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Review

Conditioning Regimens for Frail Patients with Acute Leukemia Undergoing Allogeneic Stem Cell Transplant: How to Strike Gently

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ABSTRACT

Despite the recent dramatic progress in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) therapy, allogeneic transplant remains a mainstay of treatment for patients with acute leukemia. The availability of novel compounds and low intensity chemotherapy regimens made it possible for a significant proportion of elderly and comorbid patients with AML or ALL to undergo curative treatment protocols. In addition, the expansion of donor availability and the recent dramatic progress in haploidentical stem cell transplant, allow the identification of an available donor for nearly every patient. Therefore, an increasing number of transplants are currently performed in elderly and frail patients with AML or ALL. However, allo-Hematopoietic stem cell transplant (HSCT) in this delicate setting represents an important challenge, especially regarding the selection of the conditioning protocol. Ideally, conditioning intensity should be reduced as much as possible; however, in patients with acute leukemia relapse remains the major cause of transplant failure. In this article we present modern tools to assess the patient health status before transplant, review the available data on the outcome of frail AML an ALL patients undergoing allo-HSCT, and discuss how preparatory regimens can be optimized in this setting.

1. INTRODUCTION

Hematopoietic allogeneic stem cell transplant (allo-HSCT) represents the only curative strategy for a significant proportion of patients diagnosed with acute leukemia. Nevertheless, this procedure is saddled with a significant risk of mortality, especially in patients undergoing transplant with an impaired physical condition. The availability of novel compounds and low intensity chemotherapy regimens made it possible for a significant proportion of elderly and unfit patients with Acute Myeloid Leukemia (AML) or Acute Lymphoblastic Leukemia (ALL) to undergo curative treatment protocols [1]. In addition, the expansion of donor availability and the recent dramatic progress in haploidentical SCT currently allow the identification of an available donor for nearly every patient. Finally, the last decade has witnessed a significant improvement in supportive care and deeper knowledge of pathophysiology of transplant complications, thus reducing mortality following allo-HSCT. Therefore, an increasing number of transplants are currently performed in elderly and frail patients with AML or ALL. However, transplant in this delicate setting represents an important challenge, especially with regards to the selection of the conditioning protocol. Ideally, conditioning intensity should be reduced as much as possible; however, in patients with acute leukemia relapse remains the major cause of transplant failure. In this article we discuss the available tools to assess patient health status before transplant, and review common preparatory regimens for elderly and unfit patients with AML and ALL undergoing allo-HSCT.

2. DEFINING THE FRAIL PATIENT

Patients with acute leukemia who are considered for allo-HSCT undergo a thorough pre-transplant assessment with the aim to predict the individual risk of treatment-related toxicity, to inform risk/benefit assessments and to aid clinical decision making. Different models have been designed with the aim to identify patients which could be able to tolerate a transplant, and to adjust the procedure according to patient fitness. Commonly used scales are the Charlson Comorbidity Index [2], Hematopoietic Cell Transplantation (HCT)-specific Comorbidity Index [3], its derivative Comorbidity-Age Index [4] and Karnofsky Performance Status (KPS) score [5], each catching different aspects of patient health status before transplant. Further, different scores combining patient, disease and transplant characteristics have been developed. European Society for blood and marrow transplantation (EBMT) score includes characteristics of the patient (age), disease (status, time from transplantation), and donor (relation, donor–recipient HLA match, and sex match) [6]. It has been repeatedly validated [7], but lacks information about patient global health status. The Pretransplantation

