Hematopoietic stem cell transplantation in the treatment strategy of acute leukemia

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This review article discusses the current indications for allogeneic hematopoietic stem cell transplantation in adult patients with acute myeloid or lymphoblastic leukemia.
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Introduction

For many patients with acute leukemia, allogeneic hematopoietic stem cell transplantation (HSCT) has provided the best chance for long-term survival.[1-3] Anti-tumour activity of conventional (myeloablative) allogeneic HSCT has relied on both the administration of high-dose chemo/radiotherapy given within the conditioning regimen, and on the eradication of residual leukemic cells by graft-versus-leukemia effects.[4] The power of graft-versus-leukemia effects has been best demonstrated by the observation that acute myeloid leukemia (AML) patients given grafts from identical twins after myeloablative conditioning had a 2.5-fold higher risk of relapse than those given grafts from human leukocyte antigen (HLA)-identical siblings.[4] The main complications of myeloablative allogeneic HSCT include toxicity of the conditioning regimen, infections, and graft-versus-host disease (GVHD; a life-threatening disease due to the destruction of host healthy organs by donor immune cells).

Autologous HCST has been developed as a way to administer high-dose chemoradiotherapy in young leukemic patients lacking a human leukocyte antigen (HLA)-matched donor. Limitations of this approach include the possible contamination of the autologous grafts by residual leukemic (stem) cells, and the absence of graft-versus-leukemia effects. More recently, allogeneic HSCT following reduced-intensity conditioning (RIC) or truly non-myeloablative conditioning has been developed as a way to perform allogeneic HSCT in patients who are too old or too sick to tolerate high-dose chemoradiotherapy.[5] In these approaches, the burden for tumour eradication depends mainly (RIC) or nearly exclusively (non-myeloablative conditioning) on graft-versus-leukemia effects (*Table 1, page 119*).[6,7] This review discusses the current indications for autologous and allogeneic HSCT in adult patients with AML or acute lymphoblastic leukemia (ALL).

Hematopoietic stem cell transplantation as treatment for acute myeloid leukemia

AML in first complete remission

Younger patients (<55 years of age)

The indications for allogeneic HSCT have been defined most clearly for younger patients with HLA-identical related donors. Prospective (genetically

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Table 1. Anti-tumour mechanisms of allogeneic and autologous hematopoietic stem cell transplantation (HSCT).

	High-dose chemo/radiotherapy	Graft-versus-leukemia effects
Myeloablative allogeneic HSCT	++++	++++
Reduced-intensity allogeneic HSCT	++	++++
Non-myeloablative allogeneic HSCT	+/-	++++
Autologous (or syngeneic) HSCT	++++	-

randomized) studies have demonstrated a survival advantage for allogeneic HSCT over chemotherapy for patients <55 years of age with high risk cytogenetics (defined as any cytogenetic abnormality excepted -Y, -X, t(8;21) or inv(16)), and intermediate-risk cytogenetics (defined as normal cytogenetics or –Y, -X).[1,3] This advantage was mainly seen in patients younger than 40 years of age. In contrast, there was no advantage (but no disadvantage either) for allogeneic HSCT in patients with good-risk cytogenetics (core binding factor leukemia; t(8;21) or inv(16)), while patients with promyelocytic (t(15;17)) leukemia are generally not transplanted in first complete remission (CR).

More recently, 2 molecular abnormalities have allowed separating patients with normal cytogenetics into a high-risk molecular group (*FLT3* internal tandem duplication (FLT3-ITD) or wild type *NPM1* and *CEBPA*) that benefits from allogeneic HSCT, and a low-risk molecular group (mutated *NPM1* without *FLT3*-ITD or mutated *CEBPA* without *FLT3*-ITD) that does not benefit from allogeneic HSCT.[8] Furthermore, patients with t(8;21) and c-*KIT* mutation or *FLT3*-ITD are also reclassified into the high-risk molecular group.

Most groups also recommend performing allogeneic HSCT in CR1 in patients who required 2 induction courses to achieve a CR, in those with secondary AML, and in those with evidence of molecular disease (such as persistent WT1 expression) after consolidation chemotherapy.[9,10] Patients >40 years of age with medical comorbidities might benefit from a RIC/non-myeloablative conditioning instead of a myeloablative conditioning, as recently suggested by Sorror et al.[11]

With recent progress in HLA typing, the results of allogeneic HSCT with 10/10 HLA-allele-matched unrelated donors are now approaching those observed with HLA-identical sibling donors.[12] Although there is thus far insufficient evidence to routinely recommend allogeneic HSCT with unrelated donors in patients in first CR, several investigators advocate that the indication of allogeneic HSCT with HLA-identical sibling or HLA-matched unrelated donors might be similar (*Table 2*) since the 2 procedures are associated with almost similar risks of non-relapse mortality.[13] This is particularly accepted for patients in the high-risk group.

