

* CHAPTER 21

HSCT for acute lymphoblastic leukaemia in adults

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1. Introduction

Haematopoietic stem cell transplantation (HSCT) has gained an increasingly important role in the treatment of adult ALL. The majority of large prospective studies in adult ALL have addressed the issue of HSCT, but indications for HSCT in first CR, scheduling and procedures are still not satisfactorily defined (1, 2). The advantages of HSCT (short treatment duration, favourable outcome in some trials) must be compared to the disadvantages (mortality and morbidity, late complications) and assessed in relation to the outcome of increasingly effective conventional and targeted chemotherapy regimens. The focus of debate is still the question whether all adult ALL patients with a sibling donor should proceed to HSCT, or only those with specific risk factors.

2. Indications for transplantation

Most European ALL study groups define an indication for HSCT in patients with unfavourable prognostic factors associated with a survival probability of less than 40% with chemotherapy alone (3). Both matched related (SIB) and matched unrelated (MUD) HSCT are considered as alternatives. The prognostic models differ slightly as well as the upper age limits.

The presence of detectable minimal residual disease (MRD) beyond first consolidation chemotherapy (CT) provides an important new indication for HSCT. Two major questions can be raised about MRD based indications for HSCT:

- Is HSCT really a recommendable option in patients with high MRD, since they are prone to a higher relapse rate after HSCT?
- Is HSCT justified in patients with conventional high-risk (HR) features but negative MRD status?

Some study groups define an indication for SIB-HSCT in all patients with a sibling donor. Most recently this recommendation was reconsidered and SIB-HSCT particularly suggested for young standard risk (SR) patients (4). This is in contrast to the strategy of adopting paediatric intensive chemotherapy regimens, rather than HSCT, in adolescents and young adults, in order to avoid acute mortality and long-term effects. There is general agreement that all patients in 2nd or later remission are candidates for HSCT. This includes molecular relapse, defined as reappearance of MRD above 10^{-4} – 10^{-3} . In advanced disease, depending on donor availability and general condition, experimental HSCT procedures (see below) may be considered, ideally within clinical trials.

2.1. Evidence-based recommendations for HSCT in adult ALL

An evidence based review underlined that HSCT offers an advantage compared to

chemotherapy in HR patients and in 2nd remission (5). A meta-analysis of 7 studies showed a broad variation in terms of the proportion of patients allocated to transplant who actually received a transplant, which varied between 68–96% for allo- and 9–81% for auto-HSCT. Outcome in patients with a donor was correlated with the proportion who actually received an allo-HSCT. Again the survival for HSCT was superior to chemotherapy; the advantage was particularly evident in HR patients (6). However the role of allo-HSCT in SR ALL remains unclear. [Table 1](#) outlines the indications for HSCT in the German Multicenter Study Group for adult ALL (GMALL) as an example of a risk adapted approach.

Table 1: Indications for HSCT in the GMALL trials

	Indication	Priorities *	Controversies
High Risk	All patients within 3–4 months from diagnosis	1. Allo sibling 2. Allo MUD**	No HSCT in MRD negative pts
Standard Risk	Molecular non-responders	See above	Allo sibling HSCT in all young SR pts with donor
Relapse (including molecular relapse)	All patients in 2 nd CR (if necessary in good PR or early relapse)	See above (consider cord blood or haploidentical HSCT if no donor available)	

**Decision depends on age, patient's general condition and donor availability. **Matched or one antigen mismatch*

3. Role and outcome of HLA-identical sibling transplant

According to the EMBT and CIBMTR registries, survival after SIB-HSCT in 1st CR is about 48–49% in adults (7, 8). Relapse rate (RR) and transplant related mortality (TRM) range both between 25–30%. Although TRM is strongly correlated with age, the upper age-limit for SIB-HSCT has increased continuously up to 50–55 years. Survival after HSCT is poorer for patients in 2nd remission (29–34%) and with advanced disease (15–18%) (7, 8). This is mainly due to an increasing RR.

