



Stem Cell Transplantation for Acute Lymphoblastic Leukemia

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Introduction

Standard treatment of ALL is generally divided into three phases: (1) induction chemotherapy, for rapid restoration of normal bone marrow function, (2) CNS prophylaxis and/or treatment, and (3) post-remission therapies to eliminate minimal residual disease (MRD). In the MRC UKALL XII/ECOG E2993 study, the largest prospective international trial involving adults with ALL, induction chemotherapy achieved a CR rate of 91% for all 1521 patients¹. Patients at standard risk (Ph⁻ and no other adverse risk factors) had a CR rate of 97%, however, even those at higher risk did well, with CR rates of 83% in Ph⁺ patients, and 90% in Ph⁻ patients with high risk features (age >35 and/or WBC >30 x10⁹/L for B-lineage or >100 x10⁹/L for T-lineage). Despite having initial response rates almost as high as those seen with pediatric ALL, treatment-related mortality is significantly higher (4.8%, majority due to infection), as is the risk of relapse, with an overall 5-year survival rate of 38% for all patients in the study, a stark contrast to the approximately 80% long-term survival seen in children². Of note, those who were unable to achieve CR had an overall survival of 5%. The presence of CNS disease at diagnosis is associated with poorer outcomes (29% overall survival vs. 34% in patients without CNS disease, p=0.03), thus these patients will require additional CNS therapy including intrathecal and systemic chemotherapy, and cranio-spinal irradiation³. Post-remission therapy can consist of either intensified chemotherapy treatments followed by prolonged maintenance therapy, or the use of hematopoietic stem cell transplantation, which will be the focus of this review.

Allogeneic Transplantation in Standard Risk ALL in CR1

Adults with ALL are considered standard risk if they are <35 years of age, and present with a low WBC count (<30 x10⁹/L for B-lineage or <100 x10⁹/L for T-lineage) in the absence of any other poor-risk cytogenetic abnormalities (Table 1)^{1,4}. Historically, allogeneic HSCT in first CR was reserved for patients with high-risk features as they appeared to receive the greatest benefit from allogeneic HSCT^{5,6}. Patients with standard risk enjoyed fewer relapses after allogeneic HSCT but at the expense of unacceptable treatment-related mortality, such that long-term leukemia-free survival was similar to that achieved with conventional chemotherapy alone⁶⁻⁸. Long-term follow-up results of the prospective LALA-87

trial revealed that standard risk patients (n=75) had similar outcomes whether or not they received an allogeneic HSCT in first CR (10 yr OS 49% in the allo-HSCT group vs. 43% in the chemotherapy group)⁶. Thus most clinicians offered HSCT if relapse occurred after chemotherapy in this risk group.

In the MRC/ECOG study, patients in remission after two phases of induction chemotherapy were assigned to allogeneic transplantation if they had a HLA-matched sibling donor, while those who did not have donor were randomized to receive either chemotherapy for 2.5 years or autologous transplantation for consolidation⁹. In an intention-to-treat donor vs. no donor analysis, patients at standard risk enjoyed the greatest benefit after allogeneic HSCT, with a 5 year OS of 62% vs. 52% in those without a donor (p=0.02). Relapse rates were also lower in the donor group (24% vs. 49%, p<0.001). As expected, the non-relapse mortality of 20% was higher in the donor group, as compared to 7% in the no donor group. In a smaller study, patients age<55 in CR after induction/intensification treatment received consolidation with either an HLA-matched sibling HSCT or autologous transplantation¹⁰. In a donor vs. no donor analysis, standard risk patients with a donor had lower relapse rates (14% vs. 52%), improved DFS (69% vs. 45%), and OS (69% vs. 49%).

Given the conflicting results of the available published literature, the use of transplantation to treat all adults with standard-risk ALL in first CR remains controversial. The detection of minimal residual disease during remission may identify those at higher risk who would ultimately benefit from HSCT, sparing others from the toxicity of HSCT (discussed below).

