VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2021
Number 4, Volume 52, pages 237–241
DOI: 10.5603/AHP.2021.0046
ISSN 0001–5814
e-ISSN 2300–7117

Optimal timing and conditioning regimen in allogeneic hematopoietic cell transplantation for AML

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Abstract

In all stages of the disease, allogeneic stem cell transplantation (allo-SCT) plays an important role in the treatment of acute myeloid leukemia. It is an ongoing challenge to find the right balance between the chance of a cure and the risk of dying from side effects of the procedure. With respect to the conditioning, the large number of available protocols, ranging from non-myeloablative to a classical high-dose regimen, offers the opportunity to individualize the treatment, considering both the clinical situation and patient-specific factors such as age and co-morbidities.

As a consequence, allo-SCT has become available to a larger percentage of patients, and the question as to whether or not to undergo a transplantation needs to be answered more frequently. The factors to be considered vary widely among patients in remission, those with relapsed disease, and those who never responded to conventional therapy. This review addresses this discussion, focusing on how to define an individualized and weighted treatment concept for each patient.

Key words: AML, allogeneic transplantation, timing, conditioning

Acta Haematologica Polonica 2021; 52, 4: 237–241

Introduction

Allogeneic stem cell transplantation (allo-SCT) is the treatment modality with the highest potential to cure acute myeloid leukemia (AML). However, antileukemic efficacy is often counterbalanced by a unique treatment-relapse mortality (TRM). Hence, the decision to undergo allo-SCT needs to be thoroughly weighed in each individual patient, considering both the risk of the leukemia and the individual risk factors for TRM. This is of particular importance in the early stages of the disease, when it is crucial to identify those patients who might not require an allo-SCT to achieve long-term disease control, and should therefore not be exposed to the risk of treatment-related toxicity and mortality at that stage.

At the other end of the spectrum, in patients with relapsed or refractory AML, allo-SCT definitely represents the only chance for long term remission, making every patient at this stage a potential transplant candidate. However, both relapse incidence and TRM are high in this patient population, which is why deciding between a high-risk transplant approach and palliative treatment is a challenge. The indication for allo-SCT requires careful consideration on the transplanter's side, as well as extensive discussion with the patient and his or her family.

This review was aimed to discuss factors that might play a role in the decision-making around allo-SCT in the different stages of AML. Particular attention has been paid to the conditioning regimen to be used in each stage, given the fact that both antileukemic control and TRM,

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Received: 30.04.2021 Accepted: 12.05.2021

among other factors, are highly influenced by the preparative protocol.

General remarks on conditioning for allogeneic transplantation in AML

Historically, conditioning for allo-SCT has been applied for three major reasons:

- eradication of leukemia;
- immune suppression to allow engraftment and prevent graft-versus-host disease (GvHD);
- providing space in recipient's bone marrow for transplanted donor hematopoiesis.

During the development of allo-SCT, this third purpose has been questioned by animal studies showing engraftment without conditioning after the transfusion of mega doses of stem cells and repeated administrations, and by the development of non-myeloablative, purely immunosuppressive, conditioning regimens, whose therapeutic efficacy is based on the allogeneic graft-versus-leukemia (GvL) effect alone.

Over time, a large number of conditioning regimens has been developed, and only a minority have been prospectively validated or compared in randomized trials. At the upper end of the spectrum, a traditional myeloablative conditioning (MAC) regimen incorporating high-dose cyclophosphamide (usually 120 mg/kg), plus either total body irradiation (TBI) at a dose of 12 Gy, or busulfan 16 mg/kg per os/12.8 mg/kg intravenous are used. At the other end of the range, a non-myeloablative regimen (NMA) comprising fludarabine and 2 Gy TBI has been shown to allow engraftment.

In between, a wide range of more or less reduced intensity protocols have been published as reduced toxicity (RCT) regimens. As shown in several retrospective comparative studies, TRM was significantly reduced by RCT/NMA. However, this advantage came at the cost of increased relapse incidence, resulting in overall comparable outcomes. In prospective trials comparing RIC to MAC, results were identical in both groups in one trial using two TBI based regimen, whereas in another trial mainly using a chemotherapy-based regimen, MAC was of advantage [1, 2]. Nevertheless, the introduction of RIC/NMA definitely has opened up the opportunity of allo-SCT for elderly patients up to the age of 75, and to patients with co-morbidities who are unable to tolerate a MAC regimen. As a further variant initially designed for high-risk myeloid malignancies, in 2005 the sequential regimen approach was introduced, aiming to combine increased antileukemic efficacy and reduced non-relapse mortality (NRM) [3]. Initial results of this regimen, called FLAMSA-RIC, were promising, in particular in high-risk and advanced disease [4]. However, no advantage could be shown in a recent prospective trial comparing a variant of the original protocol to a fludarabin/busulfan regimen in patients transplanted in complete remission (CR) [5].Further variants of the sequential regimen approach have been developed [6].

