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Current Approach to Allogeneic Hematopoietic Stem Cell Transplantation

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1. Introduction

1.1. Aims of chapter

In this Chapter we will discuss the indications for allogeneic hematopoietic stem cell transplantation (HCT). We will focus on the appropriate timing of this procedure for the different hematologic malignancies. We reviewed past approaches using myeloablative conditioning and present some of the newer reduced intensity therapies. Allogeneic transplantation is one of the first known uses of stem cells. Born from the need to rescue damaged bone marrow, it was first used in the setting of aplastic anemia and acute leukemia. Over the years, the technique has changed steadily and support for this procedure has improved immensely. Today this procedure is used to treat multiple malignant blood disorders, bone marrow failure syndromes, immune deficiency syndromes, and hemoglobinopathies. This chapter will focus on the malignant hematopathies. Another aspect of this Chapter will be to review the conditioning regimens used in allogeneic HCT.

2. Indications for transplantation

2.1. Acute myeloid leukemia

Acute myeloid leukemia (AML) Is heterogeneous group of clonal disorders. The disease can present at all ages, but this disorder is most commonly seen in older patients, with a median age at presentation of 67 years. [1] AML can present in a de novo fashion or can progress from antecedent hematological disorders, including myelodysplasia and myeloproliferative neoplasms (secondary AML), or after prior exposure to chemotherapy and/or radiation

therapy (treatment-related AML). Patients who are deemed fit enough to receive therapy can be given various combinations of chemotherapy to induce a remission of the disease. The most common induction therapy is that of cytarabine given as a continuous infusion for 7 days in combination with an anthracycline for 3 days (the 7+3 regimen). This approach has been used for over 40 years with very good results [2-6]. Attempts to improve on this by adding other therapies have not resulted in improved outcomes. More recently, dose intensification of the anthracycline has resulted in improved complete remission (CR) rates and more importantly overall survival (OS) for patients below the age of 65 years [7-10]. Although current induction chemotherapy regimens are successful in obtaining a CR with rates approaching 70-80%; without consolidation chemotherapy, most patients will relapse and die of the disease. Because of the high risk of relapse, AML is the leading indication for allogeneic transplant.

There are several significant prognostic factors that will affect the patient's ability to achieve a CR. The most important is that of age. Other recognized factors are cytogenetic risk profile, molecular mutations, prior exposures to chemotherapy and radiation therapy, and antecedent hematological disorders. [11] These factors also impact on the patient's ability to maintain long-term remission and be cured of the disease. More recently, molecular mutations have come to the forefront in determining overall prognosis. These mutations include nucleophosmin-1 (*NPM1*), fms-like tyrosine kinase-3 (*FLT3*), *CAAT* enhancer binding protein alpha (*CEBPA*), and c-KIT. Retrospective analyses have shown that, in cytogenetically normal individuals, *NPM-1*and *CEBPA* have improved survival in comparison to those with other mutations [12]. *FLT3-ITD* negatively impacts all cytogenetic and molecular risk groups [12-14]. The European Leukemia Network proposed a new prognostic designation based on both accepted cytogenetic and molecular abnormalities [15]. More recently, newer molecular mutations have been described which in the future may help further delineate the prognostic risk [14]. A recent retrospective study from the Center for International Blood and Marrow Transplantation Research has also re-classified the cytogenetic risk for those patients proceeding to transplantation. [16]

The potential for relapse and the patient's clinical status are factors that determine the consolidation approach. Currently, prognostic factors are used to decide on the most appropriate consolidation therapy for patients with this disease. Multiple studies have demonstrated that patients with the core binding factor AML (*AML/ETO* and *RUNX/RUNX1*] have an excellent response to induction and consolidation chemotherapy. [17] For these patients, allogeneic hematopoietic cell transplantation (HCT) should be reserved for relapse of the disease. Contrary to this, an unfavorable risk profile usually portends a very poor prognosis. Patients with unfavorable cytogenetics (complex cytogenetics, single or multiple monosomal karyotype, *MLL* (11q23) [18]) respond very poorly to induction chemotherapy, and remissions are usually shorter. In patients with cytogenetically normal AML, the presence of *FLT3, MLL, DNMT3A*, and others have also demonstrated shorter disease-free survival (DFS) and OS [12, 19-21].

For more than 15 years, the standard of consolidation therapy for patients with AML in first CR (CR1) has been intensive chemotherapy using high-dose cytarabine. However, this approach is only effective in patients who are below the age of 60 years and have favorable risk cytogenetics [22]. Initially, allogeneic HCT was used as salvage therapy for patients who failed conventional chemotherapy. The sentinel paper was published by Thomas et al., who used allogeneic HCT as

salvage therapy for 100 patients who had relapsed or refractory AML. The 13% OS gave great hope to the use of this modality [23] Subsequent reports from the same group promoted the use of allogeneic HCT as front-line consolidation therapy [24-27]. Randomized trials using genetic randomization demonstrated an improved DFS in patients receiving allogeneic transplantation [28]. Although the US Intergroup trial demonstrated there was no advantage to allogeneic transplantation compared to intensive chemotherapy in patients with de novo AML below the age of 60in CR1[29], more recent studies have demonstrated effectiveness of this approach. The US Intergroup trial had a significant flaw in that a large number of patients allocated to transplantation did not receive the intended therapy. However, retrospective subset analysis did note a significant improvement in patients with unfavorable-risk cytogenetics [30]. A meta-analysis of five trials performed by Yanada et al. (3100 patients) demonstrated an improved OS for patients with unfavorable-risk cytogenetic profiles. Until recently, there was no consensus as to how to treat patients with intermediate risk AML in CR1. Meta-analyses by the HOVON-SAKK group (925 patients) and a systematic review by Koreth et al. (6007 patients) all showed an improved OS for patients with intermediate- and unfavorable-risk cytogenetic profiles. These analyses were limited to related donor transplantations and to younger patients. [31-33] A Markov analysis of 2090 Japanese patients with *de novo* AML in CR1 confirmed the appropriateness of a related or alternative donor HCT over chemotherapy in this setting but not for patients without a matched donor [34]. A recent evaluation of patients with AML with a monosomal karyotype also demonstrated a benefit of allogeneic HCT in this group. [35] The appropriate intensity of the conditioning regimen for patients with myeloid malignancies in first CR is currently being evaluated by the Bone Marrow Transplant Clinical Trials Network (BMT-CTN) in a prospective randomized multi-center trial (0901).

