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Allogeneic Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia (ALL) in Adults

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Abstract

Purpose of review—Acute lymphoblastic leukemia (ALL) is a heterogeneous disease, for which treatment guidelines are still evolving. Allogeneic hematopoietic cell transplantation is a potentially curative therapeutic modality for ALL and this review describes recent studies and current practice patterns concerning the *who*, *when*, and *how* of alloHCT in the management of ALL.

Recent findings—Allogeneic stem cell transplantation is the treatment of choice for patients with ALL after first relapse, and is also recommended for high-risk patients in first complete remission (CR1). Minimal residual disease evaluation and monitoring is developing as an important prognostic factor and could guide physicians in determining which patients, especially those with standard risk, might require transplant. Tyrosine kinase inhibitor (TKI) therapy allows a much higher proportion of Philadelphia-chromosome-positive ALL patients to attain remission and proceed to transplant with improved results; post-transplant TKI maintenance therapy may also provide survival benefit. Reduced-intensity conditioning regimens are a reasonable alternative for patients who would otherwise be ineligible for transplant due to age or co-morbidity.

Summary—For patients with high-risk features, there is general agreement that allogeneic hematopoietic cell transplantation in CR1 is a potentially curative option; however, there is no consensus on early transplant for standard risk patients.

Keywords

Acute lymphoblastic leukemia; Hematopoietic stem cell transplantation; Graft-versus-leukemia; Philadelphia chromosome; ALL; Minimal residual disease

INTRODUCTION

Approximately 5,000 patients annually are diagnosed with acute lymphoblastic leukemia (ALL), of which about 1,400 will die (1). Despite high induction remission rates for ALL (80–90%), the overall survival rate is low in the adult population (30–40%) (2). Over the last few years a variety of factors have contributed to prolongation of survival in adult ALL: improved outcomes with allogeneic hematopoietic cell transplantation, addition of tyrosine kinase inhibitors for Philadelphia chromosome positive ALL, and increased use of intensified pediatric-like chemotherapy protocols for adolescent and young adult

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CONFLICT OF INTEREST

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populations. This article will focus on the role of allogeneic hematopoietic cell transplantation (alloHCT) in treatment of adult ALL.

WHICH PATIENTS SHOULD BE TRANSPLANTED?

The high relapse rate of ALL has increasingly led us to consider alloHCT as a post-induction consolidation modality, especially in the high-risk ALL population.

Prognostic factors in ALL

Prognostic factors in ALL determine not only the likelihood of long-term survival, but the need for intensive post-induction therapy, particularly alloHCT. Known adverse prognostic factors at diagnosis include age, high white blood cell count, cytogenetic status [t(9;22), t(4;11), -7, +8](3, 4)] and CD20 positivity (5, 6). Post-induction prognostic factors include prolonged time to reach complete remission, the need for more than one induction cycle to achieve remission, induction failure and frank relapse. Other factors that have recently acquired significance are persistence of minimal residual disease post-induction, molecular and genetic markers such as BCR-ABL, IKAROS and BAALC; and pharmacogenetics (7–9*). Table 1 shows prognostic markers that typically confer eligibility for alloHCT at first possible remission (10).

Philadelphia Chromosome positive BCR-ABL ALL

The incidence of Philadelphia chromosome positivity (Ph⁺) in ALL is 15–30% with some evidence that incidence increases with age, reaching up to 50% in elderly patients (11–14). The prognosis of Ph⁺ ALL is poor, especially in older populations, and alloHCT remains the only potential curative option (15). In the French LALA94 trial the estimated 3-year overall survival (OS) for patients who had donors and achieved CR1 was 37% versus 12% for other patients ($P=0.02$) (16). The benefit of alloHCT has also been observed in long-term followup of patients receiving alloHCT in CR1 at City of Hope (COH) and Stanford University, with a 10-year OS of 54% (17). Since introduction of imatinib, a tyrosine kinase inhibitor (TKI), for treatment of BCR-ABL malignancies, there has been interest in combining TKIs with induction chemotherapy and/or HCT in patients with Ph⁺ ALL. Imatinib has been studied both as a single agent and incorporated within induction chemotherapy regimens for newly diagnosed Ph⁺ ALL, demonstrating high response rates, improved survival in combination settings, and feasibility and tolerability in older populations (18–22*). TKIs such as imatinib, dasatinib and nilotinib are now standard therapy for Ph⁺ patients and the resultant increase in initial remission rates has allowed greater eligibility for alloHCT. A recent study by Mizuta *et al.* compared 51 patients who received imatinib in combination with chemotherapy followed by alloHCT in CR1, with 122 patients who received alloHCT in CR1 during the pre-imatinib era. The 3-year OS of the imatinib group was 65% compared to 44% for the pre-imatinib group (23). Patients with *BCR-ABL* transcript positivity after alloHCT seem to experience higher relapse rates compared to *BCR-ABL*-negative patients (45% vs. 23%, $P=0.0013$) (24). This phenomenon led to early initiation of post-transplant TKI therapy, when leukemic cell burden is minimal; some suggest beginning at 90 days post transplant (25, 26). The optimal duration of TKI therapy post-alloHCT has not yet been determined, but some physicians continue using TKI as long as patients tolerate it. In a recent study the median duration of imatinib therapy after alloHCT was ~1 year (range, 3–50 months) (27).