4. Role and outcome of matched unrelated (MUD) allogeneic transplant

The role of MUD becomes more important since only 1/3 of patients have a matched sibling donor. The survival for MUD-HSCT in 1st CR is around 42–45%, with a lower RR and higher TRM (around 32%) compared to SIB-HSCT (7, 8). It has to be borne

in mind that MUD series generally comprise selected HR patients. In 2nd remission MUD-HSCT results in a long term survival of 28% and in advanced disease of around 11%, due to a higher RR but particularly to a higher TRM of 43–48% (7). Due to improved supportive care, better donor selection and extension of indications beyond very high-risk patients, the results of MUD-HSCT are nowadays almost equivalent to those of SIB-HSCT.

5. Role and outcome of autologous transplant

According to published studies the overall survival of patients receiving auto-HSCT in 1st CR is 42%. The major problem is the high RR of 50% or more. The intensity of pre-treatment has an important impact on outcome of auto-HSCT, since it leads to a reduction of tumour load. Thus auto-HSCT may be an option in HR patients with negative MRD status. Maintenance therapy after HSCT e.g. with mercaptopurine and methotrexate, or imatinib in Ph-positive ALL – particularly in MRD positive patients – is also an effective approach.

Several randomised studies showed no difference for the comparison of chemotherapy versus auto-HSCT or even a significantly inferior outcome for auto-HSCT (4). Most comparisons of allo- and auto-HSCT have shown an inferior outcome of auto-HSCT.

6. Comparisons of chemotherapy and HSCT based approaches

To circumvent the problem with comparability of HSCT and chemotherapy, several groups have designed prospective trials with a “genetic” randomisation offering SIB-HSCT in CR1 to all patients with donor. Results certainly strongly depend on the compared “conventional” treatment approach and on whether those patients with a donor actually receive HSCT. The majority of studies did not show an overall advantage for patients with donor; however in the HR group generally patients with a donor had a superior outcome (1). Recently the ECOG/MRC group reported their results comparing patients with a donor (SIB-HSCT) to those without donor (randomised comparison of chemotherapy and auto-HSCT). The special feature of this trial was the use of age (< or >35 years) as a prognostic factor. SR patients were by definition younger than 35 years without adverse prognostic factors. Ph-negative patients with a donor had a superior OS (53%) compared to those without a donor (45%), mainly due to a lower RR. The difference was particularly evident in SR (OS 62 vs. 52%) but not in HR (OS 41 vs. 35%) patients (4). The TRM reached 20% even in the young SR patients and 39% in the older HR patients. Two conclusions can be drawn:

- The outcome of HSCT is better in younger patients
- In older HR patients the outcome is similarly poor with chemo and HSCT.

It is likely that outcome with optimal chemotherapy is similarly good or even better than HSCT in young SR patients, as demonstrated in paediatric studies. For older HR patients the results underline the need to improve conditioning regimens and reduce pre-transplant morbidity and TRM.

7. Role and outcome of haploidentical transplant

For haploidentical HSCT experience is restricted mainly to paediatric patients, where it may be considered in patients without donor and with urgent need of HSCT. In adults haploidentical HSCT is an experimental approach and should be restricted to specialised centres and later stage of disease, and should preferably be performed within clinical trials.

8. Role and outcome of cord blood transplant (UCB)

The experience with UCB transplantation in ALL mainly comes from paediatric patients. In adults the limited cell dose is one of the major obstacles. Initial registry results for younger adults with acute leukaemia indicate however that UCB (single or double) can be considered as an alternative source, if available (9).

9. Conditioning

There is also no standard for the conditioning regimen before HSCT in ALL. Most regimens are based on total body irradiation (TBI). The usual dose is 12 Gy. TBI is most frequently combined with cyclophosphamide (Cy) or VP16. A recent analysis of EBMT registry patients showed no difference in outcome for SIB-HSCT with TBI/VP16 or TBI/Cy in CR1. In second remission the TBI/VP16 combination was associated with a lower relapse risk (10). Clearly inferior results were reported for busulfan-based preparative regimens compared to TBI based regimens. With RIC-HSCT one third of patients may survive if transplant is performed in 1st CR (11).