About two-thirds of the patients with AML will not have a matched related donor (MRD). For these patients, matched unrelated donor (MUD) transplantation is an option particularly for those patients with unfavorable-risk profiles. A retrospective study from the CIBMTR reviewed MRD, MUD and partial MUD transplantation in patients with unfavorable-risk cytogenetics. Here the investigators found that MRD and MSD had similar leukemia-free survival and OS. The benefit was not seen in partially MUD or those over the age of 50 years. Other studies have demonstrated the similarities in outcomes compared to sibling transplants. [36-39] The trade-off is an increase in graft versus host disease (GVHD) and its associated mortality for increased disease control (graft versus leukemia effect). The only randomized trial using MUD was a German AML 01/99 trial. Here patients < 60 years of age with high-risk features (non CBF AML and > 5% blasts on the day 15 bone marrow biopsy) who did not have a MRD were randomized to a MUD allogeneic versus autologous HCT. The patients who had a MUD HCT had a superior OS to those treated with an autograft. [36]

Improvements in human leukocyte antigen (HLA) sequencing and selection of donors have reduced the effect of GVHD in this setting. [40] Better treatment options for the conditioning regimen and preventing and treating acute GVHD have provided more confidence in the procedure. [41] Tacrolimus and methotrexate are widely used as GVHD prophylaxis with or without anti-thymocyte globulin (ATG). Newer GVHD prophylaxis combinations such as sirolimus and tacrolimus [42-44], and ATG-Fresenius have reduced the incidence of both acute and chronic GVHD without impacting relapse or OS. [45]

A major challenge which remains is the older patient conventionally described as older than 60 years of age. [46] Interestingly in the case of allogeneic transplantation the threshold for the older patient is closer to 50 years. These patients are affected by worse prognostic factors, comorbidities, and intolerance to therapy. [47] However, multiple reports have demonstrated that transplant is possible with the appropriate conditioning regimen utilizing a non-myeloablative or reduced intensity dosing of therapy. [48]Although no randomized trial between conventional therapy and HCT has been reported to date, results suggest that outcomes are better than conventional chemotherapy for this group of patients. [49, 50] More on this will be discussed later in this chapter.

3. Chronic myeloid leukemia

Translocation between chromosomes 9 and 22 (t(9;22) or Philadelphia chromosome (Ph+) leads to an abnormal fusion protein (BCR-ABL) with dysregulated tyrosine kinase activity resulting in a myeloproliferative disorder characterized by abnormal white cell production known as chronic myeloid leukemia (CML). Without therapy, CML has a predictable progression from a chronic phase (CP) to the more advanced accelerated (AP) and/or blast (BP) phases.Since the introduction of tyrosine kinase inhibitors (TKIs) in October 2001, allogeneic hematopoietic stem cell transplant (HCT) has shifted from a first-line treatment option and to a second-, third-, or even a fourth-line option [51, 52]. The number of allogeneic transplantations in the post-TKI era has significantly decreased in CP CML patients; however, the number of patients transplanted in AP or BP remains the same [53].

Given the excellent results of studies using TKIs as upfront treatment for CP CML, a randomized trial to compare HCT to TKIs has not been performed and has not been justified. The use of TKIs as standard front-line therapy has been supported by few retrospective and/or genetically randomized studies [54, 55]. Imatinib mesylate has activity against progenitors and mature cells but has limited activity against leukemia stem cells [56, 57]. Unfortunately, the majority of patients achieving remission with imatinib mesylate continue to have molecular evidence of persistent disease [58]. Even in those patients who are treated for over 4 years with imatinib mesylate and in remission, BCR-ABL + stem cells are still detected in bone marrow [59].

Allogeneic HCT remains a curative approach with long-term molecular remissions, seen only rarely with TKIs, as the mechanism of the graft versus leukemia effect relies on the presence of antigens on leukemia stem cells [60]. Current indications of transplant are reserved, according to the European leukemia net [61], to the following CML subjects:

• At diagnosis for patients presenting in AP or BP

• Imatinib failure (after second-generation TKI pretreatment) progressing to AP or BP

• Patients with TKI resistant mutations such us T315I

• All patients failing second-generation TKI treatment.

Definitions of imatinib mesylate failure are: 1) a lack to achieve complete hematological remission at 3 months; 2) failure to achieve any cytogenetic response at 6 months; 3) persistence of more than 35% Ph+ metaphases at 12 months; or 4) less than complete cytogenetic response at 18 months. Resistance to imatinib mesylate is defined as loss of complete hematological response or complete cytogenetic response or development during imatinib mesylate treatment of an ABL kinase mutation leading to its resistance.

In summary, the present use of allogeneic HCT is reserved for patients with poor response to TKIs and/or those with advanced disease. Saussele et al. reported an interim analysis from the German CML Study group IV in patients who underwent a 5-arm randomization where 84 patients underwent allogeneic HCT as second-line therapy after imatinib mesylate failure [62].The 3-year survival in CP was 91%, with 59% in AP. The majority of patients (88%) achieved a molecular remission and reported a very low treatment-related mortality (TRM) (8%).The authors at that time concluded that allogeneic HCT could become the preferred second-line option after imatinib mesylate failure for suitable patients with a donor.

Because most patients are treated with TKI before transplant, it is important to understand whether this strategy could potentially jeopardize HCT results. Retrospective comparison of patients treated with imatinib mesylate pre-HCT compared with historical controls showed no effect on OS, progression-free survival, and non-relapse mortality [63]. Based on a Center for International Blood and Marrow Transplant Research (CIBMTR) study reported by Lee et al., imatinib mesylate before HCT in patients with CP CML leads to a better survival but no statistically significant difference in TRM, relapse, and leukemia-free survival and no differences reported in advanced CML. These results are re-assuring for the majority of patients that today are treated with TKIs prior to allogeneic HCT [64]. In summary, imatinib mesylate use before HCT has been shown to not increase toxicity and/or engraftment of subsequent allogeneic HCT [65-68]. Interestingly, risk of chronic GVHD may be decreased with the use of imatinib mesylate pre-HCT [67] and may potentially target GVHD-related fibrotic features if they developed post-HCT[69, 70]. In addition, the use of TKIs before HCT has been shown to improve outcomes if a patient achieves major cytogenetic remission compared to those who do not [67].

