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Allogeneic hematopoietic cell transplantation for acute myeloid leukemia during first complete remission: a clinical perspective

Masamitsu Yanada

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Abstract Allogeneic hematopoietic cell transplantation (HCT) is the most potent therapy for preventing relapse of acute myeloid leukemia (AML). Although its efficacy is compromised by a high risk of treatment-related morbidity and mortality, an accumulating body of evidence has led to the general recommendation favoring allogeneic HCT from a matched sibling donor during first complete remission (CR1) for younger patients with cytogenetically intermediate- or high-risk AML. Over the past few decades, this field has seen a great many advancements. The indications for allogeneic HCT have been refined by taking into account the molecular profiles of leukemic cells and the degree of comorbidities. The introduction of high-resolution human leukocyte antigen-typing technology and advances in immunosuppressive therapy and supportive care measures have improved outcomes in alternative donor transplantation, while the parallel growth of unrelated donor registries and greater use of umbilical cord blood and haploidentical donors have considerably improved the chance of finding an alternative donor. The development of reduced-intensity and non-myeloablative conditioning has made it possible to receive allogeneic HCT for patients who might once have been considered ineligible due to advanced age or comorbidities. Thanks to these advances, the role of allogeneic HCT during CR1 has become progressively more important in the treatment of AML.

M. Yanada (✉)
Department of Hematology, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake 470-1192, Japan
e-mail: myanada@fujita-hu.ac.jp

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Introduction

Achievement of complete remission (CR) is the first step in improving outcomes for patients with acute myeloid leukemia (AML). With standard induction chemotherapy, more than 70 % of younger patients and approximately 50 % of older patients can achieve CR [1, 2]. Post-remission chemotherapy plays a critical role in eradicating residual leukemic cells and obtaining long-term disease control, because CR cannot last long without further therapy [3]. However, the same holds true even if post-remission chemotherapy is used for a substantial proportion of patients.

In this context, allogeneic hematopoietic cell transplantation (HCT) is currently the most potent therapy for preventing relapse of AML, owing to cytoreduction induced by the pre-transplantation conditioning therapy and the post-transplantation graft-versus-leukemia effect. The efficacy of allogeneic HCT is, however, compromised by a high risk of treatment-related morbidity and mortality, making it a matter of continuing debate whether allogeneic HCT during first CR (CR1) yields net benefits for patients with AML.

Recently, there have been great many advancements potentially related to this question, including refinements of AML risk stratification, increased availability of alternative donors, and widespread use of reduced-intensity conditioning (RIC). This article reviews and discusses current clinical aspects of allogeneic HCT for AML during CR1, with the focus on indications for allogeneic HCT, timing of transplantation, donor sources, and conditioning regimens.

Who will benefit from allogeneic HCT during CR1?

AML represents a heterogeneous disease consisting of various biological, clinical and prognostic subgroups. While the anti-leukemic effect of allogeneic HCT is more powerful than that of standard chemotherapy, the associated morbidity and mortality warrant careful selection of patients who are most likely to benefit from the procedure. Thorough assessment is, therefore, needed when determining whether to opt for allogeneic HCT during CR1 in terms of balancing between the risks of non-relapse mortality and of relapse, with special emphasis on the anticipated risk of relapse following chemotherapy and that of non-relapse mortality following allogeneic HCT.

Prediction of outcomes following chemotherapy

Several factors are known to differentiate AML patients at different levels of risk of relapse following chemotherapy. These include age, initial white blood cell count, cytogenetics, molecular status, prior history of myelodysplastic syndrome or cytotoxic therapy for another disorder, and number of induction courses required to achieve CR1. Among these, cytogenetic findings identified at diagnosis have been the mainstay for prognostication of AML. On the basis of these findings, patients are generally stratified into favorable, intermediate and adverse risk categories (Table 1) [4–6]. Although not included in these risk-stratification systems, the monosomal karyotype, defined as two or more distinct autosomal monosomies or a single autosomal monosomy in the presence of other structural abnormalities, has recently been shown to be predictive of extremely poor prognosis, with virtually no long-term survival expected without allogeneic HCT [7–11].