Relapsed and Refractory Patients

Patients with ALL refractory to primary chemotherapy or who relapse have extremely poor prognoses; alloHCT is the only curative option if they can achieve remission pre-transplantation. According to the LALA94 study, OS at 5 years is only 9% for relapsed

patients after alloHCT; however, for the patients who had available donors and were able to achieve a second CR and survive until alloHCT (61/421), 5-year OS was 33% (28). Likewise, outcomes from 609 patients on the MRC/ECOG 2993 study showed a 23% 5-year OS for patients receiving a sibling alloHCT (n=42), while patients receiving matched unrelated donor alloHCT (n=65) had a 5-year OS of 16%, compared to 15% for autologous hematopoietic cell transplantation (autoHCT) and 4% for chemotherapy (29). Marks *et al.* recently demonstrated that the relative risk of relapse is significantly higher for patients with Ph⁺ ALL in CR2 compared to CR1, particularly for those patients whose duration of CR1 was less than 1 year (30). Outcomes for patients with active disease are dismal and this contributes to the argument that perhaps all patients should be transplanted in CR1, since CR2 is frequently not achievable.

Patients with minimal residual disease (MRD)

In addition to age and cytogenetics at diagnosis, the most important prognostic factor, and a direct reflection of sensitivity to chemotherapy, is the achievement of complete remission. Assessing disease status post-induction by morphological examination of the bone marrow is limited due to the similarity between malignant lymphoblasts and B-lymphocyte progenitors. More accurate and sensitive quantification of malignant cell persistence post-induction can prevent undertreatment of patients with residual disease, and overtreatment of disease-free patients (31*). Studies in pediatric ALL populations demonstrate an association between adverse outcomes and persistence of MRD (32–37). The role of MRD quantitation to evaluate treatment response and predict relapse is evolving in adult populations, with exploration of flow cytometry and real-time quantitative polymerase-chain-reaction techniques. Presence of MRD is associated with adverse outcomes even in patients otherwise considered at standard risk and these patients may benefit from early alloHCT in CR1 (31, 35, 38–41). The question is: at what MRD level do we consider the patient at risk of disease relapse? Stow *et al.* find that pediatric patients with MRD of 0.001% (one malignant cell per 100,000 cells) have a significantly higher 5-year cumulative risk of relapse ($12.7\% \pm 5.1\%$), compared to patients with $<0.001\%$ ($5.0\% \pm 1.5\%$), with $P < .047$ (42). The authors point out that even 0.001% represents an estimated total leukemic burden of 10^7 to 10^8 malignant cells. Until further investigation, an MRD level of 10^{-4} (0.01%) or greater is the current determinant of high risk for disease relapse (43–45)*

WHEN SHOULD TRANSPLANT BE PERFORMED?

Should a patient receive a high-risk classification, there is generalized agreement to proceed to allogeneic hematopoietic cell transplant. There is a dilemma when a patient has standard risk for relapse; should we transplant in CR1 or wait until they have relapsed? In the future, MRD will play a greater role in this decision, but most previous studies on this issue do not take MRD into account.

Transplant in CR1 for high-risk patients

Early randomized trials that compared alloHCT to chemotherapy or autoHCT have relied on a genetic randomization based on the availability of an HLA-matched sibling. The French multi-center randomized trial, LALA-87, found that only patients with high-risk features (Ph⁺ ALL, WBC $>30 \times 10^9$, undifferentiated ALL, age > 35 years, or time to CR1 > 4 weeks) have better OS ($P=0.03$) and disease-free survival (DFS) ($P=0.01$) with alloHCT, while patients with standard risk showed no significant advantage of alloHCT over chemotherapy or autoHCT (46). This was confirmed in a larger study from the same group, LALA-94, which additionally concluded that there is no significant difference in DFS between autoHCT and chemotherapy for high-risk patients (47) as detailed in Table 2.