Imatinib mesylate as frontline for CP patients leads to a major cytogenetic response rate of 89% and OS of 86% at 7 years. Unfortunately, secondary resistance develops at a rate of 4% per year for CP [71] and 70-90% in AP/BP phases [72-74].With the development of second-generation TKIs (dasatinib and nilotinib) and the compelling results shown of a major cytogenetic response of up to 45% for imatinib mesylate failure patients [75, 76], recommendations for HCT are reserved for patients who have failed not only imatinib but also second-generation TKIs[61]. Front-line therapy with second-generation TKIs for CP CML it is now warranted [77, 78].

The majority of mutations are susceptible to second-generation TKIs, but some are resistant not only to first-generation but also to all second-generation TKIs. Threonine-to-isoleucine substitution at position 315 of Bcr-Abl fusion protein (T315I mutation) is well established to confer resistance to most TKIs [61]. Multiple reports have shown encouraging results with allogeneic HCT in patients for whom allogeneic HCT is recommended earlier in the disease

course [79-82]. The results from efforts to develop third-line TKIs to target resistant mutations are encouraging. On September 4, 2012, the U.S. Food and Drug Administration approved bosutinib tablets (Bosulif®, Pfizer, Inc.) for the treatment of CP, AP, and BP Ph+ CML in adult patients with imatinib-resistant mutants of Abl or intolerance to prior therapy (http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm318203.htm).   The pivotal PACE trial data have shown robust anti-leukemic activity of ponatinib in patients with CML at all stages, who are either resistant or intolerant to dasatinib or nilotinib or who have the T315I mutation [83].

For advanced patients, TKIs have facilitated a bridge to the HCT procedure. Long-term outcomes with imatinib mesylate for AP CML are only up to 47 months and 7 months for BP CML[84-86] with a 2-year OS of only 47% and 16% for patients in AP and BP, respectively [87]. The goal for advanced disease patients is to achieve a second CP in order to proceed with allogeneic HCT. Because the rate of mutations is highly increased for these patients, assessment of mutation profile is quite vital to guide TKI selection. Allogeneic HCT represents the best chance for long-term success or even cure in AP/BP CML [88]. Given selection bias, only unfavorable risk CML patients should proceed to allogeneic HCT these days. Reduced intensity conditioning (RIC) regimens have facilitated transplant access to more frail populations; unfortunately a higher relapse risk remains due to aggressive disease and reduced chemotherapy [89-92]. Therefore, there is a need for strategies to improve current leukemia-free survival post-allogeneic HCT.Measurement of minimal residual disease has become particularly important as it has been shown that patients who have increased BCR-ABL expression levels (more than 10^{-4}) experience higher relapses rates [93-95]. Serial BCR-ABL RT-PCR is considered a standard practice and can be used to guide clinical interventions. It is not unusual to decect low level molecular disease; however treatment should be reserved for those patients whose markers increase over time or remain persistently positive. Maintenance therapy with TKIs post-transplant has proven to be tolerable [96]. Carpenter et al. reported that prophylactic use of imatinib mesylate for 1 year in Ph+ acute lymphoblastic leukemia (ALL) and CML lead to a low risk of relapse (18%) [97]. Other groups have also shown that use of TKIs post-HCT can help to minimize relapse risk [98, 99] and/or effectively control relapse post-HCT [100]. Experience of second-generation TKIs in the post-HCT setting are currently being explored in clinical trials (http://clinicaltrials.gov/ct2/show/NCT00702403). An early approach is to consider maintenance with a TKI in those who have shown activity prior to transplant, and BCR-ABL mutation analysis should guide TKI selection. Role of TKIs in the post-HCT setting should also be studied in the context of donor lymphocyte infusions (DLI) as immunotherapy, as it has been shown to be effective for management of early relapse in the pre-TKI era. The synergistic role of TKI with DLI should be further explored [101].

In conclusion, several effective drugs are available today to treat CML upfront during the chronic phase of the disease. Careful monitoring for BCR/ABL and mutation analysis are warranted to determine which patients will be in need of second- or third-line therapies. For patients with advanced-phase disease, HCT remains the option of choice, using a TKI to bridge to allogeneic HCT.

4. Myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is a clonal stem cell disorder that results in a heterogeneous group of disorders characterized by excessive apoptosis of bone marrow cells. It is character‐ized by low peripheral counts, marrow dysplasia, proliferation and loss of differentiation of hematopoietic progenitors with a median age of 60-70 years at presentation. Mortality is related to bone marrow failure and evolution to secondary AML [102]. Despite development of novel therapeutic agents over the past decades, allogeneic HCT remains the only curative option in this disease. To date, HCT indications, timing, and incorporation of novel drugs before and/or after HCT remains a challenge. Additionally, whether novel treatment agents for elderly MDS patients should be pursued instead of allogeneic HCT remains unanswered. A recent retrospective cohort analysis suggested a survival advantage for allogeneic HCT (39%) compared with azacytidine (23%) therapy in medically fit patients with high-risk MDS of 60-70 years of age [103]. The German MDS study group is testing 5-azacytidine compared to allogeneic HCT in a prospective study for patients with International Prognostic Scoring System (IPSS) intermediate II or high-risk up to age 70 years (NCT01404741).

The IPSS system is based on peripheral blood cytopenias, cytogenetics, and marrow myeloblast percentages and is generally used to identify HCT candidates [104]. A limitation of the IPSS score is that it does not take into account patient age; therefore, development of other scoring system has been proposed. The World Health Organization classification and the World Health Organization classification–based Prognostic Scoring System have both shown relevant prognostic values in post-HCT MDS outcome for OS and relapse [105, 106]. In a recent analysis of 1915 patients with MDS, only 26% had primary MDS without prior therapy that could be classified with the IPSS system. A multivariate analysis of prognostic factors determined worst outcome for poor performance, older age, thrombocytopenia, anemia, increased bone marrow blasts, leukocytosis, chromosome 7 or complex (≥3) abnormalities, and prior transfusions. This new MDS prognostic model divided patients into 4 prognostic groups with significantly different outcomes with the advantage that it accounts for duration of MDS and prior therapy and is applicable to any patient with MDS at any time during the course of MDS [107].

