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General review

How to prevent relapse after allogeneic hematopoietic stem cell transplantation in patients with acute leukemia and myelodysplastic syndrome

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ABSTRACT

Disease relapse remains the first cause of mortality of hematological malignancies after allogeneic hematopoietic stem cell transplantation (allo-HCT). The risk of recurrence is elevated in acute myeloid leukemia (AML) patients with high-risk cytogenetic or molecular abnormalities, as well as when allo-HCT is performed in patients with refractory hematological malignancies or with persistent molecular or radiological (PET-CT scan) residual disease. For high risk AML and myelodysplasia (MDS), a post transplant maintenance strategy is possible, using hypomethylating agents or tyrosine kinase inhibitors (TKI) anti-FLT3 when the target is present. For Philadelphia positive acute lymphoblastic leukemia (ALL), there is a consensus for the use of TKI anti BCR-ABL as post transplant maintenance.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is considered as a curative option for high-risk hematological malignancies. Relapse remains one of the major causes of treatment failure [1]. Reduced intensity or non-myeloablative conditioning regimens and improved supportive treatments have resulted in a significant increase in the number of patients eligible for allo-HCT, including elderly and/or patients with morbidities. However, relapse rate after this type of conditioning is high [2]. The incidence of relapses for patients with acute myeloid leukemia (AML) in first complete remission (CR1) is approximately 30–40%, with a particularly poor prognosis because most relapses occur in the first year after transplant [3]. The chances for long-term survival are very low in this situation, with a median overall survival of 3 to 4 months and overall survival less than 20% at 2 years [4,5]. Similarly, approximately 30% of patients allografted for acute lymphoblastic leukemia (ALL) with Philadelphia chromosome (Ph) eventually relapse. The rate of relapse is even higher for patients transplanted beyond CR1 or in a situation of refractory disease [6]. Unfortunately, therapeutic options for patients who relapse after allo-HCT are limited and dependent on the general condition of the patient at the time of relapse. Treatments often used in patients eligible for intensive treatment include chemo-

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therapy, often associated with donor lymphocytes infusion (DLI), or even a second transplant from the same or from a different donor. On the other hand, in patients not eligible for intensive treatment, treatment options include discontinuation of immunosuppression (first strategy to be used in the event of loss of donor chimerism and/or MRD positivity by immunophenotype or molecular techniques), DLI, participation in clinical trials, low-dose chemotherapy, hypomethylating agents for AML and myelodysplastic syndromes (MDS) and even palliative treatment.

Alternative strategies such as maintenance treatments (for all patients with high-risk of relapse), or preemptive approaches (for patients with a biological marker indicating a risk of imminent recurrence), are increasingly considered for preventing post-transplant relapse.

Since 2010, the French society of marrow transplantation and cell therapy (SFGM-TC) has set up workshops to harmonize practices in the transplantation of hematopoietic cells [7]. Within the frame of the 7th annual workshops took place in September 2016 in Lille, the working group reviewed the literature in order to elaborate unified guidelines for the prevention and treatment of relapse after allo-HCT. Here, we focus our recommendations on preventives strategies on acute leukemia and MDS.

Table 1
Predictive risk factors for post-transplant relapse.

Parameters	Prognostic variables	Incidence of relapse
Disease risk factors		
Cytogenetic group	Favorable	Low
	Intermediate	Intermediate
	Unfavorable	High
Other cytogenetic abnormalities	Monosomal karyotype	High
Molecular markers	NPM1-mut, FLT3-wt	Low
	Bi allelic CEBPA-mutation	Low
	FLT3-ITD	High
	NMP1-wt, FLT3-wt, CEBPA-wt	Intermediate
	RUNX1, TP53 mut, ASXL1, TET2 for MDS	Intermediate
Disease status before transplant	CR1	Low
	> CR1	High
	Positive MRD at time of transplant	High
Transplant factors		
Conditioning	Reduced intensity conditioning	High?
GVH prophylaxis	ATG-based conditioning regimen	Controversial
GVH	Absence of chronic GVHD	High
Chimerism	Loss of chimerism	High

mut: mutated; wt: wild type.