In general, no single regimen has been identified as being definitely superior to any other. Hence, no clear standard has been established. To classify the increasing number of protocols, the definitions for MA and NMA protocols have been published on the EBMT website [7]. A more detailed classification was proposed in 2009, using strict definitions for MA protocols (causing irreversible pancytopenia and requiring mandatory stem cell (SC) support) and for NMA regimen (causing minimal cytopenia only and allowing engraftment without SC transfusion). All regimens not fulfilling either definition are categorized as reduced intensity conditioning (RIC) [8]. Most recently, the Acute Leukemia Working Party (ALWP) of the EBMT finally developed a new classification based on intensity weight scores for frequently used conditioning regimen components, using their sum to define the transplant conditioning intensity (TCI) score [9].

Timing of allo-SCT in AML

Aspects for the optimal timing and execution of allo-SCT in AML are different among clinical stages at which the procedure is considered.

Allo-SCT in primary refractory AML (PREF AML)

Primary refractory AML is defined by either morphologically persisting leukemia or by hematological CR with incomplete reconstitution of hematopoesis (CRi) after at least two courses of induction therapy, usually including at least one course that contains high-dose cytosine arabinoside (Ara-C) [10]. In some studies, patients with persisting minimal residual disease (MRD), or patients with >15% blasts or a <50% proportional reduction of blasts after the first course of induction, had a similar prognosis [11]. Risk factors for refractoriness primarily include older age and adverse genetic aberrations. Independently of the exact definition, the overall survival (OS) of patients with PREF AML after conventional chemotherapy is below 10%. Hence, there is broad consent that allo-SCT is the treatment of choice for these patients, who represent about 10–40% of all adults with AML [12].

Following allo-SCT, long-term disease control can be achieved in 25–35%. In fact, it is not completely clear which patients with PREF AML will benefit most from allo SCT, although those proceeding to transplant as soon as possible after a diagnosis of PREF AML without repeated courses of chemotherapy [13] and those transplanted with a lower tumor burden, seem to achieve the best outcome. Hence, starting the search for a donor immediately after initial diagnosis is mandatory among patients with a high risk of developing PREF AML who are able to undergo allo-SCT.

The optimal conditioning for patients with PREF AML remains to be defined. MAC should probably be preferred in patients <50 years, whereas a reduced regimen has led to equivalent or even superior results in older patients. Sequential protocols such as the FLAMSA regimen represent an attractive option up to the age of 65 [4]. Definitely, maintenance therapy after allo-SCT is recommended in patients with PREF AML, either using DLI or pharmacological treatment [14].

Allo-SCT in first complete remission (CR1)

Patient selection and timing of allo-SCT in CR1 is probably the most hotly debated question in the field of AML therapy. In general, for each individual patient, the task is to define the specific balance between the reduction of the risk of relapse and leukemia-associated death by allo-SCT compared to conventional treatment, against the risk of TRM.

Determinants of relapse risk

Besides increasing age, two major determinants for the risk of relapse have been identified: Firstly, adverse genetics at diagnosis as defined by the European LeukemiaNet (ELN) [10] clearly define the biological risk for adverse outcomes. Secondly, the detection of MRD before allo-SCT either by molecular genetics including next generation sequencing (NGS) [15, 16] or by flow cytometry [17], has been shown to be a highly predictive variable for increased relapse incidence and inferior survival post-transplant. Unfortunately, MRD measurement is difficult to standardize both among AML subtypes and among different laboratories, which is why it is hard to define clear cutoff values generally indicating a clinically relevant risk modification. Moreover, in contrast to other markers, detection of mutations in several epigenetic regulators (e.g. *ASXL1, DNMT3A* and *TET2*) did not influence the risk of relapse and these are therefore difficult to be considered for the indication for allo-SCT [15]. Hence, the inclusion of MRD in general into risk estimates remains challenging. Beyond genetics and MRD, some study groups include variables such as leukocyte counts at diagnosis or the quality of response to the first course of induction therapy into the decision for allo-SCT [18].