Several other reports indicate that alloHCT offers some groups of high-risk patients in CR1, long-term survival rates of between 40% and 60% (48–51). COH and Stanford University updated two series of patients with high-risk features who underwent allogeneic HCT in CR1 with a median follow-up of greater than 5 years. Selection criteria included white blood cell count (WBC) >25,000/ml, chromosomal translocations t(9;22), t(4;11), t(8;14); age older than 30 years; extramedullary disease at the time of diagnosis; and/or requiring >4 weeks to achieve CR1. AlloHCT during CR1 in this patient population, who would otherwise have been expected to fare poorly, led to an event-free survival (EFS) of 64% with a relapse rate of 15% (52).

Transplant in CR1 for standard-risk patients?

The recently reported MRC/EGOG trial compared alloHCT, auto HCT and chemotherapy alone, in ALL patients in CR1. ALL Ph⁺ patients with either a related or unrelated donor proceeded to alloHCT, but standard and high-risk patients underwent a sibling donor versus no-sibling donor biological allocation to alloHCT. Patients without donors were then randomized to autoHCT or chemotherapy. AlloHCT resulted in improved disease control in all adult patients with ALL, but with long-term benefit seen most significantly in younger patients with lower-risk disease (Table 3) (53, 54). Considering the previously reported data indicating benefit from transplant in high-risk patients in CR1, and the high treatment-related mortality from alloHCT, this trial has led to considerable debate about the implications for patients with ALL; some experts advocate early transplant for nearly all patients, whereas others caution for continued individual assessment.

WHICH TRANSPLANT REGIMEN?

Traditionally, high intensity preparative regimens are used for ALL, but more recently, there have been multiple observations pointing to a graft-versus-leukemia effect that have led to the introduction of less toxic regimens, making transplant more feasible for patients who otherwise would not be candidates.

Myeloablative regimens

The ideal preparative regimen for alloHCT in ALL should maximize anti-leukemic effects while maintaining efficient engraftment and tolerable toxicity. Total body irradiation (TBI)-based regimens have been the mainstay of ALL preparative regimens due to their ability to eradicate leukemic cells within the central nervous system and testicles, providing prolonged EFS and lower relapse rates (55–57). TBI in combination with cyclophosphamide (TBI/Cy) is the most common ALL transplant preparative regimen. Due to radiation toxicities including secondary malignancies, cataracts and interstitial pneumonitis, other preparative regimens have been explored.

Busulfan/cyclophosphamide (Bu/Cy) conditioning shows comparable OS, relapse rate, and DFS to the TBI/Cy regimen; however, it is also associated with serious side effects, including hepatic sinusoidal obstruction syndrome (SOS) – previously veno-occlusive disease, VOD – and hemorrhagic cystitis (58–60). Conversion from oral to IV busulfan in the Bu/Cy regimen, has decreased incidence of SOS and improved 100-day survival (61). More recently IV Bu/Cy in CR1 patients produces 30-month OS and relapse rates of 65.7% and 40% with decreased transplant-related mortality (TRM) and SOS (62).

City of Hope substituted etoposide (VP16) for cyclophosphamide in combination with fractionated TBI (13.2 Gy) followed by alloHCT for ALL (63). DFS was 57% with a 32% relapse rate, suggesting the regimen has significant activity in patients with advanced ALL. This result was confirmed in a subsequent trial by the Southwest Oncology Group comparing TBI/VP16 with Bu/Cy (64). A comparative analysis of TBI combined with either

cyclophosphamide or etoposide chemotherapy (65) concluded there is an advantage in substituting etoposide for CY or, when CY is used, in increasing the TBI dose to >13 Gy.

The role of the graft versus leukemia effect and reduced intensity conditioning

Although the primary therapeutic effect of alloHCT in ALL is believed to result from eradication of the leukemic cells using high-dose therapy, there is also evidence of a graft-versus-leukemia (GVL) effect. Observations of higher relapse rates after autologous or syngeneic HCT compared with alloHCT, lower incidence of relapse in patients with GVHD, and increased relapse rates in recipients of T-cell-depleted marrow grafts, all point to GVL (66). A recent report from Fred Hutchinson Cancer Research Center indicates that early withdrawal of immunosuppressive therapy in patients who do not develop GVHD decreases the risk of disease relapse in the first 18 months after transplant (67).

The general consensus that the intensity of myeloablative conditioning is important for disease control after alloHCT has limited its availability to patients with advanced age or comorbidities. Results of the MRC/EGOG study revealed significant TRM for ALL alloHCT patients over age 35 compared to consolidation chemotherapy, resulting in no improvement in DFS despite better disease control. This and similar data stimulated investigations of reduced intensity conditioning (RIC) therapy (68, 69). A retrospective analysis of high-risk ALL patients receiving alloHCT demonstrates a promising 2-year OS/DFS of 61%, relapse rate of 21%, and non-relapse mortality (NRM) of 21.5% (70). An EBMT retrospective study compares RIC with conventional myeloablative conditioning, finding a higher relapse rate with RIC ($P = 0.03$, HR = 0.59), but a correspondingly decreased NRM ($P = 0.0001$, HR = 1.98) (71*). More recently, a prospective study of 51 patients with high-risk ALL, reveals a 3-year relapse rate of 40% with 28% NRM. The 3-year OS for patients in CR1 are: 52% for CR1, 62% for CR1 Ph⁺ (received imatinib post-engraftment), and 73% for patients with no evidence of MRD (27). These studies contradict the dogma that RIC is inadequate to affect cure in ALL, and indicate it is a reasonable choice for patients with advanced age or co-morbidities.