A Markov decision analysis model designed by Cutler et al. showed that for low and inter‐mediate-1 IPSS groups, delayed transplantation maximized OS; for intermediate-2 and high IPSS groups, HCT at diagnosis maximized OS and was associated with maximal life expect‐ancy [108]. In contrast, other studies have suggested that younger patients with less advanced disease have a better transplantation outcome [105, 109]. An evidence-based review consensus by the American Society of Blood and Marrow Transplantation recommended early HCT for patients with IPSS intermediate-2 or high-risk at diagnosis and selected patients with lower risk disease at diagnosis who have poor prognostic features (such as older age, refractory cytopenias, and/or transfusion dependence) [110]. The American Society of Blood and Marrow Transplantation recommendations are limited as they are based on studies using IPSS score instead of more comprehensive ones; in addition, it only applies to newly diagnosed patients and excludes MDS subjects with treatment-related MDS/t-AML and chronic myelomonocytic leukemia subtype [111].

Factors that determine risk of progression from MDS to t-AML and that more accurately predict disease progression and HCT indication have been studied in the context of MDS phenotype and/or disease biology. With a patient group of 692 MDS patients, a European group analyzed outcome and reported worse OS and relapse rates based on poor cytogenetics [112]. In a multivariate analysis by Chang et al. comparing patients with secondary MDS or transformed to AML(t-AML) to de novo MDS, no significant differences in outcome were shown between the 2 cohorts and overall inferior outcome was shown in patients with secondary MDS/tAML, as the majority of advanced patients has increased frequency of high-risk cytogenetics [113]. Flow cytometric scoring system is predictive of post-HCT outcomes even after adjusting for risk factors such as marrow myeloblast percentage and IPSS score [114]. Cases of MDS classified as AML by microarray-based GEP assays had more aggressive disease and more rapid progression to AML, whereas MDS cases classified as "none-of-the-targets" had a more indolent clinical course [115]. Tumor necrosis factor-α polymorphisms affect HCT outcome in a disease-dependent manner [116]. There are many others risk categorization factors in MDS like FISH, spectral karyotyping, and mutation or deletion analyses [117-119], although clinical significance remains controversial [120]. Development of a revised scoring system is warranted to guide the decision-making process to recommend HCT for such a diverse and heterogeneous clonal condition.

Clinical evolution of disease such us increased transfusion, recurrent infections or bleeding may also precipitate the decision to proceed with HCT. Elevated serum ferritin levels, as reflection of increased body iron storage, have been showed to be associated with decreased OS and DFS, acute GVHD, and infections with myeloablative HCT [121, 122]. Ferritin levels should guide the need of chelation therapy prior to HCT and/or may guide conditioning regimen selection [123]. Co-morbidity as a determinant of HCT outcomes has been elegantly studied by Sorror et al. [124] and applied in the context of AML-MDS [125]. This group investigated the role of comorbidities, among other risk factors, in stratifying and comparing patients conditioned with non-myeloablative or myeloablative regimens. Patients with low HCT-CI scores and either low or high disease risks had probabilities of OS at 2 years of 70% and 57% after nonmyeloablative conditioning compared to 78% and 50% after myeloablative conditioning, respectively. Patients with higher HCT-CI scores ($\geq$ 3) and either low or high disease risks had probabilities of OS of 41% and 29% with nonmyeloablative conditioning compared with 45% and 24% with myeloablative regimens, respectively. After adjusting for pretransplantation differences, stratified outcomes were not significantly different among patients receiving nonmyeloablative compared with myeloablative conditioning, with the exception of lessened nonrelapse mortality (hazard ratio, 0.50; P =.05) in the highest risk group. This group concluded that patients with low comorbidity scores could be candidates for prospective randomized trials comparing nonmyeloablative and myeloablative conditioning regardless of disease status [125]. An additional scoring system has also emphasized the negative influence of comorbidities on HCT outcomes [126].

Based on published literature, patients up to 70 years of age can tolerate allogeneic HCT and age per se should not be a criterion for patient selection and/or intensity of the conditioning regimen rather than performance status, comorbidity, and disease status [127].Results from a

European Group for Blood and Marrow Transplantation (EBMT) report suggested that age is not a contraindication to HCT; the cumulative incidence of non-relapse mortality at 4 years was 36% in the 50- to 60-year-old patient group and 39% for the group 60 years or older (P =.39], with OS not differing between the groups (34% versus 27%, P =.2). In a multivariate analysis for OS, only advanced stage of the disease at time of transplantation (hazard ratio = 1.55] was associated with inferior survival [128]. Similar results were reported by the CIBMTR; in a multivariate analysis, they showed that OS was inferior with low performance status, mismatched unrelated donors, and unfavorable cytogenetic, but age had no impact [129].

To facilitate HCT access to the majority of MDS patients, a RIC regimen has been developed. The rationale for RIC is to promote graft-versus-leukemia effect without excessive toxicity to minimize TRM. Many RIC regimens have been developed using combinations of busulfan with cyclophosphamide or fludarabine, fludarabine with cyclophosphamide, or low-dose total body irradiation (TBI) (200cG) among others versus the more intense or conventional regimens based on TBI or busulfan/cyclophosphomide-based regimens. Unfortunately, due to the lack randomized prospective trials, it remains unknown which conditioning regimen should be chosen and how "intense and/or reduced" the conditioning should be. In general, the highest tolerable regimen should be chosen since reduced intensity is associated with a higher relapse rate, as suggested in multiple retrospective studies [130-136]. RIC HCT with fludarabine/melphalan and tacrolimus/sirolimus-based GVHD prophylaxis resulted in a relapse incidence of 20.9% with low-grade acute GVHD [137]. An ongoing prospective randomized trial comparing RIC versus myeloablative conditioning has been developed to address selection bias for allogeneic HCT by the EBMT group (NCT00682396).