Despite the clinical usefulness of risk stratification based on cytogenetics, patients in each cytogenetic risk group remain prognostically heterogeneous. This is especially true for those with cytogenetically normal AML (CN-AML), which accounts for approximately 40–50 % of all AML cases [12].

Recent advances in understanding the molecular pathogenesis of AML have further refined prognostication of patients with CN-AML. Specifically, the presence or absence of genetic aberrations in the FLT3, NPM1, and CEBPA genes has proven helpful for categorizing patients with CN-AML into different prognostic subgroups [13–24]. By integrating cytogenetic and molecular profiles, an expert panel of the European LeukemiaNet proposed a risk-stratification system for AML (Table 2) [25]. In addition, the expansion of molecular testings to other mutations involving genes such as KIT, DNMT3A, TET2, IDH1, IDH2 can be expected to further refine our current ability to predict outcomes following chemotherapy for AML patients [26–33].

In addition to these disease-related factors, recent studies have shown that findings for minimal residual disease detected by flow cytometry or quantitative reverse-transcribed polymerase chain reaction during or after chemotherapy can identify patients in CR who are at high risk of subsequent relapse [34, 35]. Further information regarding such response-related factors may well improve the currently available risk stratification, for which the results of ongoing and future investigations are eagerly awaited.

Table 1 Definitions of cytogenetic risk categories

	SWOG/ECOG criteria [4]	CALGB criteria [5]	Revised MRC criteria [6]
Favorable	t(15;17), inv(16)/t(16;16)/del(16q), t(8;21) wo del(9q) or complex	inv(16)/t(16;16), t(8;21), del(9q)[a]	t(15;17), inv(16)/t(16;16)/del(16q), t(8;21), all irrespective of additional abnormalities
Intermediate	Normal, +6, +8, −Y, del(12p)	Normal, −Y, del(5q), loss of 7q, t(9;11), +11, del(11q), abn(12p), +13, del(20q), +21	Entities not classified as favorable or adverse
Adverse	del(5q)/−5, del(7q)/−7, t(6;9), t(9;22), abn(3q), abn(9q), abn(11q), abn(17p), abn(20q), abn(21q), complex (3 or more)	inv(3)/t(3;3), t(6;9), t(6;11), −7, +8[b], t(11;19), complex (3 or more)	abn(3q) [excluding t(3;5)], inv(3)/t(3;3), add(5q), del(5q), −5, −7, add(7q)/del(7q), t(11q23) [excluding t(9;11) and t(11;19)], t(9;22), −17/abn(17p), complex (4 or more)
Unknown	All other abnormalities	All other abnormalities excluding t(15;17)	Cytogenetic results not available

SWOG Southwest Oncology Group, *ECOG* Eastern Cooperative Oncology Group, *CALGB* Cancer and Leukemia Group B, *MRC* Medical Research Council

[a] Assigned to the intermediate-risk group if only patients not undergoing transplantation were analyzed

[b] In the absence of t(8;21), t(9;11), or inv(16)/t(16;16)

Table 2 European LeukemiaNet standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data [25]

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD (normal karyotype)
	Mutated CEBPA (normal karyotype)
Intermediate-I	Mutated NPM1 and FLT3-ITD (normal karyotype)
	Wild-type NPM1 and FLT3-ITD (normal karyotype)
	Wild-type NPM1 without FLT3-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLLT3-MLL
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
	t(6;9)(p23;q34); DEK-NUP214
	t(v;11)(v;q23); MLL rearranged
	−5 or del(5q); −7; abn(17p); complex karyotype (3 or more)

