transplantation in a timely manner. Auto-SCT has been used infrequently in recent years but may be considered as post remission therapy in patients who are MRD-negative and do not have high-risk disease. Consolidation with auto-HCT may therefore be an option for patients in MRD-negative intermediate-risk AML in CR1 who do not have allo-HCT options or in acute promyelocytic leukaemia in CR2 [32].

Relapse after HSCT

Even though HSCT is one of the most potent treatment methods mediated by the GVLE, the proportion of patients with relapse after HSCT is significant. Up to 70% of AML patients will relapse based on disease risk and status at transplant. Thus, relapse is the most common failure of HSCT for AML [33]. The prognosis for the patient is dismissal as the probability of long-term survival is less than 20% in patients who relapse early of the HSCT. Therefore, several approaches have been studied for the prevention of disease relapse, especially for high-risk AML. Still, there is no proper preferred management of relapse after HSCT [33, 34]. Conventional treatment options include supportive care, chemotherapy, the second HSCT using the same or alternative donor, donor lymphocyte infusion (DLI), and cytokines, still, the second HSCT after the failure of the first HSCT has limited efficacy in patients with AML. Data from previous studies suggest that the duration of remission after first HSCT is the most important prognostic factor for relapse. In a recent study Hypomethylating agents, such as azacitidine (AZA) and decitabine, were found to have a direct anti-leukemic effect in patients with AML independent from a distinct molecular phenotype and have both been tested after HSCT [35]. Different ongoing studies are exploring other targets as maintenance therapy after HSCT, such as the isocitrate dehydrogenase (IDH) inhibitors for patients with IDH-mutated AML. A reasonable outcome can be expected in selected patients, whose duration of remission after the first HSCT is 1 year, and who achieve CR before a second HSCT. A maintenance therapy with low-dose venetoclax plus AZA has been added to explore the potential to decrease relapse rate post-transplant [36]. Even though DLI has limited efficacy in patients with AML, prevention of relapse could potentially be achieved without prolonged therapy post-transplant by remission induction using cellular therapy after HSCT to patients having the goal of consolidation of response. The selection of second HSCT versus DLI is completely individualized based on donor availability and achievement of remission before DLI or second HSCT. It is recommended to have an aggressive administration of immune suppressants in all high-risk patients with AML. Myeloid surface antigen targeting therapy on CD33 and CD123 was found to impact normal haematopoiesis and represent a major limitation to the use of chimeric-antigen-receptor-modified T cells (CAR-T). Another promising approach is the pre-activation of Natural Killers (NK) with interleukins which results in a memory-like NK cell differentiation, enhancing the adoptive allogeneic NK cell therapy to prevent relapse [37].

Thus, more researches are needed to understand the biology of relapse and to develop a novel therapy for this major problem.

Extending HSCT for Elderly

The median age of patients getting diagnosed with AML exceeds 65 years. With the advancement in age the adverse association with non-relapse mortality increases. With their poor performance status and high comorbidity risk, they are usually not recommended for HSCT. However recent improvements in graft-versus-host disease prophylaxis and supportive-care measures along with the application of reduced-intensity preparative regimens have expanded the application of HSCT to patients up to age [38]. Although the CR rate is around 50-60%, the 2 years survival is only in the magnitude of 10-20% in comparison with approximately 50% for patients younger than 50 years. This is mainly due to the difference in disease pathology and an over-representation of adverse prognostic factors present in elderly AML [39]. Improvements in conditioning regimens, supportive care, and older fit patient's intensive conditioning regimens have allowed the transplantation of older patients more beneficial. Numerous regimens have been described for the elderly varying from truly non-myeloablative (single dose TBI) to those that cause profound cytopenia (Fludarabine/Busulphan) requiring blood and platelet support [40]. Recently, the introduction of venetoclax-based treatment for older patients who are considered to be ineligible for standard induction chemotherapy was found beneficial. High toxicity and mortality rates, uncertainty regarding outcomes of HCT, lack of comparative data on the outcomes of HCT versus nontransplant treatments in older patients, and insurance coverage are some of the barriers that limited the use of HSCT until 2000 to young and medically fit patients. A recent study of the donor-versus-nondonor comparison showed 35% Progression-free survival and 38% overall survival rates were noted for those older patients who underwent HSCT. The proportion of HSCT in patients over 70 years old has increased considerably from 0.1% in 2000 to 3.85% in 2013 to more than 7% in 2016, AML being the main indication. Patients ≥65 years old undergoing auto-HSCT increased from 3.4% (443 out of 13,163 autologous HSCT) in 2000 to 9.8% () in 2014. Allo-HSCT activity increased from <1% (37 out of 6413 allo-HSCT) in 2000 to 6.7% (1057 out of 16,765 allogeneic HSCT) in 2014 [41]. Approximately only 50% of patients over 60 years who achieve CR are evaluated promptly by the transplant team, with approximately a third of those who do not receive a consultation are considered too ill for the procedure which decreases the treatment outcome. Treating malignancies in elderly patients less aggressively before HSCT may potentially increase the risk of disease relapse. Lack of MSD or MUD is also one of the main reasons for failure to undergo HSCT [42]. The lack of an optimal conditioning regimen for this population is a major reason for decreasing the HSCT rate. Various studies are going on for framing an optimal regimen for patients above 50 years. With improvements in the quality-of-life supportive care, HSC mobilization, use of RTC and RIC regimens, and longevity of the general population have contributed to increasing the numbers of patients older than 50 years who are now actively undergoing

HACT. With sustained improvement in these areas, and as the population ages, these numbers will only continue to increase. And performance status could lead to higher transplant-related morbidity and mortality. [38] It is now clear that age alone should not be used to exclude patients from undergoing transplantation. Comorbidities and performance status outweigh age in predicting how well intensive preparative regimens will be tolerated. Allogeneic transplantation is an established standard of care for older patients with AML.

Conclusion

Critical advancements had been made in the past decade in HSCT for AML which contributed to bringing up HSCT as a good post-remission treatment strategy for high and intermediate-risk AML patients. HSCT is now done to all patients in need regardless of age or donor availability. The Risk stratification of MRD monitoring pre- or post-transplant is being progressively explained which will permit patients to settle on better-informed choices and doctors choose to whom to offer this treatment and potentially how to treat these patients. Which effectively defines a subgroup of AML patients who have a high relapse risk. Patients with steady MDR show a dire need for transplantation. Steady MRD before allo-HSCT generally shows the dire requirement for transplantation. Transplantation using alternative donors, especially haplo-donors will ideally result not just in more patients really getting this life-saving method, yet in addition, more to be relieved from their disease.

Prevention of relapse and prophylaxis or maintenance therapy on risk stratification especially for high-risk AML patients, including those with high-risk cytogenetics or molecular markers, persistent MRD, and those who responded poorly to prior therapy, will lead to more accurate therapy, reduce the risk of relapse and improve survival after allo-SCT. This is presently the principal need, and the current strategies for managing patients with relapsed AML are still challenging, future studies will probably reveal insight into what will be the best treatment strategies for these patients.

Newer less toxic conditioning regimens increase the application of HSCT for elder patients, and the use of haploidentical donors has shown as an effective approach for the elderly, which will probably keep on driving the utilization of transplantation for patients with AML later on. Newer studies concerning antibody-based or cell-based treatment may assist with further developing treatment outcomes in AML patients.

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