Allogeneic Transplantation in High-risk Ph⁻ ALL in CR1

High risk patients include those that have at least one adverse risk factor listed in Table 1. Approximately 80% of adult ALL cases demonstrate an abnormal karyotype, either in chromosome number or structure (i.e. translocation, inversion, deletion)⁴. Unlike in children, the majority of the cytogenetic abnormalities in adults are associated with poor prognosis. In addition, the presence of poor-risk cytogenetics correlates with other adverse factors such as older age, higher WBC count, and lower incidence of T-cell phenotype⁴. As shown in Table 2, the presence of these cytogenetic abnormalities confers a dismal prognosis, with the exception of hyperdiploidy and 9p deletion.

As such, allogeneic HSCT in high-risk patients has been used extensively to improve outcomes. A meta-analysis to evaluate the role of allogeneic HSCT was performed on 7 studies of adult ALL that prospectively assessed overall survival using genetic randomization based on donor availability⁵. This study included >1000 patients and demonstrated that patients in the donor group had

significantly better survival than patients in the no-donor group (HR 1.29). In particular, when only high-risk patients were included, the survival advantage was even higher (HR 1.42). In the multicenter LALA-94 trial, allogeneic HSCT in adults with t(1;19)/*E2A-PBX1* or t(4;11)/*MLL-AF4* positive B-cell ALL was associated with higher DFS (>60%) when compared to those patients without a donor who subsequently underwent an autologous HSCT or had further chemotherapy intensification (DFS <20%)¹¹.

These results, however, are in contrast to the results of the MRC/ECOG study, which showed that patients at high-risk had similar outcomes regardless of donor group (OS 41% vs. 35% for donor vs. no-donor, respectively, p=NS)⁹. Although the donor group had significantly lower relapse rates (37% vs. 63%), the non-relapse mortality was much higher (36% vs. 14%), mostly due to GVHD and infection. The authors attributed the higher TRM in the high-risk patient to the older age of this group.

Thus the decision to proceed with a myeloblastic allogeneic HSCT in CR1 in patients with high risk ALL will remain a risk-benefit analysis in the individual patient. It is clear that these patients have poor overall outcomes, regardless of therapy chosen, and further management, such as the less toxic non-myeloblastic allogeneic HSCT, in the context of a clinical trial, should be considered.

Allogeneic Transplantation in Ph⁺ ALL

The Philadelphia chromosome, a balanced translocation between chromosomes 9 and 22 resulting in a *BCR-ABL* fusion gene and consequent functional tyrosine kinase that promotes leukemogenesis, is present in 25% of adult ALL⁴. Ph⁺-ALL constitutes the largest cytogenetic subgroup and is unfortunately associated with the poorest prognosis. It is generally accepted that the only curative option is allogeneic HSCT.

Standard induction chemotherapy has been shown to achieve high CR rates (e.g. 82% in MRC/ECOG study) however they are lower than their Ph⁻ counterparts. Those that receive allogeneic HSCT in CR1 have improved survival outcomes and lower relapse rates as compared to those that are transplanted with more advanced disease (>CR1)¹²⁻¹⁴. Interventions to improve the CR rate as a bridge to transplant are thought to improve survival outcomes. Imatinib mesylate, a potent selective inhibitor of BCR-ABL protein kinase, when used in combination with standard induction chemotherapy is associated with CR rates as high as 96% in phase II studies, and has allowed a greater number of patients to undergo HSCT in first CR^{15,16}. The 18 month relapse rate, DFS, and OS were all

significantly improved in patients treated with imatinib, as compared to historical controls¹⁵. The true impact of imatinib on long-term survival will require longer follow-up.