2. Acute myeloid leukemia and myelodysplastic syndromes

2.1. Identify the risk of relapse

Relapse of AML or MDS is one of the main causes of allograft failure. Several risk factors for relapse have been identified for these affections. These factors are related, on the one hand, to the characteristics of the disease and on the other hand to the treatments preceding transplantation.

In the case of AML, the prognostic factors intrinsic to the disease are the cytogenetic risk groups defined in particular by the European Leukemia Net (ELN) [8,9] with update of the classification in 2017 [10], the disease status (high risk includes more than one induction chemotherapy needed to obtain CR1, CR2, or refractory disease) and the presence of a positive residual disease at the time of transplant or post-transplant [11–13]. For MDS, a prognostic score "Index prognostic system scoring (IPSS)" or "Revised index prognostic system R-IPSS" ≥ 2 [14,15], the absence of CR1, and a percentage of circulating blasts $> 3\%$ [16] are classically risk factors for relapse. The presence of high-risk mutations in TP53, EZH2, ETV6, RUNX1, ASXL1 genes are associated with adverse survival of MDS, independent of other risk factors such as IPSS [17].

Among the risk factors associated with transplantation, reduced intensity conditioning (RIC) [18], the absence of chronic graft versus host disease (cGVHD) [19], and the loss of donor chimerism are associated with a greater risk of relapse [20,21] (Tables 1 and 2).

Table 2
Recommendation on risk factors for relapse of AML/MDS.

Patients categories	Definitions
High risk patients	AML
	ELN 2010 unfavorable or intermediate 2
	CR2 or more, or chemoresistance, or > 1 chemotherapy to obtain CR
	Residual disease (MRD) positive before transplant by flow cytometry or by PCR
	FLT3-ITD positive
	MDS
	High risk or intermediate 2 IPSS or R-IPSS ≥ 2
	Presence of high-risk mutations, for example: TP53, EZH2, ETV6, RUNX1, ASXL1
	Absence of CR after intensive chemotherapy or hypomethylating agents, proliferative disease before transplantation
Standard risk patients	AML
	ELN 2010 intermediate 1 in CR1 with negative MRD
	MDS
	Low or intermediate 1 risk IPSS or R-IPSS < 2

2.2. Which therapeutic strategy after allo-HCT: maintenance or preemptive treatment?

The risk of disease recurrence after allo-HCT in AML remains high, in the order of 30–40% at 3 years, emphasizing the importance of developing strategies to prevent relapse. The prophylactic or preemptive strategies potentially include immunomodulation by rapid reduction of immunosuppressive treatments, DLI, Fms-like tyrosine kinase 3 (FLT3) inhibitors, and hypomethylating agents.

2.2.1. Preemptive strategy

Preemptive treatment of relapse is justified when residual disease is detectable after transplantation, regardless of the tools used to detect it (flow cytometry, cytogenetic, molecular biology), and while the patient is still considered in cytological remission. This strategy may also apply to patients with loss of donor chimerism even if MRD is still negative. Whatever the intensity of the conditioning used (myeloablative or reduced intensity), it is recommended to use one or more monitoring methods if possible, to ensure sensitivity in the detection of the residual leukemic clone, or to detect the appearance of a possible new clone [22]. It seems obvious to propose a complementary treatment to avoid a relapse that is often unavoidable in these two situations. The proposed treatments for this strategy are based on immunomodulation [23,24] or hypomethylating agents [25,26]. With respect to FLT3 inhibitors, there are no studies at present reporting the use of this treatment as preemptive modality. This is mainly due to the fact that the post-transplant evaluation of the FLT3-ITD MRD is technically difficult and that the mutant may be modified at relapse [22].