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Assessment of Mortality (PAM) [8] score was validated in 2006 and simplified in 2015 [revised PAM (rPAM)] [9]. Retrospective studies showed limitations of both scores in discrimination and predictive reliability [10]. Recently, Shouval et al. [11] compared the most widely accepted prognostic models in a validation cohort of 528 patients. No score provided a satisfactory discrimination capacity, highlighting the need to incorporate "hidden" measures of frailty in pre-transplant assessment, to better predict outcome on individual basis. Although comprehensive frailty assessments have been validated to predict increased mortality in the general geriatric population [12] and in geriatric oncology patients [13,14], these time-consuming tools remain scarcely used in the setting of allo-HSCT. To date, historical models such as KPS and the Eastern cooperative oncology group performance status remain as the most widely accepted "frailty" measures in pre-HSCT evaluation. A recent study by the Acute Leukemia Working Party (ALWP)-EBMT [15] analysed transplant outcome in patients with a reduced KPS (≤80%), including almost 3000 patients with AML undergoing transplant in remission. As expected, patients with a KPS score = 80% had lower non-relapse mortality (NRM) and superior overall survival (OS) in comparison to patients with a KPS score <80% ($p < 0.001$). Interestingly, in the subgroup of patients with a KPS score = 80%, a reduced intensity conditioning (RIC) regimen was associated with an increased risk of relapse ($p = 0.002$) and lower GVHD-free, relapse-free survival (GRFS) ($p < 0.001$) compared to myeloablative conditioning (MAC). Differently, in patients with a KPS score <80%, a RIC regimen resulted in lower NRM ($p < 0.001$), whereas the relapse incidence did not differ, thus leading to an improved GRFS ($p = 0.008$) as compared to MAC. These findings confirm the strong predictive power of the KPS score. Furthermore, the allo-HSCT outcome varied significantly depending on the conditioning intensity, which should be adjusted according to the severity of KPS impairment. The combination of different scales and a more refined approach could probably enhance the risk prediction in patients undergoing allo-HSCT. In a groundbreaking work, Shouval et al. [16] developed a machine-learning algorithm to predict the NRM in patients with acute leukemia. Among patient characteristics, KPS, age and cytomegalovirus (CMV) serostatus were included in the model. Furthermore, in a recent work, Fein et al. [17] demonstrated that patient comorbidities interact with specific conditioning protocols, suggesting that the selection of the preparatory regimen for transplant should be tailored to the individual characteristics of each single patient.

In a recent EBMT study, Spyridonidis et al. [18] proposed a novel definition of conditioning intensity based on objective parameters. The authors assigned intensity weight scores to several agents commonly included in conditioning regimens, and used their sum to generate a novel transplant conditioning intensity score. This score strongly predicted NRM risk independently of other validated prognostic factors, and could be used in clinical practice with the aim of predicting NRM and relapse for each given protocol.

3. RIC REGIMENS FOR AML

Allogeneic transplant is a standard of care for AML patients with high-risk features or with detectable minimal residual disease after induction chemotherapy. RIC and non-myeloablative (NMA) regimens have been developed in this setting with the aim to extend the transplant procedure to older and comorbid patients, considering an unacceptable overall transplant-related mortality of about 40% following standard myeloablative protocols. In fact, the optimal conditioning regimen for frail AML patients should combine a reduced risk of NRM with an acceptable control of the hematological disease (Table 1). The paradigm of a NMA conditioning was designed by the Seattle group [19], which combined a single 200 cGy total body irradiation (TBI) fraction with fludarabine. In a cohort of elderly AML and myelodisplastic syndromes (MDS) patients (>60 years of age), the NRM was extremely low (16% at 1 year), but the high relapse rate led to reduced survival (33% at 5 years). RIC regimens derive from a different concept, delivering a MAC protocol with a mitigate intensity and, therefore, a reduced toxicity. In fact, the main backbone of RIC regimens for AML is represented by a combination of fludarabine with an alkylator, administered at doses which are lower than myeloablative doses. In a retrospective EBMT analysis [20] the authors compared 401 AML patients undergoing RIC with 1154 who received MAC, stratifying the analysis according to patients' age (<50 years or ≥50 years). They reported an increased relapse rate (HR 1.46, $p = 0.02$) in younger patients who received a RIC regimen, but lower NRM with no difference in relapse and leukemia-free survival (LFS) in patients >50 years between MAC and RIC. A similar analysis was conducted by the CIBMTR [21], comparing NMA, RIC and MAC regimens, resulting in excess of relapse in the NMA group, which led a to reduced OS; however, there was no significant difference in 2-year OS between RIC (33%) and MAC transplant (34%). A further analysis on 404 older patients (>60 years of age) was published by Ciurea et al. [22]. Patients received one of the following conditioning regimens: (1) fludarabine 160 mg/m^2 + melphalan 100 mg/m^2 (FM100); (2) fludarabine 160 mg/m^2 + melphalan 140 mg/m^2; (3) fludarabine (with or without clofarabine) + intravenous (IV) busulfan 4 days 130 mg/m^2; (4) fludarabine (with or without clofarabine) 160 g/m^2 + IV busulfan 4 days 110 mg/m^2 per day. The FM100 group showed a significantly better progression free survival (PFS) and GRFS compared to other groups ($p = 0.02$). The benefit of the