The published MRC/ECOG 2993 study of 267 patients with Ph⁺-ALL is the largest prospective study of allogeneic HSCT in this disease¹⁷. The 5-year EFS was 17% and the OS was 22% for all Ph⁺ patients in the study. When subdivided by type of post-remission therapy, the OS for sib-allo HSCT, MUD-allo HSCT, and chemotherapy were 44%, 36%, and 19%, respectively. There was no statistically significant difference between the sib-allo HSCT and MUD-allo HSCT groups. The leading cause of death after transplant was TRM (27% in sib-allo HSCT, 39% in MUD-allo HSCT), and the leading cause of death in the chemotherapy treated patients was relapse. The major drawback to this study is that only 28% of patients (76/267) actually received the proposed HSCT, with failure to proceed either due to advanced age or having an early event that prevented transplantation even when a donor was available. The results of the prospective LALA-94 trial (n=103) are similar, with improved survival in patients with a donor (sib-allo or MUD-allo) versus the no-donor group (37% vs. 12%, respectively)¹⁸. Relapse was the major cause of treatment failure, 50% in the donor group and 90% in the no-donor group.

It is clear that allogeneic HSCT from either a matched sibling or matched-unrelated donor in 1st CR is the best curative option in adults with Ph⁺ disease. However, interventions to reduce the relapse rate post-transplant are required to significantly improve long-term outcomes. A prospective trial evaluated imatinib as post-transplant therapy in patients with molecular evidence of recurrent leukemia in Ph⁺-ALL¹⁹. 52% of patients (14/27) achieved a molecular remission (i.e. BCR-ABL transcripts below the detection of quantitative and nested RT-PCR). Achievement of an early molecular remission (≤ 3 months of treatment) was highly predictive of favorable treatment outcome, with a 2-yr DFS of 54.5% and 2-yr OS of 80%. Those that had persistent minimal residual disease (MRD) positivity had poor outcomes, with a 2-yr DFS of 8% and 2-yr OS of 23%. Response to MRD-triggered imatinib was limited to patients who had received HSCT in CR1. The median time to relapse on imatinib was 22 months in patients in CR1 at time of HSCT and only 3 months in patients with more advanced disease. The exact role of imatinib and other kinase inhibitors pre- and post-transplantation continues to be under extensive investigation.

HSCT in Relapsed or Refractory ALL

Primary induction failure (refractory ALL) or relapse after a complete remission are associated with dismal outcomes, regardless of salvage therapy used (5-yr

OS 5% and 7%, respectively)^{1,20}. Most relapsing patients will receive some form of salvage treatment, including chemotherapy, autologous HSCT, allogeneic HSCT, or donor lymphocyte infusion if previous allo-HSCT. Achievement of a second CR in younger patients not previously treated with HSCT is usually followed by high-dose therapy and HSCT with a sibling donor if available, or an alternative donor, such a matched-unrelated, haploidentical-related, or cord blood transplant.

Of the patients in the MRC/ECOG study who achieved a CR with induction chemotherapy, 44% subsequently relapsed with the majority relapsing in the BM at <2 years from diagnosis²⁰. 72% of relapsed patients had been treated with chemotherapy alone. The median survival after relapse was 24 weeks. Long-term outcome after relapse was the same whether or not chemotherapy or high-dose therapy and transplantation was initially used. Of the patients who received chemotherapy alone as initial treatment, only 25% were able to proceed to allogeneic transplantation with either a sibling or unrelated donor. Those treated with HSCT had a superior 5-yr OS (15% for autograft, 16% for matched-unrelated allo, 23% for sib-allo), versus those receiving only chemotherapy (4%). In a smaller study, 37 patients with primary refractory or first relapse of ALL received an intensive salvage chemotherapy regimen with the intention of subsequent HSCT²¹. 29 patients achieved CR, of which 19 subsequently underwent HSCT (9 auto-HSCT, 10 allo-HSCT). In an intention-to-treat analysis, the mean overall survival was 11.3 months in the auto-SCT group, and 60.1 months in the allo-HSCT group. Given these poor results, all patients with relapsed ALL should be enrolled in a well-designed clinical trial if one is available; otherwise the best results may be achieved in the select few who are eligible for allogeneic HSCT.