2.2.2. Maintenance strategy

2.2.2.1. Tyrosine kinase inhibitors (FLT3). FLT3-ITD mutation is observed in about 20 to 30% of patients with AML and is associated with an unfavorable prognosis. Allograft is recommended in these

patients. The risk of relapse, often early, remains high after transplant. Various tyrosine kinase inhibitors such as sorafenib, midastaurin, quizartinib, crenolanib, or giltertinib, are being evaluated in this context. Sorafenib is the only currently available one outside clinical trials. Several retrospective or prospective studies on a small number of patients have demonstrated the feasibility and efficacy of sorafenib given as prophylactic treatment in patients with FLT3-ITD + AML [27–31]. Disease-free survival at 1 year is 85%. The toxicity is essentially limited to the skin and the digestive tract. However, a wider and randomized evaluation is required (several ongoing studies with different inhibitors).

2.2.2.2. Hypomethylating agents. Early administration of azacitidine, a DNA methyltransferase inhibitor, can be considered after allograft for unfavorable karyotype or relapsed AML or MDS or with a positive MRD at the time of transplantation [32–34]. Indeed, hypomethylating agents would also allow the reexpression of antigens associated with tumors and induce a specific response of the CD8+ T lymphocytes after transplant, possibly leading to increased graft versus leukemia (GVL) [35]. Small studies have shown the feasibility and good hematological tolerance of reduced-dose post-transplant azacitidine, generally in the order of 32 mg/m^2/day for 5 days [33]. A randomized trial is ongoing and the results are not expected until 2018 (Table 3).

3. Acute lymphoblastic leukemia (ALL)

3.1. Philadelphia positive ALL (Ph+ ALL)

Treatment of Ph+ ALL before allogeneic transplantation consists of a combination of chemotherapy and TKI. Currently, despite this treatment, the risk of relapse remains high and allograft is recommended especially for the poor molecular responders. The use of a post-transplant TKI is recommended either in routine maintenance therapy or in the case of persistence or recurrence of a significant post-transplant BCR-ABL transcript (preemptive strategy) [36]. The choice of TKI (imatinib 300–400 mg/day, dasatinib 50–100 mg/day [37], nilotinib 200 mg × 2/day) [38] is determined by the tolerance, the possible ABL mutational profile, and the presence of CNS involvement before allogeneic transplantation.

3.2. Philadelphia negative ALL (Ph-ALL)

The evaluation of MRD by flow cytometry or molecular biology combined with chimerism may be useful for predicting relapse. Reduction of immunosuppression and possible DLI may be proposed in the case of MRD+. There is no standardized maintenance treatment. It is likely that the use of new antibodies (blinatumomab, inotuzumab ozogamycin) will be studied preemptively in clinical trial (Table 4).

4. Neuromeningeal prophylaxis post-allograft (AML/ALL)

The incidence of relapse in the central nervous system (CNS) after allo-HCT of acute leukemia is variable according to the series, ranging from 5 to 11% for ALL (13% to 27% if prior neurological involvement) [39–45], and between 1 and 6% for AML [46,47]. The median time to relapse is between 6 and 10 months post-transplant, although isolated CNS relapses seem to occur later (28 months in the pediatric series) [42]. Overall survival varies between 18% and 30% at 3–4 years. CNS involvement prior to transplantation, TBI-free conditioning, RIC and T-depleted grafts, and advanced disease status, are associated with a higher risk of relapse [44,48], probably related to a lower GVL effect in these extramedullary sites [49]. The influence of intrathecal chemotherapy prophylaxis post-allogeneic SCT on the rate of neuromeningeal relapse is controversial, most of the series are old and the

Table 3
Recommended therapeutic strategy after allo-HCT for AML/MDS.