Table 1 | Reduced intensity conditioning regimens for acute myeloid leukemia

Regimen	Protocol details	Age	Number of patients	References
Flu/TBI	TBI 2 Gy ± Flu 150 mg/m^2	5–74	274	Gyurkocza et al. [19]
Bu/Flu	Bu 8 mg/kg po + Flu 130 mg/m^2	2–61	26	Slavin et al. [62]
Bu/Flu	Bu 130 mg/m^2 iv + Flu 150 mg/m^2	25–64	80	Mohty et al. [63]
Flu/Mel	Mel 180 mg/m^2 + Flu 125 mg/m^2	22–70	86	Giralt et al. [64]
TBF	Thiotepa 10 mg/m^2 + Bu 9.6 mg/kg + Flu 150 mg/m^2	18–66	25	Raiola et al. [37]
Flu/Treo	Treo 30 mg/m^2 + Flu 150 mg/m^2	55–65	220	Beelen et al. [32]

Bu, busulfan; DFS, disease-free survival; Flu, Fludarabine; LFS, leukemia-free survival; Mel, Melphalan; NRM, non-relapse mortality; OS, overall survival; TBF, Thiotepa, busulfan and fludarabine; TBI, total body irradiation; Treo, treosulfan.

FM100 regimen was more evident in patients with an impaired performance status and in older patients. This study demonstrated that reduced melphalan doses significantly improved NRM in such frail patients without an increase in relapse rate, when compared with other RIC regimens or to standard myeloablative busulfan-based conditioning. In a study by Eapen et al. [23] on a cohort of AML and MDS patients, fludarabine and melphalan (FM) conditioning was associated with reduced relapse as compared to fludarabine and busulfan 2 days (FB2). Similarly, Baron et al. [24] retrospectively compared FM and FB2 in AML patients, confirming better leukemia control for FM compared to FB2, though survival did not differ. In fact, when conditioning intensity is tempered, the relapse rate tends to increase, especially in patients with high-risk AML or with measurable residual disease at the time of transplant [25,26]. In a EBMT survey the authors compared 315 patients receiving RIC with 407 MAC recipients [27]. RIC was defined as the use of fludarabine associated with low-dose TBI (<3 Gy), or busulfan [total dose (≤8 mg/kg)], while MAC was defined as the use of TBI > 10 Gy or busulfan (>8 mg/kg). As expected, the NRM was higher in MAC than in RIC cohorts (32% versus 18%, $p < 0.001$); however, the cumulative incidence of relapse was significantly increased after RIC (41% versus 24%, $p < 0.0001$), while there was no significant difference for LFS and OS between RIC and MAC groups. Substantial effort has been focused on reducing conditioning toxicity by the use of pharmacokinetic (PK) information to tailor busulfan delivery, with promising results [28]. Recently, Bartelink et al. [29] developed a novel pharmacokinetic model for busulfan area under curve (AUC) monitoring in a retrospective study of children and young adults receiving allo-HSCT. A significant step forward in reducing conditioning toxicity was the inclusion of treosulfan in the preparatory regimen for AML and MDS. Treosulfan, initially used for solid tumors, holds both myeloablative and immunosuppressive characteristics, associated with a favorable toxicity profile with low extramedullary toxicity. The combination of fludarabine and treosulfan was explored in several studies in patients not eligible for standard myeloablative conditioning, with promising outcome in AML and MDS [30]. In an EBMT study [31] the authors analyzed transplant outcome following treosulfan at two dose levels (36 mg/m^2 or 42 mg/m^2), demonstrating reduced rates of NRM and graft versus host disease (GVHD). Furthermore, they defined fludarabine treosulfan (FT) 42 mg/m^2 as a myeloablative dose, while FT 36 mg/m^2 was taken as an intermediate dose between MAC and RIC. A recent randomized trial [32] compared standard busulfan 6.4 mg/kg to treosulfan 30 mg/m^2, in combination with fludarabine, as a preparatory regimen for frail patients with AML or MDS. The authors reported improved event-free survival in the treosulfan arm; therefore, the combination of treosulfan and fludarabine in the RIC setting should be considered a novel standard of care for older and unfit AML or MDS patients.