WHICH DONOR CELL SOURCE?

Matched related donors have been the ideal choice for ALL transplant, due to lower incidence and severity of GVHD. Advances in HLA typing-technology, alternative donor sources, and GVHD prophylaxis have opened up new stem cell sources for patients without available matched related donors.

Unrelated donors versus related donors

Outcomes after transplantation from unrelated donors were previously inferior to those observed after matched-sibling transplantation due to increased rates of graft rejection and GVHD. Improvements in donor/recipient allele-level molecular matching in class I and II histocompatibility genes, GVHD prophylaxis, and supportive care (72) have made donor allografts safer. Recently a retrospective analysis in 221 patients reported 5-year DFS after alloHCT in CR1 from matched unrelated donors of 45%, compared to 42% in patients with matched related donors (73). More recently a study of 1139 patients, revealed the 4-year OS for alloHCT in CR1 was not different between related versus unrelated donors at 65% vs 62%, respectively ($P = 0.19$) (74). These data suggest that unrelated donors are a reasonable option for patients with ALL who do not have an available related donor.

Haploidentical donors/umbilical cord donors

One major obstacle to initiation of transplant is the timely availability of a donor. Recent reports in pediatric populations indicate that alloHCT from haploidentical donors (75) or

from cord blood (76) is feasible and can provide promising alternatives for patients who lack HLA-matched donors. In the adult population, the data is still evolving, but early reports suggest the feasibility of such approaches (77, 78). Further development of alternative cell sources needs to be carefully evaluated in a prospective fashion.

TREATMENT STRATEGY FOR ALL

ALL is a heterogeneous disease and management should be tailored for each patient. The National Comprehensive Cancer Network is in the process of developing a general practice guideline for ALL; until then, our suggested treatment strategy is outlined in Figure 1.

CONCLUSIONS

There are multiple ALL trials in process to test immunotherapeutic modalities such as incorporation of targeted CD52 or CD22 monoclonal antibodies with chemotherapy, or bi-specific T-cell engagers (BiTEs). Very recently, reports by Brentjens, Porter and colleagues revealed the feasibility and safety of adoptive redirected CD-19 T-cell therapy in B-Cell malignancies with very promising early results in CLL (79, 80). Currently an IND and clinical protocol are under development at City of Hope to explore adoptive T-cell therapy using a similar CD-19 adoptive T-cell therapy for B-Cell ALL. In addition to development of novel therapeutic agents, a crucial area of research will be refinement of MRD monitoring to improve patient selection and timing for alloHCT. Future prospects for adults with ALL are hopeful, as we expand our understanding of the disease and incorporate multiple treatment modalities, including alloHCT.

References

1. SEER incidence and NCHS mortality statistics [database on the Internet]. 2011. Available from: <http://seer.cancer.gov/statfacts/html/alyt.html#survival>
2. Nishiwaki S, Miyamura K. Allogeneic Stem Cell Transplantation For Adult Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia. *Leuk Lymphoma*. 2011 Aug 19.
3. Wetzler M, Dodge RK, Mrozek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience. *Blood*. 1999 Jun 1; 93(11):3983–93. [PubMed: 10339508]
4. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007 Apr 15; 109(8):3189–97. [PubMed: 17170120]
5. Thomas DA, O'Brien S, Jorgensen JL, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. *Blood*. 2009 Jun 18; 113(25):6330–7. [PubMed: 18703706]
6. Maury S, Huguet F, Leguay T, et al. Adverse prognostic significance of CD20 expression in adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. *Haematologica*. 2010 Feb; 95(2):324–8. [PubMed: 19773266]
7. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med*. 2009 Jan 29; 360(5):470–80. [PubMed: 19129520]
- *8. Rowe JM. Prognostic factors in adult acute lymphoblastic leukaemia. *Br J Haematol*. 2010 Aug; 150(4):389–405. (A good review article about various prognostic factors). [PubMed: 20573154]
9. Kuhn A, Gokbuget N, Stroux A, et al. High BAALC expression predicts chemoresistance in adult B-precursor acute lymphoblastic leukemia. *Blood*. 2010 May 6; 115(18):3737–44. [PubMed: 20065290]
10. Burmeister T, Gokbuget N, Schwartz S, et al. Clinical features and prognostic implications of TCF3-PBX1 and ETV6-RUNX1 in adult acute lymphoblastic leukemia. *Haematologica*. 2010 Feb; 95(2):241–6. [PubMed: 19713226]