Prediction of outcomes following allogeneic HCT during CR1

Although previous studies have demonstrated the prognostic impact of cytogenetic findings at diagnosis on the risk of relapse after allogeneic HCT during CR1 [36–38], the degree to which they affect the outcomes for transplanted patients appears to be much smaller than for patients treated with chemotherapy alone. Results of recent studies suggest that the adverse effect of unfavorable cytogenetics on post-transplantation outcomes is due, at least partly, to poor results for those with monosomal karyotype [10, 11, 39, 40]. Post-transplantation relapse occurs significantly more frequently in patients with monosomal karyotype than in other cytogenetic subgroups, indicating that allogeneic HCT during CR1 may be able to improve, but not completely override the poor prognosis associated with monosomal karyotype. Likewise, the presence of internal tandem duplication of the FLT3 gene (FLT3-ITD) was shown to correlate with poorer outcomes for CN-AML patients undergoing allogeneic HCT during CR1 [41]. While such information can be useful for predicting outcomes after transplantation, a high risk of post-transplantation relapse alone does not abandon allogeneic HCT during CR1 as an option because much more unfavorable prognosis can be expected if allogeneic HCT is not used for such patients.

Of greater importance is the assessment of the risk of non-relapse mortality after transplantation. Investigators at the Fred Hutchinson Cancer Research Center have demonstrated that comorbidities have an independent value for predicting post-transplantation outcomes by developing a scoring system called "HCT-specific comorbidity index (HCT-CI)" (Table 3) [42, 43]. The HCT-CI evaluates 17 kinds of comorbidities, to each of which 0–3 points are assigned based on severity, and the total score has been shown to be significantly associated with overall survival (OS) for patients with AML undergoing allogeneic HCT during CR1 [43]. Another well-known risk assessment tool is the European Group for Blood and Marrow Transplantation (EBMT) risk score (Table 4) [44, 45]. The EBMT risk score has five components: disease stage, patient age, donor type, time interval from diagnosis to transplantation, and donor-recipient sex combination. Although the EBMT risk score was originally developed for patients with chronic myeloid leukemia undergoing allogeneic HCT [44], it has been subsequently validated for AML [45]. These predictive models are increasingly being used in both clinical studies and clinical practice.

Timing of transplantation

Retrospective studies reported a disease-free survival (DFS) rate of 40–50 % for patients receiving allogeneic HCT during second CR (CR2), intimating that the chance of a cure remains relatively high even if the first-line chemotherapy fails [46]. This notion often leads to the recommendation to wait until relapse to administer allogeneic HCT. However, caution should be exercised in view of the fact that such favorable results were obtained from highly selected patients who had achieved CR2 and remained relapse-free and fit enough for allogeneic HCT until transplantation could be performed. In reality, a majority of patients who have experienced relapse do not qualify for allogeneic HCT during CR2, because of failure to achieve CR2, relapse after achieving CR2, or development of organ toxicity or serious infection associated with chemotherapy for disease relapse, and the prognosis of such patients is quite dismal [47, 48]. This situation argues against the strategy of waiting until relapse to perform allogeneic HCT.

Another question regarding the timing of transplantation is, if allogeneic HCT during CR1 is chosen, when it should be performed. Moreover, do patients undergoing allogeneic HCT during CR1 benefit from receiving additional chemotherapy before transplantation? While no prospective studies have addressed the latter question, several retrospective studies have evaluated the effect of post-remission

Table 3 Hematopoietic cell transplantation-specific comorbidity index [42]

Comorbidity	Definition	Scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease,[a] congestive heart failure, myocardial infarction, or EF of ≤50 %	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic, but not controlled with diet alone	1
Cerebrovascular disease	Transient ischemic attacks or cerebrovascular accident	1
Psychiatric disturbance	Depression/anxiety requiring psychiatric consult and/or treatment at the time of HCT	1
Hepatic, mild	Chronic hepatitis, bilirubin >ULN to 1.5 × ULN, or AST/ALT >ULN to 2.5 × ULN	1
Obesity	Patients with a BMI of >35 for adults or with BMI-for-age percentile of ≥95th percentile for children	1
Infection	Documented infection or fever of unknown etiology requiring antimicrobial treatment before, during, and after the start of conditioning regimen	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, and polymyalgia rheumatic	2
Peptic ulcer	Requiring treatment	2
Renal, moderate/severe	Serum creatinine >2 mg/dL,[b] on dialysis, or prior to renal transplantation	2
Pulmonary, moderate	DLco and/or FEV_1 66–80 % or dyspnea on slight activity	2
Prior solid malignancy	Treated at any time point in the patient's history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except asymptomatic mitral valve prolapse	3
Pulmonary, severe	DLco and/or FEV_1 ≤65 % or dyspnea at rest or requiring oxygen	3
Hepatic, moderate/severe	Liver cirrhosis, bilirubin >1.5 × ULN, or AST/ALT >2.5 × ULN	3