The risk of TRM

To assess the risk of TRM, several scores have been proposed: Sorror et al. were among the first to adapt a validated comorbidity index for the setting of allo-SCT. More recently, patient age was included into a refined version of this score, allowing for a clear separation of patient cohorts with different risks of TRM based on their comorbidities [19].Using the data from >50,000 transplants reported to the EBMT registry, Gratwohl et al. have established another risk model, comprising patient, disease, and donor variables [20] that was validated for AML in CR1 [18]. More recently, the Acute Leukemia Working Party has proposed a combination of both scores adapted for reduced intensity conditioning [21].

Risk-adapted decision

In general, using genetic risk assessments, MRD and estimators of risk for TRM, the published guidelines [12,18] recommend allo-SCT as consolidation of choice for AML in CR1, if:

- the risk of relapse without allo-SCT is expected to be >35–50%, and
- the chance of achieving long-term leukemia-free survival after allo-SCT is increased by >10%, considering the patient's individual risk for TRM.

In order to further refine the risk-adapted approach, modern techniques such as knowledge bank approaches have been introduced into this field, using multistage models to simulate survival of a given patient in different treatment scenarios [22]. Refined guidance for allo-SCT in CR1 based on this strategy has been proposed [23] However, continuous integration of newly detected variables such as NGS-based genetic risk constellations on one side, and achievements in the management of transplant-associated complications on the other side, is warranted to improve these kinds of scores. Additionally, a prospective validation is mandatory.

Modifying the risk

The increasing amount of data on the prognostic importance of MRD pre-transplant offers the possibility of improving overall results by approaches to improve the quality of remission before the start of conditioning. Novel agents such as the liposomal cytarabine–daunorubicine formulation CPX-351 seem to improve outcomes post-transplant by inducing deeper levels of response [24]. More recently, initial findings were reported on the elimination of MRD pre-transplant by innovative treatments without adding intolerable toxicities [25], opening a window of opportunity to modify an important risk factor for post-transplant relapse.

Conditioning

With respect to conditioning for AML in CR1, there is no one-size-fits-all recommendation, and the ideal regimen is not yet defined. As mentioned above, a MAC regimen is usually preferred for patients below the age of 50nd without significant comorbidities, given its superior antileukemic activity [2]. In older patients, a regimen with reduced toxicity might lead to an overall improvement of survival, given the increasing importance of TRM for outcomes within this patient subgroup [26, 27]. The presence of MRD might be another reason to prefer a MAC regimen, since levels of MRD do alter outcomes after RIC, but not MAC, transplants [28]. However, intensification of the conditioning using a sequential regimen does not modify the role of MRD [5].

Maintenance

Finally, as discussed above in the section on PREF AML, there is increasing interest in the administration of pharmacological or cellular maintenance treatment in order to reduce the risk of post-transplant relapse in high-risk disease. Among others, Flt3 inhibitors such as sorafenib or midostaurin, hypomethylating agents, or HDAC inhibitors such as panobinostat have been successfully used [29–31], and synergistic effects with the graft-versus-leukemia effect [32] have been shown. Unmodified DLI, as well as specifically modified donor immune effector cells, have also been shown to be promising [33], although their prospective validation is still awaited.

Allo-SCT in beyond CR1

Once AML has reached a stage beyond CR1, the indication for allo-SCT is indisputable for all patients who can tolerate the procedure. Scoring systems have been developed to estimate the prognosis of these patients [34]. Long-term survival rates of 30–50% have been reported after allo-SCT in second CR (CR2), whereas outcomes were inferior in patients with untreated or refractory relapse. If morphological CR2 has been achieved, the patient should proceed to allo-SCT as soon as possible [12]. However, since a considerable percentage of relapsed patients will not achieve CR2 due to refractory leukemia or TRM under salvage therapy, the role of re-induction in a patient with an available donor has been questioned. Also, the number of chemotherapy courses has been a risk factor for response and survival in several studies of relapsed and refractory AML [4, 13]. This problem is currently being addressed in the prospective, randomized ETAL 3 trial in Germany (NCT02461537).

Summary

Allo-SCT is an important part of the therapeutic armoury for all stages of AML. Prognostic estimates, the introduction of new methods for disease characterization and monitoring, as well as the use of novel drugs and cellular treatments, will all improve patient selection and clinical outcomes. Increasingly, both the indication for allo-SCT, as well as the way in which the procedure is performed, have become an individualized process into which all available evidence should be included.

However, beyond data from well-designed prospective trials and retrospective studies, neither should the physician's clinical judgement nor the patient's individual preferences be neglected in the decision-making process.

Author's contributions

CS — sole author.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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