Diseases	Strategy	Interventions
Standard risk AML/MDS (see definition above, Table 2) MRD becomes detectable after transplantation (negative before transplant, molecular relapse situation) Loss of chimerism (irrespective of the MRD)	Preemptive	*One or more options are possible* Immunomodulation (in the absence of GVHD) Early discontinuation of immunosuppression (before day 100) Preemptive DLI after day 100 (standard risk, positive MRD, loss of chimerism) [21,35]. Consider escalation of DLI doses in patients at high risk of relapse (loss of chimerism, disease proliferation despite 1st DLI) Hypomethylating agents Azacitidine 75 mg/m^2/day × 7 days once a month or decitabine 20 mg/m^2/day × 5 to 10 days once a month, but significant hematological toxicity Reduced doses in the case of early treatment after allograft (< day 100) or in case of leucopenia and/or thrombocytopenia. Treatment should be discontinued if renal insufficiency, grade IV hepatic toxicity or GVHD appearance or severe exacerbation) [24,25] Starting as soon as possible after the onset of positive MRD or loss of chimerism, duration of 12 to 24 months if tolerable and according to the response
High risk AML/MDS (see definition above, Table 2)	Maintenance	*One or more options are possible* Immunomodulation (in the absence of GVHD) Early discontinuation of immunosuppression (before day 100): decrease of mycophenolate mofetil from day 30 and reduction of ciclosporin from (day 60–90) in the absence of any signs of GVHD Prophylactic DLI may be proposed beyond day 100 and 1 month after discontinuation of immunosuppression, and if the patient does not have GVHD or an obvious relapse. These DLI can be repeated at escalated doses Hypomethylating agents Reduced doses: azacitidine (32 mg/m^2/day × 5 days) once a month or decitabine (5 to 10 mg/m^2/day × 5 days) once a month Starting on day 60 if possible, duration of 12 to 24 months if tolerable FLT3 inhibitors (if FLT3 ITD) Sorafenib 200 to 400 mg × 2/day (to be adapted according to the tolerance) Starting on day 60 if possible, duration of 12 to 24 months if tolerable Transient activity in the treatment of relapse Randomized studies are ongoing with other TKI (midostaurin, gilteritinib)

Table 4
Recommended therapeutic strategy after allo-HCT for ALL.

Diseases	Strategy	Interventions
Philadelphia positive ALL	Maintenance	Irrespective of MRD, TKI post-transplant therapy should be prescribed. Imatinib should be started between day 60 and day 100 at 300 or 400 mg daily for at least 2 years of molecular remission. Another TKI can be proposed if resistance before allograft or intolerance post-allograft or CNS involvement (dasatinib) If negative MRD and maintenance are not performed, mandatory close monitoring of the bcr-abl transcript. If signal appearance, consider discontinuation of immunosuppression and onset of TKI
Philadelphia negative ALL	Preemptive	Evaluation of MRD by flow cytometry or molecular techniques combined with donor chimerism may be useful for predicting relapse Reduction of immunosuppression if possible and DLI may be proposed in the case of MRD positivity There is no standardized maintenance treatment. It is likely that the use of new antibodies (blinatumomab, inotuzumab ozogamycin) will be studied pre-emptively in clinical trials

conclusions are contradictory. Two recent publications compared retrospectively the incidence of CNS relapse in two groups of patients with or without post-transplant prophylaxis. The first [43] compared 238 allograft that received intrathecal prophylaxis with methotrexate alone or combined with cytarabine and 219 allograft that did not receive prophylaxis. All patients were allografted between 2000–2011 in three centers (MDACC, FHCRC, RMC) for ALL in CR1 or CR2. This study did not show a significant difference between the two groups in terms of CNS relapse post-transplant (1.5% vs 6%, $P = 0.08$). A high incidence of CNS relapse was observed in both groups in patients with pre-transplant CNS involvement. The second study [42] compared in a series of pediatric transplants, mostly ALL, 136 patients who received prophylaxis to 261 patients who did not received prophylaxis. The incidence of relapse was similar in both groups (4.5% vs 3%).

5. Recommendations for the prevention of neuromeningeal relapse

No systematic intrathecal chemotherapy prophylaxis post-allogeneic transplantation.

Disclosure of interest

The authors declare that they have no competing interest.

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