Disease relapse post-HCT remains a critical issue as long-term outcome is compromised. Approaches to tackle this issue include pre-HCT induction chemotherapy and/or novel agents for high-risk patients or drug maintenance to prevent relapse pre-emptively post-HCT, as opposed to strategies for relapse treatment. Still debatable to date is whether pre-HCT induction chemotherapy has a role to minimize relapse post-HCT for patients with advanced MDS. Unfortunately, this remains unanswered due to lack of randomized and/or definitive data [138-141]. Introduction of novel agents in the pre-HCT setting seems feasible, associated with less toxicity, and may allow for similar post-HCT outcomes when compared to chemotherapy [142]. Another approach is to use low-dose 5-azacytidine as maintenance post-HCT. De Lima et al. determined that the optimal combination was 32 mg/m^2 given for at least 4 cycles, with reversible thrombocytopenia as the dose-limiting toxicity. The authors suggested that this treatment prolonged event-free survival (EFS) and OS [143]. In the event of disease relapse post-HCT, azacytidine administration is feasible and may induce durable remissions [144]. DLIs can result in complete remission in some patients, but long-term survival is infrequent [145]. The Azarela trial, a prospective multicenter phase II trial, was developed to test whether a combination of 5-azacytidine and DLI would benefit patients with relapsed MDS post-HCT. Overall response rate was 64% with 20% achieving and staying in CR, 12% achieved partial response, and 32% showed stable disease with low incidence of acute GVHD occurring (24%). These data suggest that salvage therapy with combination azacytidine + DLI is feasible and has significant anti-leukemic activity in relapsed MDS post-HCT [146].

In conclusion, several factors influence HCT indication and timing for MDS patients. Incorporation of evolving prognostic indicators might help to develop treatment algorithms to decide the appropriate timing for allogeneic HCT. The ultimate objective is to proceed with HCT when non-transplantation approaches would result in outcomes lower than those that would result with allogeneic HCT. Currently, novel HCT approaches are allowing the consideration of older patients and/or the use of alternative donors to treat MDS. A remaining question is how to incorporate HCT for those patients that are achieving a CR with hypomethylating agents and/or other novel agents. Development of prospective clinical trial may help to elucidate these questions within a fast evolving field.

5. Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a bone marrow clonal disease characterized by the rapid proliferation of immature lymphoblasts. Despite initial control of the disease, the majority of adult patients will relapse with poor long-term outcomes. Allogeneic HCT has been used as a salvage therapy for both relapsed patient and high-risk patients with ALL early in the disease process. The availability of unrelated donors and/or alternative stem cell sources and the development of RIC transplants have resulted in far more allogeneic transplants being performed for this rare disease. For adults with ALL, indication and timing of allogeneic HCT remains debatable as defining the optimal role for allogeneic HCT has been limited by the lack of prospective data that can only be gained by large multicenter-national trials.

Historically, allogeneic HCT was reserved for high-risk patients, especially for those with Ph + ALL. Patients with high-risk features benefit from upfront HCT, including those with increased white blood count at presentation (>25,000/μL), chromosomal translocations [t(9;22), t(4;11), t(8;14)], older age (≥30 years), extra-medullary disease at diagnosis, and/or requiring more than 4 weeks to achieve CR [147]. Strategy to take ALL patients in CR1 for t(9;22) and t(1;19) have been supported by a trial by the French Group of Therapy for adult ALL (LALA-94) in a subgroup analysis [148]. Improvement in detection of minimal residual disease has also helped to assess disease risk, as 10% of patients with a rapid MRD decline to lower than 10(-4) or below detection limits at day 11 and day 24 were classified as low risk as their 3-year relapse rate was 0% [149]. Testing MRD with flow cytometry and/or molecular analysis for gene rearrangements may help to guide transplant decisions.

The largest prospective study of HCT in adult ALL was conducted by the Medical Research Council in Great Britain (UKALL XII) and the Eastern Cooperative Oncology Group in the United States (ECOG 2993). In this trial, allogeneic HCT resulted in improved disease control in all adult patients with ALL, with younger patients with low-risk disease benefiting the most with allogeneic HCT [150]. This international collaboration prospectively evaluated the role of allogeneic HCT for adults with ALL and compared autologous HCT with standard chemotherapy. Patients received 2 phases of induction and, if in remission, were assigned to allogeneic HCT if they had a compatible sibling donor. Patients without a donor were randomized to chemotherapy for 2.5 years versus an autologous HCT. A donor versus no-

donor analysis showed that Ph- ALL patients (standard risk) with a donor had a 5-year improved OS of 53% versus 45% for no donor (P =.01). The relapse rate was significantly lower (P ≤.001) with HCT in the standard-risk ALL patients. The survival difference was significant only in standard-risk patients, but not in high-risk patients, who had an impressive reduction in relapse rate but increased non-relapse mortality that abrogated the OS benefit of allogeneic HCT. For the no donor group, patients randomized to chemotherapy had a higher 5-year OS (46%) than those randomized to autologous transplantation (37%; P =.03). In conclusion, MRD allogeneic HCT for ALL in CR1 provide the most potent anti-leukemic therapy and considerable survival benefit for standard-risk patients. We may also conclude that there is no role for a single autologous HCT to replace consolidation/maintenance in any risk group.

For high-risk patients, results are conflicting with a recent large meta-analysis from seven studies of adult high-risk ALL (n=1274) using natural randomization based on donor availability combined with intent-to-treat analyses. This study demonstrated that patients in the donor groups had significantly better survival than patients in the no-donor groups (hazard ratio, 1.29; 95% confidence interval [95% CI], 1.02-1.63 [P =.037]). When only high-risk patients were included in the analysis, the superiority of the survival advantage was even greater (hazard ratio, 1.42; 95% CI, 1.06-1.90 [P =.019]) [151]. In addition, a recent systematic review and meta-analysis supported MRD HCT as the optimal post-remission therapy in ALL patients aged 15 years or over, resulting in improved OS and DFS with a significant reduction of disease relapse but with increased non-relapse mortality[152]. Interpretation of the results of the multicenter international trial has led to advocating early allogeneic HCT for patients with standard risk for some transplantation teams while others have preferred a more personalized approach as reports from various study groups differ and are often contradictory, leading to difficulty in interpreting the data [153, 154].