The role of autologous HSCT in AML patients in CR1 remains debated. Since the relapse incidence after autologous HSCT in patients with high-risk cytogenetics is very high, this treatment option is being abandoned in this group of patients.[1] In contrast, large meta-analyses are ongoing to define the role of autologous HSCT, if any, in patients with good-risk cytogenetics or good-risk molecular AML. Currently, the results of autologous HSCT, and of 3-4 courses of high-dose cytarabine consolidation are considered equivalent in term of overall survival, and the choice may rely on patient preference. Autologous HSCT with peripheral blood stem cells should always be performed after ≥2 courses of consolidation chemotherapy, and should not be performed with peripheral blood stem cells (PBSC) containing >7.5x10^6 CD34/kg.[14]

Older patients (>55-60 years of age)

Early results with allogeneic HSCT after non-myeloablative conditioning and RIC for patients with AML in CR1 are encouraging, with 2-year survival rates ranging from 48-79% among studies.[5] Furthermore, several retrospective studies have demonstrated similar outcomes in adult patients with AML in CR given either myeloablative or non-

Table 2. Classification of acute myeloid leukemia (AML) according to genetic and molecular factors.

	Factor
Low-risk AML	- inv(16) or t(16;16) - t(8;21) without *c-KIT* mutation and with <20,000 WBC - t(15;17) - normal cytogenetics with mutated *CEBPA* but without *FLT3*-ITD - normal cytogenetics with mutated *NPM1* but without *FLT3*-ITD
Intermediate-risk AML	- normal cytogenetics with wild type *NPM1* and *CEBPA*, and without *FLT3*-ITD - -X, -Y, +6, del(12p) - t(8;21) without *c-KIT* mutation but with ≥20,000 WBC
High-risk AML	- abnormal cytogenetics not belonging to the low-risk or standard-risk groups - t(8;21) with *c-KIT* mutation - normal cytogenetics (or –Y?) with *FLT3*-ITD - secondary AML (after MDS or chemotherapy) - 2 courses of induction needed to achieve CR - minimal residual disease after consolidation chemotherapy

WBC=white blood cells, ITD=internal tandem duplication, MDS=myelodysplastic syndrome, CR=complete remission.

myeloablative conditioning.[15,16] Based on these results, several investigators advocate performing RIC or non-myeloablative HSCT in patients with high-risk AML (as defined above) in first CR, at least in patients without significant comorbidities. A prospective randomized trial comparing RIC transplantation versus no transplantation is ongoing in Europe in order to better define the role of RIC transplantation in elderly patients with AML.

Advanced AML

Refractory AML

Patients with refractory AML are defined as those who never achieve a CR, as well as patients who experience leukemia relapse within 6 months of diagnosis. Those patients have a poor prognosis with chemotherapy, but also with allogeneic HSCT. Indeed, for patients with primary refractory AML, conventional myeloablative HSCT results in about 10% long-term survival. However, recent strategies combining intensive rescue chemotherapy with reduced-intensity conditioning allogeneic HSCT (sequential regimens) are encouraging. For example, a 40% survival rate at 2 years has been achieved in patients with refractory/relapsed AML with the FLAMSA-RIC-ATG regimen combining fludarabine 30 mg/m^2, high-dose cytarabine 2 g/m^2, and amsacrin 100 mg/m^2 from days -12 to -9, 4 Gy total body irradiation (TBI) on day -5, cyclophosphamide (40 mg/kg with HLA-identical sibling, 60 mg/kg with unrelated or mismatched donors) on days -4 and -3, and rabbit antithymocyte globulin (10 mg/kg for HLA-identical sibling, 20 m/kg for unrelated or mismatched donors) from days -4 to day -2.[17]

Relapsed AML

Even though prolonged second remissions can be achieved with chemotherapy in some patients with relapsed AML associated with inv(16) or with relapsed promyelocytic leukemia, no chemotherapy regimen has offered durable second remissions or long-term survivals. This is in sharp contrast with results reported by the Center for International Blood and Marrow Transplant Research (CIBMTR), where patients with AML in second CR had 5-year probabilities of survival of about 35% after allogeneic HSCT, and about 25% after autologous HSCT.[18] An open question is whether patients with AML in first untreated relapse should go directly to transplant or should first be re-induced with conventional chemotherapy.[19] At least in patients with only cytogenetic or molecular relapse, allogeneic HSCT without re-induction appears as a good option.