11. Pullarkat V, Slovak ML, Kopecky KJ, et al. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. *Blood*. 2008 Mar 1; 111(5):2563–72. [PubMed: 18156492]
12. Moorman AV, Chilton L, Wilkinson J, et al. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. *Blood*. 2010 Jan 14; 115(2):206–14. [PubMed: 19897583]
13. Juliusson G, Karlsson K, Hallbook H. Population-based analyses in adult acute lymphoblastic leukemia. *Blood*. 2010 Aug 12; 116(6):1011. author reply 2. [PubMed: 20705768]
14. Larson RA. Management of acute lymphoblastic leukemia in older patients. *Semin Hematol*. 2006 Apr; 43(2):126–33. [PubMed: 16616046]
15. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. *Blood*. 2009 May 7; 113(19):4489–96. [PubMed: 19244158]
16. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia--results of the prospective multicenter LALA-94 trial. *Blood*. 2002 Oct 1; 100(7):2357–66. [PubMed: 12239143]
17. Laport GG, Alvarnas JC, Palmer JM, et al. Long-term remission of Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation from matched sibling donors: a 20-year experience with the fractionated total body irradiation-etoposide regimen. *Blood*. 2008 Aug 1; 112(3):903–9. [PubMed: 18519812]
18. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood*. 2002 Sep 15; 100(6):1965–71. [PubMed: 12200353]
19. Lee KH, Lee JH, Choi SJ, et al. Clinical effect of imatinib added to intensive combination chemotherapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Leukemia*. 2005 Sep; 19(9):1509–16. [PubMed: 16034462]
20. Delannoy A, Delabesse E, Lheritier V, et al. Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRAALL AFR09 study. *Leukemia*. 2006 Sep; 20(9):1526–32. [PubMed: 16838024]
21. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol*. 2006 Jan 20; 24(3):460–6. [PubMed: 16344315]
22. Ribera JM, Oriol A, Gonzalez M, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. *Haematologica*. 2010 Jan; 95(1):87–95. [PubMed: 19797728]
23. Mizuta S, Matsuo K, Yagasaki F, et al. Pre-transplant imatinib-based therapy improves the outcome of allogeneic hematopoietic stem cell transplantation for BCR-ABL-positive acute lymphoblastic leukemia. *Leukemia*. 2011 Jan; 25(1):41–7. [PubMed: 20944676]
24. Stirewalt DL, Guthrie KA, Beppu L, et al. Predictors of relapse and overall survival in Philadelphia chromosome-positive acute lymphoblastic leukemia after transplantation. *Biol Blood Marrow Transplant*. 2003 Mar; 9(3):206–12. [PubMed: 12652472]
25. Carpenter PA, Snyder DS, Flowers ME, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood*. 2007 Apr 1; 109(7):2791–3. [PubMed: 17119111]
26. Chen H, Liu KY, Xu LP, et al. Administration of imatinib in the first 90 days after allogeneic hematopoietic cell transplantation in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Chin Med J (Engl)*. 2011 Jan; 124(2):246–52. [PubMed: 21362375]
27. Ram R, Storb R, Sandmaier BM, et al. Non-myeloablative conditioning with allogeneic hematopoietic cell transplantation for the treatment of high-risk acute lymphoblastic leukemia. *Haematologica*. 2011 Aug; 96(8):1113–20. [PubMed: 21508120]