The results of these studies indicate that the vast majority of adults with relapsed ALL cannot be rescued with current therapies. Investigation of minimal residual disease by immunophenotyping and/or molecular techniques is increasingly being used to identify patients at high risk of subsequent relapse after conventional chemotherapy. A prospective trial on the predictive significance of MRD monitoring in 196 adults with standard-risk ALL showed that patients with a rapid decline in MRD by quantitative PCR ($< 10^{-4}$ after day 24 of induction) had a 3-year relapse rate of 0%, DFS and OS of 100%, compared with a 94% RR, DFS 5.8%, and OS 45.1% in those with persistent MRD positivity (≥ 16 weeks on chemotherapy)²². In patients who were in hematologic remission and MRD negative following consolidation chemotherapy, a conversion to MRD positivity was associated with a high rate of relapse (61% at 16 month follow-up) compared to only 5% in those who were continuously MRD negative²³. Immunophenotypic evaluation of MRD has produced similar results, with longer relapse-free survival in patients with $< 0.05\%$ residual blasts at Day +35 of

induction therapy, than those with higher levels of MRD (42 months vs. 16 months, respectively)²⁴. In addition, those with <0.03% residual blasts at Day +14 had a 90% 5-yr RFS. Persistent MRD positivity in this study was associated with other high risk features (advanced age and adverse karyotype). It is clear that persistent MRD positivity post-induction or conversion to MRD positivity following consolidation is highly predictive of subsequent hematologic relapse. The impact of MRD-based risk stratification on selection of post-remission therapy has yet to be prospectively evaluated.

Autologous Transplantation in ALL

For patients who are not eligible for allogeneic HSCT due to lack of suitable donor or advanced age, post-remission therapy involves either prolonged chemotherapy treatment or high-dose therapy and autologous transplantation. Treatment outcomes following auto-HSCT are clearly inferior to those obtained with allo-HSCT, regardless of disease risk or status at time of transplantation^{9,10,25}. In both the MRC/ECOG 2993 study and an analysis of the LALA-85, -87, and -94 trials patients who did not have a donor were randomized to receive consolidation treatment with either chemotherapy alone or autologous HSCT^{9,26}. In the former study, patients randomized to chemotherapy had significantly improved 5-yr EFS (41% vs. 32%) and OS (46% vs. 37%), irrespective of risk group, and no difference in non-relapse mortality⁹. The results of the LALA trials show no significant difference between the two treatment arms with respect to DFS, OS, or non-relapse mortality²⁶. There was, however, a slight reduction in relapse in the ASCT arm at 10 years (66% vs. 78%). Thus there is no advantage to the use of autologous HSCT over conventional chemotherapy as part of an antileukemia treatment strategy.

Alternative Donor Myeloblastic HSCT and Non-Myeloblastic HSCT

For patients who lack a related histocompatible donor, but are otherwise eligible for allogeneic HSCT, the use of an alternative donor, such as a matched-unrelated, haploidentical-related, or cord blood, may be an option. Unrelated donor transplantation is considered standard therapy in Ph⁺-ALL and in relapsed disease as it offers better protection against leukemia relapse as compared to autologous transplantation²⁷. Due to improvements in HLA-typing and matching as well as better supportive care, survival outcomes with matched-unrelated allogeneic HSCT are similar to those with matched-sibling allogeneic HSCT^{13,28}. As with matched-sibling HSCT, unrelated allo-HSCT is associated with superior outcomes when performed in CR1 than beyond CR1^{27,29}. Unfortunately,

treatment-related mortality is quite high (~40%), mostly due to GVHD and infection²⁸.