Finally, the recent significant developments in haploidentical transplant (haplo-HSCT) led to the opportunity for older and comorbid patients to undergo this procedure. In fact, most elderly patients have at least one child available for stem cell collection. Furthermore, T-repleted haplo-HSCT using post-transplant cyclophosphamide represents an attractive option for frail patients, particularly regarding the reduced incidence of chronic GVHD associated with this platform [33]. Slade et al. [34] reported the results of a retrospective analysis conducted on 112 patients receiving haplo-HSCT grouped by age: 61 patients ≤55 years (Age 1), 29 patients 55–65 years (Age 2), and 22 patients ≥65 years (Age 3). Survival was significantly different ($p = 0.03$) according to age group, being 39%, 34% and 15% for Age 1, 2 and 3, respectively. The authors reported a trend toward a lower 100-day cumulative incidence of grades II–IV acute GVHD (aGVHD) in older patients, with the 1-year cumulative incidence of chronic GVHD (cGVHD) (any grade) being significantly reduced in older patients (36% versus 35% versus 9%, $p = 0.04$), while no difference was observed in severe cGVHD. Another study by Ciurea et al. [35] included patients with AML or MDS older than 55 years who underwent an haplo-HSCT between 2009 and 2015. All patients received fludarabine combined with a single dose of melphalan (100–140 mg/m^2) with either thiotepa 5 mg/kg or 2-Gy TBI. Post-transplant, they were treated with cyclophosphamide (50 mg/kg/day) on days +3 and +4, followed by mycophenolate mofetil and tacrolimus. The authors observed a trend for lower PFS in older age groups; interestingly, factors associated with poor OS were high cytogenetic risk and donor age >40 years. Thiotepa is an alkylating agent with antineoplastic activity and immunosuppressive properties that can penetrate the blood–brain barrier. Recently, the combination of thiotepa, busulfan and fludarabine led to the design of the so-called TBF regimen, which showed promising outcome in cord blood and haplo-HSCT [36]. Raiola et al. [37] reported the outcome of 50 patients with different hematological malignancies (including 25 with AML) following TBF or FluTBI preparatory regimens. Interestingly, the TBF protocol was adapted reducing the dose of alkylators for older and comorbid patients. The authors reported low rates of NRM and relapse, particularly in patients undergoing transplant in remission (9% and 17% at 1 year, respectively); disease-free survival was 51% at 18 months. Nevertheless, it should be highlighted that the combination of two alkylators could be particularly toxic to mucosal cells, especially when busulfan or thiotepa are given at higher doses. Interestingly, in a recent EBMT study comparing transplantation outcomes of patients who received 5 mg/kg thiotepa and 2 days of intravenous busulfan at 6.4 mg/kg (T1B2F) versus those who received 10 mg/kg thiotepa with the same T2B2F, the authors observed higher aGVHD rates in the T2B2F group, with similar survival. Taken together, these data suggest that transplant should not be withdrawn in older and medically infirm patients with AML, as the conditioning intensity can be adjusted according to patient age and health status.