28. Tavernier E, Boiron JM, Huguet F, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia*. 2007 Sep; 21(9): 1907–14. [PubMed: 17611565]
29. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007 Feb 1; 109(3):944–50. [PubMed: 17032921]
- *30. Marks DI, Wang T, Perez WS, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. *Blood*. 2010 Jul 22; 116(3):366–74. (An excellent review article about MRD and its role in ALL; it also illustrates different methods to measure MRD). [PubMed: 20404137]
31. Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2010; 2010:7–12. [PubMed: 21239764]
32. Foster JH, Hawkins DS, Loken MR, et al. Minimal residual disease detected prior to hematopoietic cell transplantation. *Pediatr Blood Cancer*. 2011 Jul 15; 57(1):163–5. [PubMed: 21370437]
33. Elorza I, Palacio C, Dapena JL, et al. Relationship between minimal residual disease measured by multiparametric flow cytometry prior to allogeneic hematopoietic stem cell transplantation and outcome in children with acute lymphoblastic leukemia. *Haematologica*. 2010 Jun; 95(6):936–41. [PubMed: 20179088]
34. Sutton R, Venn NC, Tolisano J, et al. Clinical significance of minimal residual disease at day 15 and at the end of therapy in childhood acute lymphoblastic leukaemia. *Br J Haematol*. 2009 Aug; 146(3):292–9. [PubMed: 19500099]
35. Brisco MJ, Latham S, Sutton R, et al. Determining the repertoire of IGH gene rearrangements to develop molecular markers for minimal residual disease in B-lineage acute lymphoblastic leukemia. *J Mol Diagn*. 2009 May; 11(3):194–200. [PubMed: 19324994]
36. Morley AA, Latham S, Brisco MJ, et al. Sensitive and specific measurement of minimal residual disease in acute lymphoblastic leukemia. *J Mol Diagn*. 2009 May; 11(3):201–10. [PubMed: 19324989]
37. Schwarz AK, Stanulla M, Cario G, et al. Quantification of free total plasma DNA and minimal residual disease detection in the plasma of children with acute lymphoblastic leukemia. *Ann Hematol*. 2009 Sep; 88(9):897–905. [PubMed: 19165483]
38. Campana D. Progress of minimal residual disease studies in childhood acute leukemia. *Curr Hematol Malig Rep*. 2010 Jul; 5(3):169–76. [PubMed: 20467922]
39. Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18–20 September 2008. *Leukemia*. 2010 Mar; 24(3):521–35. [PubMed: 20033054]
40. Kikuchi M, Tanaka J, Kondo T, et al. Clinical significance of minimal residual disease in adult acute lymphoblastic leukemia. *Int J Hematol*. 2010 Oct; 92(3):481–9. [PubMed: 20830615]
41. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood*. 2009 Apr 30; 113(18):4153–62. [PubMed: 19141862]
42. Stow P, Key L, Chen X, et al. Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia. *Blood*. 2010 Jun 10; 115(23):4657–63. [PubMed: 20304809]
43. Mortuza FY, Papaioannou M, Moreira IM, et al. Minimal residual disease tests provide an independent predictor of clinical outcome in adult acute lymphoblastic leukemia. *J Clin Oncol*. 2002 Feb 15; 20(4):1094–104. [PubMed: 11844835]
44. Bruggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood*. 2006 Feb 1; 107(3):1116–23. [PubMed: 16195338]
45. Patel B, Rai L, Buck G, et al. Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993. *Br J Haematol*. 2010 Jan; 148(1):80–9. [PubMed: 19863538]

46. Sebban C, Lepage E, Vernant JP, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *J Clin Oncol*. 1994 Dec; 12(12):2580–7. [PubMed: 7989932]
47. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol*. 2004 Oct 15; 22(20):4075–86. [PubMed: 15353542]
48. Attal M, Blaise D, Marit G, et al. Consolidation treatment of adult acute lymphoblastic leukemia: a prospective, randomized trial comparing allogeneic versus autologous bone marrow transplantation and testing the impact of recombinant interleukin-2 after autologous bone marrow transplantation. BGMT Group. *Blood*. 1995 Aug 15; 86(4):1619–28. [PubMed: 7632972]
49. Doney K, Fisher LD, Appelbaum FR, et al. Treatment of adult acute lymphoblastic leukemia with allogeneic bone marrow transplantation. Multivariate analysis of factors affecting acute graft-versus-host disease, relapse, and relapse-free survival. *Bone Marrow Transplant*. 1991 Jun; 7(6): 453–9. [PubMed: 1873592]
50. Blume KG, Forman SJ, Snyder DS, et al. Allogeneic bone marrow transplantation for acute lymphoblastic leukemia during first complete remission. *Transplantation*. 1987 Mar; 43(3):389–92. [PubMed: 3547796]
51. Chao NJ, Forman SJ, Schmidt GM, et al. Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia during first complete remission. *Blood*. 1991 Oct 15; 78(8):1923–7. [PubMed: 1912575]
52. Jamieson CH, Amylon MD, Wong RM, Blume KG. Allogeneic hematopoietic cell transplantation for patients with high-risk acute lymphoblastic leukemia in first or second complete remission using fractionated total-body irradiation and high-dose etoposide: a 15-year experience. *Exp Hematol*. 2003 Oct; 31(10):981–6. [PubMed: 14550815]
53. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. 2008 Feb 15; 111(4):1827–33. [PubMed: 18048644]
54. Fielding AK, Goldstone AH. Allogeneic haematopoietic stem cell transplant in Philadelphia-positive acute lymphoblastic leukaemia. *Bone Marrow Transplant*. 2008 Mar; 41(5):447–53. [PubMed: 17968326]
55. Thomas ED, Storb R, Clift RA, et al. Bone-marrow transplantation (second of two parts). *N Engl J Med*. 1975 Apr 24; 292(17):895–902. [PubMed: 235092]
56. Thomas E, Storb R, Clift RA, et al. Bone-marrow transplantation (first of two parts). *N Engl J Med*. 1975 Apr 17; 292(16):832–43. [PubMed: 234595]
57. Yee GC, McGuire TR. Allogeneic bone marrow transplantation in the treatment of hematologic diseases. *Clin Pharm*. 1985 Mar-Apr; 4(2):149–60. [PubMed: 3886273]
58. Carreras E, Bertz H, Arcese W, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. *Blood*. 1998 Nov 15; 92(10):3599–604. [PubMed: 9808553]
59. Shi-Xia X, Xian-Hua T, Hai-Qin X, et al. Total body irradiation plus cyclophosphamide versus busulphan with cyclophosphamide as conditioning regimen for patients with leukemia undergoing allogeneic stem cell transplantation: a meta-analysis. *Leukemia & lymphoma*. 2010; 51(1):50–60. [PubMed: 20055658]
60. Grochow LB, Jones RJ, Brundrett RB, et al. Pharmacokinetics of busulfan: correlation with veno-occlusive disease in patients undergoing bone marrow transplantation. *Cancer Chemother Pharmacol*. 1989; 25(1):55–61. [PubMed: 2591002]
61. Kashyap A, Wingard J, Cagnoni P, et al. Intravenous versus oral busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic venoocclusive disease (HVOD), HVOD-related mortality, and