Historically, allogeneic HCT has been the standard of care for patients with high-risk Ph+ ALL in CR1. With the introduction of TKIs over the past decade, a treatment algorithm introducing TKIs in combination with allogeneic HCT for adult patients with Ph+ ALL is mandated. TKIs have been used in the upfront induction/maintenance chemotherapy setting and as maintenance post-HCT to prevent disease relapse in Ph+ ALL patients. Whether use of TKIs has an impact on OS when combined with HCT or whether TKIs will replace the use of allogeneic HCT remains unanswered to date. Multiple studies have shown the advantage of using imatinib mesylate in the induction/consolidation phase, allowing better remission rates and durable response with minimal toxicity as well as facilitating access and planning for an allogeneic HCT [154-159]. Review of these trials has suggested that over 90% of patients achieved a complete response as previously reviewed [154, 160]. Dasatinib, a multi-target kinase inhibitor of BCR-ABL and SRC family kinases, has been shown to induce responses in patients with imatinib-resistant or intolerant Ph+ ALL. In the START-L trial, major hematologic responses were achieved in 42%(15/36) of patients, 67% of whom remained progression-free when used at a dose of 140 mg. Complete cytogenetic responses were attained by 58% (21/36) of patients. The presence of BCR-ABL mutations conferring imatinib resistance did not preclude a response to dasatinib in this trial [161], suggesting a role for dasatinib to manage Ph+ ALL upfront [161]. Ravandi et al. examined the efficacy and safety of combining chemo-

therapy with dasatinib in patients with Ph+ ALL and determined that 94% achieved CR with an estimated 2-year survival of 64%. The combination of chemotherapy with dasatinib is effective in achieving long-term remissions in patients with newly diagnosed Ph+ ALL[162]. Nilotinib has also been tested for the management of relapsed/refractory Ph+ ALL with encouraging results[163].

TKI treatment is also a promising strategy when used as a consolidation strategy to in-duce and/or maintain molecular responses to decrease relapse rate after allogeneic HCT. Carpenter el al. reported safety data in 15 patients with Ph+ ALL who were enrolled in a prospective study and given imatinib from the time of engraftment until day 265 after HCT [97]. A clinical trial is currently ongoing to determine the safety of the administra-tion of nilotinib between day 81 and day 365 after HCT in patients with Ph+ leukemia (http://clinicaltrials.gov/show/NCT00702403). Lastly, TKIs have been shown to be effec-tive for management of relapse in Ph+ ALL in the post-HCT setting, although these data are based on few reports [160]. In summary, TKIs should be incorporated as a pre-HCT strategy to facilitate higher response rate and to improve both quality and durability of responses prior to allografting. TKIs are also a reasonable and promising strategy after allogeneic HCT to consolidate and maintain molecular responses that may ultimately im-prove survival for patients with Ph+ ALL. The optimal duration of therapy post-HCT, particularly in patients with sustained molecular response, remains to be determined. Whether TKI incorporation in the treatment strategy would impact OS is still unclear. In the absence of large prospective randomized trials comparing imatinib-chemotherapy regimens versus allo-HCT as a consolidative strategy, allo-HCT remains the best thera-peutic approach that offers a possibility of cure in Ph+ ALL [160].

There is increased interest in developing strategies to minimize toxicity associated with allogeneic HCT, especially after the results of the UK ALL XII ECOG 2993 study, which showed a significant TRM in patients over the age of 35 years despite better control of disease [150]. Several groups have sought to minimize morbidity and mortality in this group of patents through reduced intensity approaches, allowing for access to HCT for majority of Ph+ ALL subjects [164]. Unfortunately, there is no prospective trials using RIC for this disease published in the literature. Few recent retrospective series have been reported with 2-year OS and DFS between 50 and 61.5% [165]. We previously published our initial experience with FLU and BU in adult ALL patients, which showed a 2-year cumulative incidence of relapse of 19% (95% CI 8%-41%) for those transplant-ed in CR1 and 48% (29%-80%) in those with more advanced disease, with a 2-year OS of 54% (95% CI 39%-69%). Relapse-free survival at 2 years was 63% (95% CI 45%-81%) for patients transplanted in CR1 and 34% (95% CI 11%-57%) for patients transplanted in more advanced disease. We concluded that, compared to irradiation-containing regi-mens, FLU and PK-targeted BU appear safer and similarly effective in controlling ALL, providing a treatment option for adult patients with ALL [166]. Nonmyeloablative allo-geneic HCT approach is promising but its role for management of Ph+ ALL requires further investigations [154].

6. Lymphoma

Both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) represent a large group of diverse diseases. They are characterized by enlarged lymph nodes, splenomegaly, and constitutional symptoms. These disorders can present with bone marrow and extramedullary consequences. As a whole, they respond to combination chemotherapy. For patients who have relapsed or are refractory to initial therapy autologous HCT is the treatment of choice. The Parma group study, established the superiority of high-dose chemotherapy and autologous HCT over conventional salvage chemotherapy in a randomized multi-center trial for relapsed aggressive NHL [167]. Based on this study, autologous HCT became the standard of care for chemotherapy-sensitive relapsed or primary refractory aggressive NHL. There are instances where allogeneic HCT is the preferred approach for lymphoma.

6.1. Non-hodgkin lymphoma

6.1.1. Diffuse large B cell lymphoma (DLBCL)

The number of published studies using allogeneic HCT in DLBCL are limited and do not allow definitive conclusions. Allogeneic HCT has generally been used as treatment for patients who have relapsed after autologous HCT and on occasion for relapsed high-risk or refractory disease. No prospective comparative studies are available in this setting. A retrospective study by the CIBMTR compared the outcomes of DLBCL patients undergoing first autologous HCT (n = 837) or HLA-identical MSD allogeneic HCT with myeloablative conditioning (n =79). Allogeneic HCT was associated with higher TRM but with a similar risk of disease progression compared with lower-risk patients who received autologus HCT. [168] The European Group for Blood and Marrow Transplantation (EBMT) registry published a retrospective analysis of 101 patients. Approximately two-thirds of the patients received a reduced-intensity conditioning (RIC) regimen and 70% had an MSD. Non relapse mortality (NRM) was low with a rate of 28.2%, a relapse rate of 30% and an OS rate of 53%. Patients with a long remission after autologous HCT and with sensitive disease at allogeneic HCT appear to be the best candidates for this approach. [169] Thus, the use of allogeneic transplantation should be reserved for relapsed and refractory DLBCL that is responsive to the last line of therapy.