4. REDUCED INTENSITY CONDITIONING REGIMENS FOR ALL

Hematopoietic allogeneic stem cell transplant for ALL is a standard of care in patients with high-risk features or poor response to induction chemotherapy. In fact, historical donor versus no-donor studies have clearly shown an improved outcome following allo-HSCT as compared to conventional chemotherapy in this setting [38]. Such data, together with the evidence of a strong graft-versus-leukemia effect in ALL, prompted the use of allo-HSCT in first complete remission (CR1) to prevent leukemia relapse [39]. Older adults with ALL have a significantly poorer outcome following transplant; long term event-free survival (EFS) is reported to be lower than 35% in such population [40]. In fact, there is no consensus about indications for transplant in this setting, and most authors consider transplant an "option" which should be

carefully evaluated, balancing comorbidity score, kind of donor and disease characteristics. In fact, standard transplant platforms for ALL are based on the combination of TBI with an alkylator as cyclophosphamide or etoposide [41]. These protocols have been designed in the context of young, fit patients, and are not applicable to elderly and frail patients, due to significant toxicity and high risk of transplant-related mortality. RIC protocols have been developed with the rationale of allowing for a graft-versus-leukemia effect with reduced toxicity in older adults and those with comorbidities or poor performance score (Table 2). Recently, the European Working Group for Adult Acute Lymphoblastic Leukemia and the ALWP of the EBMT groups joined together with the aim of producing a position statement on transplantation in ALL [42]. When addressing transplant in older and frail patients, recommendations varied among experts: while some ALL study groups restrict indication of transplant to patients with poor-risk features, in particular poor response at the matched-related (MRD) level, others do not consider allo-HSCT for older patients with Philadelphia (Ph)-negative ALL at all. In fact, there is lack of evidence in this setting. Furthermore, there have been no prospective studies comparing outcomes of patients with ALL who undergo MAC compared to RIC conditioning. Nevertheless, different retrospective studies have addressed this question. In a CIBMTR analysis, Marks et al. [43] included adults >35 years of age with Ph chromosome negative ALL, comparing the outcome following standard TBI-based MAC protocols or RIC regimens. As expected, patients who received a RIC were older, with almost half of this group being >50 years of age. Apart from age, other reasons for selecting a RIC regimen were KPS score <80%, organ dysfunction or a history of invasive fungal infection. No significant difference was observed between the two groups in terms of NRM, while there was a non-significant trend toward higher risk of relapse in the RIC group (26% MAC versus 35% RIC, $p = 0.08$). Furthermore, the OS did not differ, suggesting that RIC might represent a suitable alternative to MAC for frail patients with ALL. A more recent CIBMTR study including older adults who underwent RIC allogeneic HCT for ALL reported 3-year NRM, CIR, and OS of 25%, 47%, and 38%, respectively. Older age (>65 years) and lower performance status scores were associated with inferior survival [44]. In both CIBMTR studies, the RIC regimen was defined as follows: Busulfan 9 mg/kg or less; melphalan 150 mg/kg or less; TBI < 500 cGy single dose or < 800 cGy fractionated, in combination with fludarabine. An analysis conducted by the EBMT [45] focused on a more homogeneous population of ALL patients older than 45 years receiving a matched sibling donor (MSD) allo-HSCT in complete remission (CR). Interestingly, the 2-year NRM was significantly reduced