Key messages for clinical practice

1. Patients <55 years of age with high-risk acute myeloid leukemia (AML; as defined in Table 2) might benefit from an allogeneic hematopoietic stem cell transplantation (HSCT) with a human leukocyte antigen (HLA)-matched related or unrelated donor.
2. Patients <55 years of age with high-risk acute lymphoblastic leukemia (ALL) benefit from an allogeneic HSCT with a HLA-matched related or unrelated donor.
3. Older patients with high-risk AML or ALL might benefit from reduced-intensity allogeneic HSCT.

Hematopoietic stem cell transplantation as treatment for acute lymphoblastic leukemia

ALL in first complete remission

Given the accumulating new data regarding risk stratification of adult ALL on the one hand, and the development of RIC regimens on the other hand, the indications for allogeneic HSCT in ALL in CR1 are a moving target. Historically, poor-risk factors for ALL included age >35 years, elevated white blood cells (WBC) at diagnosis (defined as >100x10^9/l for B-cell ALL and >30x10^9/l for T-cell ALL), T-cell lineage versus B-cell lineage, presence of adverse cytogenetics (Philadelphia chromosome (Ph; t(9;22)), t(4;11)), slow response to induction, and mature B-cell phenotype.[20] Recent studies have improved the cytogenetic classification of ALL. Patients with t(9;22), t(4;11), t(8;14), complex caryotype (defined as ≥5 chromosomal abnormalities), or low hypodiploidy/near triploidy were shown to have the worse survival, while patients with high hyperdiploidy or a del(9p) had a favorable survival.[21] Furthermore, the presence of a *NOTCH1/FBXW7* mutation was associated with favorable outcome in patients with T-cell ALL.

Ph+ ALL patients have a very poor outcome with chemotherapy, and allogeneic HSCT with a HLA-identical donor or an alternative donor should be proposed to all eligible patients. In 2005, Yanada et al. reported the results of a meta-analysis of 1,274 patients with ALL in first CR included in either one of 7 prospective studies reported between 1994 and 2005.[22] Results of the meta-analysis demonstrated a survival benefit for patients with a donor that was significant in high-risk ALL patients. Goldstone et al. reported the results of the largest ALL trial to date in which all patients with a sibling donor were referred to allogeneic HSCT in first CR, whereas those without a donor were randomized between chemotherapy or autologous HSCT.[23] The 5-year survival rate was 53% in patients with a donor versus 45% in patients without donor (p=0.01). Interestingly, high-risk patients (defined as patients older than 35 years or those with a high WBC count at presentation (≥30x10^9/l for T-cell lineage and ≥100x10^9/l for B-cell lineage)) along with all Ph+ patients had a survival of 41% versus 35% for donor versus no donor, respectively, which was not significantly different (p=0.2). However, 5-year survival was significantly improved among patients at standard risk (62% versus 52% for donor versus no donor, respectively (p=0.02)). High-risk patients had significantly lower risk of relapse in the donor group (p<0.0001), but this was offset by a higher risk of transplant-related mortality, perhaps because age >35 years was one of the factors classifying patients in the high-risk group. Patients without a donor randomized to autologous HSCT had worse 5-year survival than those randomized to receive additional chemotherapy (37% versus 45%, p=0.03), but the survival advantage for the donor arm persisted when patients randomized to the autologous HSCT arm were censored at the time of autologous HSCT.

For patients without a HLA-identical sibling, a recent analysis by the CIBMTR observed similar outcomes in ALL patients transplanted from a 8/8

HLA-allele-matched unrelated donor than in those transplanted from a HLA-identical sibling donor.[24] Furthermore, Mohty et al. recently reported encouraging results for ALL patients given RIC allogeneic HSCT in first CR in European Group for Blood and Marrow transplantation (EBMT)-affiliated centers, with a 2-year overall survival rate of 52%.[25] This suggests that RIC allogeneic HSCT might be a reasonable option for older patients with ALL in first CR.

Advanced ALL

The outcome in patients with relapsed ALL is poor, and in many cases salvage after relapse is not feasible.[26] Nevertheless, adult patients who can achieve a second CR might benefit from allogeneic HSCT with a 5-year survival of about 25%.[18] Furthermore, survival for infants with ALL in CR2 offered an allogeneic HSCT is more encouraging.

Conclusions

Recent analyses based on cytogenetics, molecular markers and status of minimal residual disease have helped to better stratify patients among those who might benefit from allogeneic HSCT and those who might not.

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