6.2. Follicular lymphoma (FL)

FL comprises approximately 25% of all newly diagnosed NHL cases. As an indolent lymphoma, the disease course is one of remissions and relapses with chemotherapy, followed inevitably by resistance and transformation to a more aggressive NHL histology. Trials from the several European Groups compared consolidative autologous HCT to chemotherapy ± interferon alfa (IFN-α) maintenance therapy or rituximab. [170-173] As autologous HCT provides no benefit in OS in FL it is currently not recommended as consolidation therapy.

The graft-vs-lymphoma effect afforded by allogeneic HCT is appealing as a potential curative approach in FL. Myeloablative conditioning allogeneic HCT, due to high TRM has not resulted in an improved OS in this disease. [174, 175] RIC allogeneic HCT is associated with a lower

TRM and the graft-vs-lymphoma effect may be beneficial in this indolent disease. Several studies have been published using this approach. The MD Anderson BMT program published results of their single institution trial of 43 patients with relapsed/refractory FL receiving a RIC allogeneic HCT with high doses of rituximab during and after conditioning. The PFS and OS rates were robust at 83% and 85%, respectively. [176] Currently, the BMT-CTN (0701) is confirming these results in a multi-institution trial.

6.3. Mantle cell lymphoma (MCL)

MCL is an aggressive NHL that often is responsive to initial chemotherapy but has a very high relapse rate and is incurable with conventional chemotherapy. With intensified induction regimens and the addition of rituximab, a higher proportion of patients achieve complete remission; however, long term cures are rare. [177] Autologous HCT provides very good control of the disease particularly in patients who received transplants in CR1. [178, 179] The Mantle Cell Lymphoma International Prognostic Index (MIPI) predicted good outcomes for patients in the good- and intermediate-risk. Unfortunately the poor-risk group had a disappointing survival, suggesting that these patients may be better suited for allogeneic HCT. [180]

To reduce toxicity and mortality in these heavily pretreated and older patients, RIC allogeneic HCT has been proposed with promising results. Treatment with a nonmyeloablative conditioning regimen and allogeneic HCT in 33 patients with relapsed and refractory MCL resulted in an OS rate of 65%. None of the patients transplanted in CR had relapsed after a median follow-up of 2 years. [181] Long term follow upof RIC allogeneic HCT in 35 patients with relapsed or refractory MCL demonstrated a low TRM rate and outcomes in which median OS had not been reached. [182] Finally, The British Society for Blood and Marrow Transplantation published the results of a retrospective analysis of 70 heavily pretreated patients with relapsed/refractory MCL who received RIC allogeneic HCT with or without alemtuzumab with or without DLI to boost the graft vs-lymphoma effect. The 3-year OS rate for patients who received donor lymphocyte infusions for relapse was 79%. [183] All of these studies demonstrated a plateau on the survival curves. Based on these reports, allogeneic HCT appears to be effective therapy for relapsed and refractory MCL and the only one associated with long-term remission. It will be necessary to complete a prospective, randomized study to define the role of upfront allogeneic HCT in MCL patients.

6.4. T-cell lymphoma

T-cell NHL (Peripheral T-cell lymphoma-not otherwise specified, angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL)) are a heterogeneous group of lymphomas which for the most part have an inferior prognosis when compared to B-cell NHL after CHOP therapy. With the exception of anaplastic large-cell kinase-positive (ALK) positive anaplastic large-cell lymphoma, T-cell NHL Carries a poor prognosis with low DFS and OS with standard chemotherapy. Several studies have demonstrated the use of autologous HCT in T-cell lymphoma has similar results to DLBCL. [184-189].

Allogeneic HCT has been proposed for the treatment of T-cell Lymphoma because of the potential graft-vs-lymphoma effect. There are limited studies in this field but the results have been promising. A retrospective analysis from France on 77 patients who underwent allogeneic HCT for PTCL resulted in a 5-year OS rates of 57%. Myeloablative conditioning was used in the majority of the patients. Patients with AITL had the best outcome, with a 5-year OS rate of 80%. Risk of relapse was low; however, the high TRM limited the benefit of the myeloablative approach. [190] RIC allogeneic HCT was published a prospective phase II trial using a reduced intensity regimen in 17 patients with PTCL. As expected TRM was low and the estimated 3-year OS was 81%. [191] In summary, the use of RIC allogeneic HCT through a lower TRM and allows transplant in older and heavily pretreated patients with reasonable OS. Certain T-cell entities such as hepatosplenic T-cell lymphoma, adult T-cell leukemia/ lymphoma, and systemic extranodal NK/T-cell lymphoma carry such a poor prognosis that allogeneic HCT is justified as part of the initial treatment. The use of prognostic indexes such help identify patients with extremely high risk of relapse who may also benefit from an allograft. Only prospective multicenter trials will define the role of allogeneic HCT in these aggressive lymphomas.

6.5. Hodgkin lymphoma

Combination chemotherapy with or without radiation therapy results in long-term DFS and OS for about 80% of newly diagnosed patients with HL. [192] As in NHL autologous HCT is well established for the treatment of disease. [193] An approach to minimize relapse after autologous HCT for high-risk patients using the anti-CD30 antibody (brentuximab) conjugated to an anti-tubulin drug (vedotin) [SGN-35][194] is currently being studied in a randomized phase III placebo-controlled trial as maintenance therapy following autologous HCT.