EF ejection fraction, *HCT* hematopoietic cell transplantation *ULN* upper limit of normal, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *BMI* body mass index, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *CTD* connective tissue disease, *DLco* diffusion capacity of carbon monoxide, FEV_1 forced expiratory volume in 1 s

[a] One or more vessel-coronary artery stenoses requiring medical treatment, stent, or bypass graft

[b] To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4

Table 4 European Group for Blood and Marrow Transplantation risk score for acute myeloid leukemia [45]

Risk factor	Scores
Age of the patient (years)	
<20	0
20–40	1
>40	2
Disease stage	
First CR	0
Second CR	1
All other disease stages	2
Time interval from diagnosis to transplantation[a] (months)	
<12	0
>12	1
Donor type	
HLA-identical sibling donor	0
Unrelated donor	1
Donor–recipient sex combination	
All other	0
Female donor and male recipient	1

CR complete remission, *HLA* human leukocyte antigen

[a] Does not apply for patients transplanted in first CR (score 0)

chemotherapy before allogeneic HCT [49–53], with none of those studies showing any benefit of adding chemotherapy prior to transplantation. Even when RIC allogeneic HCT is used, where pre-transplantation chemotherapy may conceivably have some advantage in terms of reducing the risk of post-transplantation relapse, there is no evidence to support the use of additional consolidation chemotherapy [52, 53]. On the other hand, several observational studies have reported that the primary reason for not proceeding to allogeneic HCT during CR1 was early relapse [54, 55]. There also remains concern over the possibility that the toxicity resulting from extra consolidation chemotherapy may increase the risk of transplantation-related mortality and even preclude the use of subsequent allogeneic HCT. Taking these findings and considerations together suggests it is advisable, provided a suitable donor is readily available, to perform allogeneic HCT as soon as possible after achievement of CR1.

Donor sources

A human leukocyte antigen (HLA)-identical related donor is the donor of choice for allogeneic HCT. However, since only approximately 40 % of individuals have a matched related donor [54–56], the remaining 60 % need to find an alternative donor to receive allogeneic HCT, such as a

matched unrelated donor, umbilical cord blood (UCB), and mismatched related and unrelated donors. Outcomes of alternative donor transplantation have improved over the past decades, primarily due to the introduction of high-resolution HLA-typing technology as well as improvements in immunosuppressive therapy and supportive care measures. In addition, the growth of unrelated donor registries, and the increasing use of UCB and haploidentical donors have enhanced the chances of finding an alternative donor. This section discusses allogeneic HCT from various types of donors.

Related donors

The question of whether allogeneic HCT during CR1 is beneficial for AML patients has historically been examined in prospective studies that used biologic assignment according to donor availability, in which patients with and without an HLA-identical sibling donor were assigned to allogeneic HCT and chemotherapy/autologous HCT, respectively [57–64]. The results for all patients were then analyzed in terms of intention-to-treat, that is, as belonging to the treatment group they were assigned to, regardless of the treatment actually performed. Although such a study design is not truly randomized, the methodology reduces the selection bias that could not be eliminated in retrospective comparisons. When we combine the results from such "donor vs no-donor" studies, we find that allogeneic HCT during CR1 confers a survival advantage for patients with cytogenetically intermediate and adverse risk, but not for those with cytogenetically favorable risk [62, 65, 66]. This has led to the general recommendation favoring allogeneic HCT from a matched sibling donor during CR1 for younger patients with cytogenetically non-favorable AML. More recently, studies have been conducted regarding the interactions between molecular profiles of leukemia and effects of allogeneic HCT during CR1 for patients with CN-AML. A meta-analysis using individual patient data of four "donor versus no-donor" studies conducted by the German-Austrian AML Study Group showed that patients in the donor group had significantly better relapse-free survival than those in the no-donor group if the patients presented with FLT3-ITD or with wild-type NPM1/no FLT3-ITD [67]. However, no beneficial effect of allogeneic HCT was observed for patients with mutant NPM1/no FLT3-ITD. While these "donor versus no-donor" studies undoubtedly have made significant contributions to the elucidations of the role of allogeneic HCT during CR1, they do not provide an accurate picture of current clinical practice, because an HLA-identical sibling is not the only donor source any longer. Results of previous studies, therefore, need to be interpreted with this in mind.