Full haplotype-mismatched HSCT with CD34+ cell-selected T-cell depleted stem cell grafts has been shown to be a viable alternative for patients without matched donors (2 yr EFS 46%) but has similar TRM rates (~40%)³⁰. Similarly, a retrospective study of 73 patients receiving unrelated cord blood transplants had 2-year leukemia free survival of 36%, and 2-year cumulative incidence of TRM and relapse of 41% and 23%, respectively³¹. Each of the three forms of alternative donor transplantation have their advantages and disadvantages: matched unrelated donor – accepted therapy with mature data, but long time to procure cells; haploidentical-related donor – donor availability, but poor immune recovery with high rates of infection; and unrelated cord blood donor – rapid time to transplant, tolerance of mismatch, but low cell dose, risk of graft failure, and no potential for DLI. The use of an alternative donor HSCT and its inherent risk of high TRM may be justified in patients with otherwise dismal outcomes.

Reduced-intensity conditioning in non-myeloblastic HSCT may offer a beneficial graft-versus-leukemia effect without the toxicities of a conventional myeloblastic HSCT. The few published retrospective studies generally involved patients with high-risk ALL (i.e. patients beyond CR1, Ph⁺, or chemo-refractory) and included those who may have failed a previous allogeneic or autologous HSCT³²⁻³⁵. In the largest study (n=97) the 2-yr OS and DFS were 31% and 21%, respectively, with a relapse incidence of 51% and NRM of 28%³². Survival outcomes were significantly better in patients transplanted in CR1 (n=28, OS 52%) compared to those transplanted in more advanced disease ($\leq 27\%$). Of note, patients with chronic GVHD had better OS compared to patients without GVHD. Death was commonly due to leukemia (61% of all deaths), likely a reflection of advanced disease status at the time of HSCT. This treatment modality requires evaluation in a prospective setting to identify the subset of individuals most likely to benefit from this type of transplantation.

Conclusions

- High CR rates are achieved with standard induction treatment, regardless of risk status. Those unable to achieve CR have poor outcomes.
- Those with standard risk ALL that have a HLA-matched sibling may benefit from allogeneic HSCT in CR1, particularly those at low risk for TRM
- Those with high-risk Ph⁻ ALL in CR1 should be enrolled in a clinical trial for post-remission therapy, or undergo HLA-matched sibling allogeneic HSCT if risk of TRM is low.

- Those with Ph⁺-ALL have the worst prognosis, and should undergo HLA-matched sibling or unrelated donor HSCT in CR1. Enrollment in a clinical trial, if one is available, is also recommended.
- Use of imatinib in Ph⁺-ALL may improve CR rates allowing more patients to proceed to HSCT in CR1, and use post-transplantation may reduce relapse rates. Impact on long-term survival will depend on further follow-up results.
- Refractory or relapsed ALL are associated with dismal outcomes, and patients should be enrolled in a clinical trial for further therapy if one is available, otherwise proceed to allogeneic HSCT if a suitable donor (related or unrelated) is available.
- There is no advantage to the use of autologous transplantation over conventional chemotherapy as post-remission consolidation.
- The use of an alternative donor HSCT (matched-unrelated, haploidentical-related, cord blood) may be justified in high-risk patients with lower risk of TRM. Non-myeloblastic HSCT should be undertaken in the context of a prospective clinical trial.

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Table 1. Adverse Prognostic Factors in Adult ALL

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|---|
| Age >35 |
| WBC >30 x10 ⁹ /L if B-lineage, >100 x10 ⁹ /L if T-lineage |
| B-cell phenotype |
| CNS involvement at diagnosis |
| Poor risk cytogenetics (Philadelphia chromosome, t(4;11), t(8;14), t(1;19), hypodiploidy, ≥5 cytogenetic abnormalities) |

Table 2. Cytogenetic abnormalities in ALL and impact on EFS and OS

| Cytogenetic subgroup | 5-yr EFS (%) | 5-yr OS (%) |
|----------------------|--------------|-------------|
| t(9;22) | 16 | 22 |
| t(4;11) | 24 | 24 |
| t(1;19) | 29 | 32 |
| t(8;14) | 13 | 13 |
| complex karyotype | 21 | 28 |
| hypodiploidy | 18 | 22 |
| hyperdiploidy | 50 | 53 |
| del(9p) | 49 | 58 |

Modified from Moorman et al. Blood. 2007;109:3189-3197