10. Nature and role of MRD monitoring after transplant

After transplantation regular evaluation of chimerism and MRD shows the individual course of disease. The outcome after HSCT is influenced by the status of MRD before and after HSCT. In Ph-positive ALL it has been demonstrated that in patients with MRD after HSCT the survival was significantly superior in those who rapidly responded to imatinib compared to those who did not respond (12). The outcome of patients with a high level of MRD before HSCT is poor. Therefore MRD status must be considered both before and after HSCT, to decide on additional treatment either before HSCT in order to reduce tumour load or after HSCT to prevent relapse.

10.1. Nature and role of any additional cellular or chemotherapy post-transplant

In early relapse, preferably molecular relapse, immunologic treatments such as reduction of GvHD prophylaxis and/or application of donor lymphocytes are promising approaches for preventing overt relapse. In Ph-positive ALL post-transplantation treatment with imatinib – either up-front or after detection of MRD – appears to be a very successful approach.

11. Stem cell transplantation in Ph+ ALL

Due to the poor outcome with intensive chemotherapy, HSCT has always been the treatment of choice for Ph+ ALL. The survival after allo-HSCT in first CR ranges between 27–65% (13). The RR is higher than in Ph-negative ALL and the outcome is compromised by TRM due to the higher median age of Ph+ ALL patients. Nowadays the majority of patients with Ph+ ALL receive imatinib as front-line therapy. Apparently there is no increase in TRM if HSCT is performed thereafter. The outcome of HSCT in Ph-positive ALL is strongly correlated with the level of MRD before and after HSCT and with the use of imatinib as part of the post-transplantation strategy (see above).

12. Prognostic factors

Prognostic factors are not only used to identify HR patients who could benefit from HSCT. To an increasing extent prognostic factors have been described which help to estimate the risks of the HSCT itself, such as patient age, donor characteristics, degree of matching etc. Bringing both risk estimates together will in future allow a more accurate definition of indications for HSCT. Besides age, scoring of comorbidities may assist decision-making regarding indication for HSCT and the intensity of conditioning.

13. Future options in HSCT

Large national and even international study groups are committed to the development of chemotherapy schedules and optimal integration of HSCT in front-line therapy. One important point is the balance between efficacy and toxicity of pre-transplant treatment and preparative regimens, in order to reduce TRM. Also the optimal timing of HSCT has to be defined. For an improvement of outcome after allogeneic HSCT a reduction in both RR and TRM is required. High resolution HLA typing and improved infection prophylaxis are important in this respect. For patients without a donor or with a contraindication to conventional HSCT alternative approaches need to be explored. MRD evaluation before and after HSCT is of interest, particularly in order to decide

on maintenance therapy and immunotherapy such as donor-lymphocyte infusions. The prophylactic application of donor lymphocytes may be considered in patients with no or low GvHD.

References

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Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **Which post-transplantation strategy is most successful in Ph/BCR-ABL positive ALL**
 - a) Imatinib
 - b) Mercaptopurine/methotrexate
 - c) No treatment (to avoid toxicities)
 - d) DLI only

2. **Is non-myeloablative HSCT an option in adult ALL?**
 - a) Not at all
 - b) Generally preferable due to lower toxicity
 - c) Within studies focussed on older and/or patient with comorbidities
 - d) Based on individual decision and patients wish

3. **What are the results of allo sibling HSCT compared to matched unrelated SCT (MUD) in adult ALL?**
 - a) Sibling SCT clearly superior
 - b) MUD SCT clearly superior
 - c) Similar overall results with higher relapse rate and lower TRM for sibling SCT
 - d) Similar for matched or mismatched donors

4. **What are the results of autologous HSCT compared to chemotherapy?**
 - a) Similar in most studies
 - b) Inferior compared to chemotherapy
 - c) Superior compared to chemotherapy
 - d) Independent of minimal residual disease and post-transplant maintenance

5. **Which is the standard for conditioning in adult ALL?**
 - a) TBI based regimens
 - b) Busulfan based regimens
 - c) Non-myeloablative regimens
 - d) Use of ATG and prophylactic DLI