Regarding HLA-mismatched related donors, several studies have made it clear that a one-antigen mismatch appears to be acceptable [68, 69]. However, an HLA-B antigen mismatch in the graft-versus-host (GVH) direction may be associated with higher risk of non-relapse mortality and inferior OS [70].

Unrelated donors

Non-relapse mortality is the primary obstacle to the success of unrelated HCT. Early studies showed less satisfactory results with unrelated HCT due to a high incidence of non-relapse mortality [71, 72]. However, there have been significant improvements in the outcome of unrelated HCT with the aid of high-resolution HLA typing, increased use of RIC, and better immunosuppressive therapy and supportive care measures. As a consequence, more recent data have shown that allogeneic HCT from an unrelated donor matched at HLA-A, -B, -C, and -DRB1 at the allelic level (hereafter referred to as an 8/8 match) yields results very similar to those of allogeneic HCT from a matched related donor [56, 73–75]. The use of an 8/8 matched unrelated donor is now a fully established choice when a matched related donor is not available. Recently, several groups have conducted prospective "donor versus no-donor" studies for patients with high-risk AML by expanding the type of donor to include unrelated donors [76, 77]. Although the number of patients in each of these studies was limited, they showed not only significantly superior OS for patients with a donor compared to those without a donor, but also similar OS for patients undergoing related and unrelated HCT.

A single HLA allele mismatch is significantly associated with development of graft-versus-host disease (GVHD) and non-relapse mortality, making outcomes for 7/8 unrelated HCT inferior to those for 8/8 unrelated HCT [78, 79]. Nevertheless, given the reported OS rate of approximately 30 % following 7/8 unrelated HCT for patients with cytogenetically unfavorable AML [74], this procedure still appears to be an acceptable choice if the patient has a high-risk disease and no alternative donor is available.

One major problem associated with unrelated HCT involves the time required for donor search, which generally takes several months and sometimes prevents the use of unrelated HCT during CR1.

Umbilical cord blood

The use of UCB as an alternative hematopoietic cell sources has been rapidly expanding in recent years. As UCB units are already cryopreserved and HLA typed, they may overcome the problems associated with lengthy search

time. Another advantage of UCB is fewer restrictions to HLA matching. On the other hand, the most important limitation of UCB is the low cell dose contained in a single unit, which can lead to delayed engraftment, with subsequent post-transplantation infection and even early death. Several large retrospective studies have been conducted to compare UCB transplantation (UCBT) and unrelated bone marrow transplantation (UBMT) [80–83]. Two earlier studies analyzed registry data of adult patients with acute leukemia who had undergone UCBT or UBMT. One of these showed that UCBT was equivalent to mismatched UBMT, but inferior to matched UBMT in terms of non-relapse mortality and OS [80], while another found no differences in outcomes [81]. A more recent study reported that UCBT exhibited worse leukemia-free survival (LFS) and OS than UBMT for patients with AML, with the difference seemingly more pronounced if the analysis was restricted to those receiving their transplantation during CR1 [82]. These observations lead to the notion that outcomes for the use of UCBT in AML therapy may be similar or possibly inferior to those for UBMT. However, all of these studies are confounded by significant bias, because they dealt only with patients who actually underwent transplantation, thus did not consider immediate availability of UCBT, which is a clinically significant factor for opportunities to receive allogeneic HCT before relapse occurs. Given that prospective comparisons of UCBT versus UBMT seem to be difficult to conduct practically, an alternative analytical approach such as a decision analysis is warranted to provide more accurate insights into this issue.