in the RIC group (29% MAC versus 21% RIC, $p = 0.03$); on the other hand, the relapse rate was significantly higher (31% MAC versus 47% RIC, $p < 0.001$), such translating in similar survival in MAC and RIC groups. A more recent study including adult patients with Ph+ ALL [46] compared the outcome following either MAC or RIC regimen in CR1: the NRM was significantly lower in RIC recipients (36% MAC versus 13% RIC, $p = 0.001$), while the relapse rate was higher in the RIC cohort (49% versus 28%, $p = 0.058$). Interestingly, factors associated with a higher risk of relapse in the RIC group included no pre-HSCT tyrosine kinase inhibitors (TKI) and MRD positivity at the time of HSCT. Similarly, to the studies discussed previously, survival was not significantly different between the MAC and RIC cohorts. A recent retrospective CIBMTR including only older (>55 years) patients with ALL who received a RIC regimen [47] reported a high incidence of relapse (47%), which represented the leading cause of death. As expected, a KPS ≤80 was significantly associated with an increased risk of NRM. A major concern about RIC in patients with ALL is that most protocols do not include TBI, which is known to reduce the risk of central nervous system (CNS) and sanctuary site relapse [48]. Furthermore, the low dose (i.e. lower than 3 Gy) of TBI included in some regimens has not been clearly associated with a protection against CNS disease recurrence. In the early CIBMTR study [43], the inclusion of TBI within the preparatory regimen resulted in a reduced risk of relapse. However, this finding was derived by an analysis on the whole cohort, including both MAC and RIC; in fact, the majority of patients who had received TBI were included in the MAC group. Interestingly, the Seattle group reported no increased incidence of CNS relapse in patients receiving a non-MAC regimen of fludarabine and low dose TBI [49]. Nevertheless, there is a lack of prospective trials comparing TBI- and chemotherapy-based RIC regimens for ALL; therefore, the role of irradiation in RIC protocols remains uncertain. When a radiation-free regimen is selected, thiotepa represents an alkylator commonly included in the preparatory protocol. Recent retrospective data showed similar survival of ALL patients after thiotepa-based regimens as compared to TBI [50]: the relapse incidence at 1 year was 33%, while the 1-year OS was above 60%, advocating that a thiotepa-based platform might represent a valid alternative to TBI. In fact, thiotepa is an alkylating agent with immunosuppressive properties which has been largely used in oncology, due to its favorable characteristics of being able to penetrate the blood–brain barrier, combined with a reduced non-hematologic toxicity. Those properties led hematologists to include it in different preparatory regimens for autologous and allogeneic transplantation [51,52]. Recently, Bazarbachi et al. analyzed the outcome of 122 ALL patients receiving haplo-HSCT, of whom 40% were treated with a chemotherapy-based regimen including TBF conditioning. Interestingly, the outcome was not affected by the type of preparatory regimen, calling into question the need for TBI-based regimens in this setting. Post-transplant strategies exploiting novel targeted therapies could allow a better balance between reducing the conditioning intensity and maintaining leukemia control [53].

Table 2 | Reduced intensity conditioning regimens for acute lymphoblastic leukemia

Regimen	Protocol details	Age	Number of patients	References
FluMel	Mel 140 mg/m^2 + Flu 150 mg/m^2	15–63	37	Cho et al. [65]
FluMel	Mel 140 mg/m^2 + Flu 125 mg/m^2	23–68	24	Stein et al. [66]
Flu/TBI	TBI 2 Gy + Flu 125 mg/m^2	8–69	51	Ram et al. [49]

Flu, Fludarabine; Mel, Melfalan; TBI, total body irradiation. Modified from Leonard et al. [67].