Because of prior intensive therapy, RIC allogeneic HCT is an appropriate option in candidates for patients with HL. [195-198] Recent retrospective analyses demonstrate improved PFS and OS compared to additional salvage therapy for patients treated with this approach after relapse following autologous HCT. [197, 199] More importantly, outcomes with MRD vs MUD do not appear to be different. [196, 198]

7. Conditioning regimens

7.1. Myeloablative conditioning

Allogeneic bone marrow transplantation is the most intensive post-remission therapy used for management of malignant disorders over the past decades. Toxicity of a conditioning regimen can impact on overall morbidity, including interstitial pneumonitis, sinusoidal obstruction syndrome/veno-occlusive disease, and may lead to an increased incidence of GVHD. Despite current understanding of the transplantation process, the optimal chemotherapy and/or radiation conditioning regimen remains unknown. Few data from comparative or randomized studies are available to address this issue. Allogeneic hematopoietic cells serve a dual purpose, not only to restore hematopoiesis but also to impose immunologic effects against malignant

clones, a process known as graft versus leukemia. This has led to the development of a conditioning regimen that will minimize toxicity with preservation of graft versus leukemia effect as the main mechanism of action to eradicate disease.

The spectrum of conditioning intensity has been defined in three categories: 1) myeloablative, which causes irreversible marrow aplasia if transplantation is not performed; 2) nonmyeloablative, which cause minimal marrow suppression; and 3) RIC, which causes cytopenias of intermediate duration [200]. Assignment to these categories is based on the duration of cytopenia and on the requirement for stem cell support. Myeloablative regimens cause irreversible cytopenia, and stem cell support is mandatory. Nonmyeloablative regimens cause minimal cytopenia and can be given also without stem cell support. RIC causes cytopenias of variable duration and should be given with stem cell support, although cytopenia may not be irreversible. Compared with high-dose MA preparative regimens, NMA or RIC regimens are associated with shorter inpatient hospital stays, reduced need for transfusions [201], and a shorter duration of neutropenia with fewer bacterial infections [202-204]. There is current trend to adopt less-toxic conditioning regimens to allow access for patients to undergo HCT who has been previously been excluded because of age or comorbidities. Standardized classification of conditioning regimen intensities will allow comparisons across studies and interpretation of study results [200].

Myeloablative regimens, a combination of agents expected to produce profound pancytopenia and myeloablation within 1-3 weeks from administration, have caused pancytopenia that is long lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by hemopoietic stem cell infusion [200]. Early use of this approached invested on the theory of dose intensity to eradicate disease. [205]. The two most commonly used myeloablative conditioning regimens for allografts for leukemia/lymphoma use a combination of high-dose busulfan combined with cyclophosphamide and cyclophosphamide in combination with TBI. The Cyclophosphamide-TBI regimen uses a cyclophosphamide dose of 120 mg/kg and 10–15 Gy TBI [23] and busulfan-cyclophosphamide uses a busulfan dose of 16 mg/kg orally and Cy 120 mg/kg [206]. From the available data, there are no significant differences in survival with these two regimens. There is also no evidence that intensified conditioning improves survival, as a higher dose of TBI is associated with increased toxicity [205]. Cyclophosphamide or TBI has also been tested in addition to other chemotherapy agents like melphalan, thiotepa, etoposide, and dimethylbusulfan. The problem with myeloablative conditioning is the high TRM that ultimately jeopardizes overall success. The risk of TRM after a myeloablative regimen has decreased over time, attributed to improved HLA-typing and better supportive care [207]. Neither regimen explored in the myeloablative setting is suitable for all the situations and a particular regimen should be selected depending on the clinical situations if myeloablative approaches are still an option nowadays [208] with the introduction of less toxic transplantation approaches.

Several attempts have been made in the past 30 years to limit early transplant toxicity, by reducing the intensity of the conditioning regimen as previously reviewed [200]. Within the past 20 years, the introduction of fludarabine (Flu) [209, 210] and further dose reductions of alkylating agents [211, 212] or TBI has led to minimized toxicity.

These regimens were designed to allow access to HCT for older patients or because of comorbidities that would preclude HCT. Enthusiasm in the transplant community has led to adoption of these reduced toxicity modalities [213]. A workshop convened by the CIBMTR addressed the dose spectrum, which defines a RIC regimen [214]. A total of 56 participants were surveyed, and 67% agreed that a RIC regimen should cause reversible myelosuppression when administered without stem cell support, result in low nonhematologic toxicity, and, after transplantation, result in mixed donor–recipient chimerism at the time of first assessment in most patients. Likewise, the majority (71%) agreed or strongly agreed that regimens including <500 cGy of TBI as a single fraction or 800 cGy in fractionated doses, busulfan dose <9 mg/kg, melphalan dose <140 mg/m^2, and thiotepa dose < 10 mg/kg should be considered RIC regimens. However, only 32% agreed or strongly agreed that the combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) should be considered a RIC regimen. These results demonstrate that, although HCT professionals have not reached a consensus on what constitutes a RIC regimen, most accept currently used criteria and operational definitions [214].

RIC is an intermediate category of regimens that causes pancytopenia and requires stem cell support if prolonged and autologous recovery is possible. An improved rate of toxicity is achieved by reducing the dose of alkylating agents or TBI by at least 30%. Most often, these regimens combine Flu with an alkylating agent, melphalan [215],Bu [211],thiotepa[212] in reduced doses, or Flu with reduced-dose TBI [216]. Decreased TRM has been successfully achieved with this approach [217, 218] Among the published phase II trials, leukemia relapse remained consistently the main cause of treatment failure after RIC or nonmyeloablative conditioning, with 2- to 4-year relapse rates ranging from 30% to 61%. Mohty et al.recently updated results of the first prospective trial directly comparing RIC allogeneic HCT versus consolidation chemotherapy in patients with AML using "genetic allocation." In an intent-to-treat analysis, leukemia-free survival was superior in the donor group (60% versus 23% at 7 years; P =.003) but with a significant relapse risk [219]. Recent retrospective analysis demonstrated that RIC has similar outcomes to MAC in patients with AML or MDS. [217, 220] Because of prior therapy and older age, as described above in the Lymphoma section RIC allogeneic HCT is appropriate for most those patients. Allogeneic transplantation has evolved significantly in the last 40 plus years of use as stem cell therapy. To further improve its outcomes patients should be selected early and the appropriate regimen should be used to optimize the anti-malignancy effect.

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