Many attempts have been made to improve UCB outcomes, while others are in progress. Several investigators have used the strategies of double UCB transplantation [84], intra-bone marrow injection of UCB [85], and expansion of UCB units [86]. These efforts are expected to overcome the current limitations of UCBT, especially the relatively high risk of non-relapse mortality.

Haploidentical donors

Allogeneic HCT from haploidentical donors has the unique advantages of rapid availability and a very high chance of finding a donor (theoretically 100 % for a biological parent or child, and 50 % for a sibling). The major obstacle to the success of haploidentical HCT is intense alloreactivity via T-cells both in the GVH and host-versus-graft (HVG) directions. Early attempts to use T-cell-replete grafts resulted in unacceptable rates of GVHD, graft rejection, and non-relapse mortality [87, 88], while ex vivo T-cell depletion reduces the risk of GVHD, but likely produces graft failure [89, 90]. The problem of graft failure may be overcome by infusing a large dose of donor hematopoietic cells [91]; however, this approach is limited by slow immune recovery, resulting in high risks of post-transplantation infectious complications and non-relapse mortality. These attempts, made over a few decades, have, on the one hand, evidenced the considerable difficulties in overcoming the HLA barriers, but have also contributed to improvement in outcomes of haploidentical HCT. In their recently published prospective study, investigators in China compared T-cell-replete haploidentical HCT using G-CSF-primed grafts and anti-thymocyte globulin, with chemotherapy alone as post-remission therapy for patients with AML with intermediate- or high-risk cytogenetics [92]. They were able to demonstrate that haploidentical HCT produced a significant survival advantage over chemotherapy in terms of DFS and OS. The introduction of post-transplantation cyclophosphamide represents a recently developed alternative approach for improving T-cell-replete haploidentical HCT. When administered just after transplantation, high-dose cyclophosphamide depletes alloreactive T-cells from the donor and host, and prevents both GVH and HVG reactions. By employing this approach, acceptable rates of GVHD and non-relapse mortality have been reported [93, 94]. Haploidentical HCT is currently being developed, and further research is needed to establish optimal conditioning regimens and methods for GVHD prophylaxis. However, more favorable results can be expected to have a profound impact on the future alternative donor selection.

Conditioning regimens

The conditioning regimen administered prior to allogeneic HCT for AML has two aims: (1) suppression of the recipient's immune system to facilitate engraftment of donor hematopoietic cells, and (2) exertion of anti-leukemic effect. Historically, myeloablative conditioning regimens were used for allogeneic HCT based on the concept that conditioning regimens must be intensive to ensure engraftment and eradicate the disease. As a matter of course, conventional conditioning regimens caused substantial morbidity and mortality, and thus limited the use of this potentially curative treatment to young patients in good medical condition. However, the development of methods to enable engraftment of donor hematopoietic cells with less intensive conditioning regimens has opened the door to a new era for allogeneic HCT [95–97]. Currently, RIC and non-myeloablative conditioning regimens are widely in use as an alternative to myeloablative conditioning regimens. Such less intensive approaches have contributed greatly to reductions in non-relapse mortality, and consequently have

expanded eligibility for allogeneic HCT to older patients and those with significant comorbidities.