5. GVHD PROPHYLAXIS AND SUPPORTIVE CARE IN FRAIL PATIENTS

Graft versus host disease is the most frequent complication affecting patients undergoing HSCT, and numerous studies have shown its risk increases with age [54]. Compared to younger patients, older ones are more susceptible to the consequences of GVHD due to their reduced adaptative response. Besides, GVHD significantly affects life quality [55]. Therefore, especially in this sub-setting of patients, it is essential to evaluate the best strategy to avoid this complication. This approach involves choosing RIC regimens [56], diminishing the incidence of grade II–IV aGVHD and cGVHD compared with the busulfan/cyclophosphamide and fludarabine/melphalan transplant regimens, and achieving NRM in older patients similar to that achieved with standard high-dose regimens in younger ones. Another important aspect involves rigorous hematopoietic stem cell source selection: it is well recognized that HLA-identical relatives and bone marrow stem cells are associated with a better outcome [57]. For the same reason, GVHD prophylaxis is a cornerstone of the therapy of frail patients undergoing allo-HSCT. Careful prophylaxis requires selecting different medications. The first one that should always be used with high GVHD risk patients is the anti-thymocyte globulin (ATG), as it reduces the rate of this complication for both related and unrelated donor transplantation [58]. Walker et al. reported that, at 12 months from transplant, 37% of patients who received ATG were free from immunosuppressive treatment compared with only 16% of those who received no ATG (adjusted odds ratio 4·25 [95% CI 1.87–9.67]; p = 0·00060). The second treatment necessary for GVHD prophylaxis is a calcineurin inhibitor (CNI): cyclosporine (CSA) and tacrolimus are considered similar for GVHD and survival outcomes [59]. In a recent paper, Kanada showed that the incidence of grades II–IV and III–IV acute GVHD were 39.6% and 7.5% for the CSA group, and 33.3% and 9.4% for the FK group (respectively p = 0.41 and 0.76), while the other clinical outcomes were equivalent. Thirdly, in combination with the CNI, the use of an antimetabolite is recommended: methotrexate (MTX) and mycophenolate mofetil (MMF) are the possible choices. In MAC regimens, the superiority of MTX over MMF has been widely demonstrated, as testified by higher acute GVHD rates in patients treated with MMF. In non-MAC and RIC settings, there is a lack of prospective studies to establish which the best prophylaxis is. In particular, there is no research comparing all four possible regimens (CSA + MMF, CSA + MTX, FK + MMF, FK + MTX). Currently the association MMF + CSA remains the most commonly used, and the EBMT also recommends it [60]. Lastly, special consideration should be taken in the case of T cell-replete allo- from a haploidentical donor. In this particular situation, to promote tolerance in the alloreactive host and donor T cells, leading to suppression of both graft rejection and GVHD, post-transplantation-cyclophosphamide (PTCy) should be recommended. In a seminal work, Blaise et al. [61] recently demonstrated that older adults could safely be treated with non-MAC haplo-HSCT using PTCy. This study focused on a population with age over 55, comparing outcomes after haplo-HSCT to age-matched controls receiving grafts from MRD or unrelated donors (UD). No significant difference in outcomes between the groups emerged, except for a lower incidence of severe chronic GVHD with haplo-HSCT than UD (p = 0.007).

6. CONCLUSION

Despite the recent dramatic progress in AML and ALL therapy, allogeneic transplant remains a mainstay of treatment for patients with acute leukemia. Further, the great developments in conditioning platforms, donor availability and GVHD prophylaxis made it possible for an increasing number of older and frail patients to be considered for transplant; however, allo-HSCT in such patients remains a challenge. Novel prognostic models and comprehensive patient evaluation tools might help physicians in adjusting transplant platforms according to patient characteristics. Particularly, conditioning intensity should be modulated to reach the optimal balance between anti-leukemic activity and reduced toxicity. Finally, post-transplant targeted therapy and immune modulation should be exploited as much as possible to prevent leukemia relapse, which remains the main cause of transplant failure.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

FS and AO wrote the first draft of the manuscript. All co-authors contributed to the manuscript and approved the final version.

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