- overall 100-day mortality. *Biol Blood Marrow Transplant*. 2002; 8(9):493–500. [PubMed: 12374454]
62. Tang W, Wang L, Zhao WL, et al. Intravenous busulfan-cyclophosphamide as a preparative regimen before allogeneic hematopoietic stem cell transplantation for adult patients with acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2011 Oct; 17(10):1555–61. [PubMed: 21549217]
 63. Blume KG, Forman SJ, O'Donnell MR, et al. Total body irradiation and high-dose etoposide: a new preparatory regimen for bone marrow transplantation in patients with advanced hematologic malignancies. *Blood*. 1987 Apr; 69(4):1015–20. [PubMed: 3548841]
 64. Blume KG, Kopecky KJ, Henslee-Downey JP, et al. A prospective randomized comparison of total body irradiation-etoposide versus busulfan-cyclophosphamide as preparatory regimens for bone marrow transplantation in patients with leukemia who were not in first remission: a Southwest Oncology Group study. *Blood*. 1993 Apr 15; 81(8):2187–93. [PubMed: 8471778]
 65. Marks DI, Forman SJ, Blume KG, et al. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. *Biol Blood Marrow Transplant*. 2006 Apr; 12(4):438–53. [PubMed: 16545728]
 66. Appelbaum, FR. Graft versus leukemia (GVL) in the therapy of acute lymphoblastic leukemia (ALL). 19970710 DCOM- 19970710(0887–6924 (Print))
 67. Inamoto Y, Flowers ME, Lee SJ, et al. Influence of immunosuppressive treatment on risk of recurrent malignancy after allogeneic hematopoietic cell transplantation. *Blood*. 2011 Jul 14; 118(2):456–63. [PubMed: 21633087]
 68. Martino R, Giralt S, Caballero MD, et al. Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study. *Haematologica*. 2003 May; 88(5):555–60. [PubMed: 12745275]
 69. Lee S, Cho BS, Kim SY, et al. Allogeneic stem cell transplantation in first complete remission enhances graft-versus-leukemia effect in adults with acute lymphoblastic leukemia: antileukemic activity of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2007 Sep; 13(9): 1083–94. [PubMed: 17697971]
 70. Stein AS, Palmer JM, O'Donnell MR, et al. Reduced-intensity conditioning followed by peripheral blood stem cell transplantation for adult patients with high-risk acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2009 Nov; 15(11):1407–14. [PubMed: 19822300]
 71. Mohty M, Labopin M, Volin L, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. *Blood*. 2010 Nov 25; 116(22):4439–43. [PubMed: 20716774]
 72. Cornelissen JJ, Carston M, Kollman C, et al. Unrelated marrow transplantation for adult patients with poor-risk acute lymphoblastic leukemia: strong graft-versus-leukemia effect and risk factors determining outcome. *Blood*. 2001 Mar 15; 97(6):1572–7. [PubMed: 11238093]
 73. Kiehl MG, Kraut L, Schwerdtfeger R, et al. Outcome of allogeneic hematopoietic stem-cell transplantation in adult patients with acute lymphoblastic leukemia: no difference in related compared with unrelated transplant in first complete remission. *J Clin Oncol*. 2004 Jul 15; 22(14): 2816–25. [PubMed: 15254049]
 74. Nishiwaki S, Inamoto Y, Sakamaki H, et al. Allogeneic stem cell transplantation for adult Philadelphia chromosome-negative acute lymphocytic leukemia: comparable survival rates but different risk factors between related and unrelated transplantation in first complete remission. *Blood*. 2010 Nov 18; 116(20):4368–75. [PubMed: 20664060]
 75. Gonzalez-Vicent M, Molina B, Andion M, et al. Allogeneic hematopoietic transplantation using haploidentical donor vs. unrelated cord blood donor in pediatric patients: a single-center retrospective study. *Eur J Haematol*. 2011 Jul; 87(1):46–53. [PubMed: 21692851]
 76. Kato K, Yoshimi A, Ito E, et al. Cord Blood Transplantation from Unrelated Donors for Children with Acute Lymphoblastic Leukemia in Japan: The Impact of Methotrexate on Clinical Outcomes. *Biol Blood Marrow Transplant*. 2011 May 25.

77. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med*. 2004 Nov 25; 351(22):2276–85. [PubMed: 15564544]
78. Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *N Engl J Med*. 2004 Nov 25; 351(22): 2265–75. [PubMed: 15564543]
- *79. Porter DL, Levine BL, Kalos M, et al. Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia. *N Engl J Med*. 2011 Aug 10. (a very recent news-breaking report illustrates the feasibility of chimeric adoptive T cell therapy for CD19 malignancies, in this report, CLL. This new technology is currently under investigation at COH to study its use in ALL).
80. Brentjens RJ, Riviere I, Park JH, et al. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. *Blood*. 2011 Aug 17.

KEY POINTS

- Allogeneic hematopoietic cell transplantation remains a potential curative therapy for patients with high risk features and patients with relapsed disease.
- Based on MRC/ECOG data, it is worth considering allogeneic transplant for standard-risk patients, as the relapse rate is high and the prospects of achieving CR2 are uncertain.
- The importance of minimal residual disease (MRD) monitoring is evolving as a prognostic factor and an indication for allogeneic transplant.
- Peri-transplant use of tyrosine kinase inhibitors might improve the outcome in adult patients with Ph⁺ ALL.
- Recent advances in transplant, including feasibility of reduced-intensity conditioning for ALL, and alternative stem cell sources have improved outcomes and made transplant accessible to a wider range of patients.

Figure 1.
Treatment algorithm for adult patients with ALL

Table 1

High-risk prognostic features for adult ALL

	B-ALL	T-ALL
At Diagnosis		
Age	>35	
WBC	$>30 \times 10^9$	$>100 \times 10^9$
Cytogenetics	t(9;22), t(4;11), -7, +8, t(8;14) Hypodiploidy	t(1;19) *
	Complex cytogenetics	
Molecular genetics	BCR-ABL IKAROS BAALC+	BAALC+ HOX11L2 ERG+
Immunophenotype	Pro B CD10-neg pre-B CD20	Early T Mature T
After Induction		
Time to CR1	> 4 weeks	
MRD	$> 10^{-4}$	
Clinical Relapse	> CR1	

* Recent report by Burmeister et. al [10]. shows no adverse prognosis with t(1;19)

WBC = white blood cell count, MRD = minimal residual disease, CR1= First complete remission

Table 2

LALA-94 Comparison of treatments based on risk

Subgroup	Age (median)	Number of Pts	OS 10-yr	P-value
Allo-BMT		116	46%	0.04
-High-Risk	<40 (26)	41	44%	0.009*
-Standard-Risk		75	49%	NS
Auto-BMT		95	34%	NS
-High-Risk	<50 (25)	32	10%	NS
-Standard-Risk		63	49%	NS
Chemotherapy		141	31%	NS
-High-Risk	<50 (28)	55	11%	NS
-Standard-Risk		86	40%	NS

Table 3

MRC-ECOG UKALLXII/EC2993: outcomes by risk classification

Patient Group	# of Patients	5-Yr Overall Survival (%)	5-Yr Relapse Rate (%)	5-Yr Non-relapse Mortality (%)
Standard Risk	512			
Sibling Donor	218	62	24	20
No Donor	294	52	49	7
High Risk	401			
Sibling Donor	171	41	37	36
No Donor	230	35	63	14
Ph⁺ Very High Risk	267			
Sibling Allo HCT	45	44	43	27
MUD Allo HCT	31	36	34	47
Chemotherapy	82	19	90	17

* High-risk is defined as age ≥ 35 years, WBC $> 30,000/\mu\text{L}$ for patients with B-cell disease or WBC $> 100,000/\mu\text{L}$ for patients with T-cell disease, or time to attain CR > 4 weeks.