Myeloablative conditioning

The combinations of cyclophosphamide and total-body irradiation (CY/TBI) and of busulfan and cyclophosphamide (BU/CY) are the two most common myeloablative conditioning regimens. Several randomized studies were conducted to compare these two regimens for patients with various diseases, including AML, but with conflicting results [98–101]. A meta-analysis of these prospective randomized studies did not show any overall difference in DFS or OS between the two regimens, although there was a trend for a better long-term survival with CY/TBI for patients with AML [102]. Here, it should be noted that all of these published prospective studies used orally administered busulfan, which is known to be subject to considerable inter-patient differences in absorption and metabolism, leading to differences in exposure to this drug. Low plasma busulfan levels are associated with relapse and rejection, and high levels with hepatic sinusoidal obstruction syndrome and other toxicities [103]. However, several studies reported that the strategy combining therapeutic monitoring of plasma busulfan concentrations and individualized adjustment of the oral dose reduced the incidence of non-relapse mortality and improved survival [104, 105]. The development of intravenous (IV) formulation was another advance in ensuring more effective use of busulfan. In contrast to the oral formulation, IV busulfan has the advantage of a higher inter-patient consistency, thus allowing for tighter control of plasma busulfan levels [106, 107]. These advances have rendered the findings of previous randomized studies using oral busulfan at a fixed dose obsolete to some degree. Two more recent studies retrospectively compared CY/TBI and IV-BU/CY [108, 109]. One study, which analyzed patients with AML transplanted from a matched sibling donor during CR1 or CR2, found that LFS and OS for CY/TBI and IV-BU/CY were comparable, but that IV-BU/CY was associated with lower risk of GVHD, higher risk of relapse, and a trend toward lower non-relapse mortality [108]. In another study, which compared CY/TBI and oral or IV-BU/CY for patients with AML who underwent allogeneic HCT from a related or unrelated donor during CR1, non-relapse mortality was lower, and LFS and OS were better for IV-BU/CY than for CY/TBI, but not for oral BU/CY [109]. Despite a lack of randomized studies, these findings indicate that IV-BU/CY is a more appealing option than oral BU/CY, and either comparable to or even better than CY/TBI as a myeloablative conditioning regimen for patients with AML.

Reduced-intensity and non-myeloablative conditioning

Due to concerns about toxicity, the upper age limit for allogeneic HCT has traditionally been considered to be around 50 years. Because AML is a disease that primarily affects older adults, this potentially curative therapy could be used for only a limited number of patients. Since their development in the late 1990s, however, RIC and non-myeloablative conditioning regimens have made it possible to receive allogeneic HCT for patients who might once have been considered ineligible due to advanced age, previous therapies, and comorbidities. Current data show that morbidity and mortality following allogeneic HCT with RIC or non-myeloablative conditioning are generally lower than those associated with myeloablative conditioning, but suggest that the relapse rate may be higher, especially for patients receiving non-myeloablative conditioning [110–115]. The majority of studies comparing outcomes of RIC and/or non-myeloablative conditioning with those of myeloablative conditioning are retrospective, and thus are confounded by selection bias. To reduce such bias, one study retrospectively compared the use of RIC allogeneic HCT with that of chemotherapy alone as part of post-remission therapy in terms of availability of a matched sibling donor for 95 patients with high-risk AML in CR1 [116]. This “donor vs no-donor” analysis showed that LFS was significantly higher for the donor group than for the no-donor group. To date, only one prospective study to address this issue has been reported [117], in which outcomes for fludarabine-based RIC and those for CY/TBI were compared in a randomized fashion for patients with AML in CR1. Although the study was terminated prematurely because of slow accrual, an analysis of 195 enrolled patients showed reduction of early mortality in the first year, the primary endpoint of the study, for patients assigned to the RIC arm. This effect was prominent for patients over 40 years old, but not for younger patients. Both treatments showed similar outcomes in terms of non-relapse mortality, relapse, LFS and OS after 3 years. Although it should be remembered that no studies have ever conclusively shown the superiority of RIC or non-myeloablative conditioning over myeloablative conditioning, accumulated evidence suggests that RIC allogeneic HCT represents a practicable therapeutic option for selected patients with AML in CR1 who are considered ineligible for myeloablative allogeneic HCT.

Conclusions

The past few decades have witnessed significant advances in allogeneic HCT for AML during CR1. These advances

have contributed to refinements of indications for allogeneic HCT by taking into account the molecular profiles of leukemia and the degree of comorbidities, more opportunities to find a donor by expanding donor sources beyond matched related donors, and augmentation of transplantation eligibility following the introduction of less intensive conditioning regimens. Thanks to these advances, the role of allogeneic HCT during CR1 has become increasingly more important in the treatment of AML. Despite such improvements, however, non-relapse mortality and post-transplantation relapse remain significant problems, so that further improvements in transplantation outcome need to be pursued. Furthermore, establishment of individualization of allogeneic HCT constitutes another future challenge, with regard to for whom, when and how allogeneic HCT should be integrated into treatment strategies. Such undertakings are sure to enhance our ability to provide a cure for patients with AML.

Conflict of interest The author declares no conflict of interest.

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