BLOOD PERSPECTIVES

The Myth of the Second Remission of Acute Leukemia in the Adult

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Short Title: The myth of CR2 in adult acute leukemia
ABSTRACT

Although the majority of adult patients with both acute lymphoblastic leukemia and acute myelogenous leukemia achieve a remission with up-front chemotherapy, many patients still suffer relapse. Often, the strategy is proposed of treating patients with relapsed leukemia into a second remission and then proceeding to allogeneic transplantation as the definitive curative approach. Long-term outcomes of such a strategy are poor; 5-year overall survival from first relapse for patients with acute leukemia is only ~10%. This Perspective highlights the problem that most patients do not achieve a second remission and, therefore, never really have an opportunity for a potential curative therapy. Although patients who undergo transplant following relapse may well be cured, those who do not achieve a second remission are rarely candidates for transplant; therefore, the overall outcome for patients who relapse is dismal. Thus, there is an urgent need not only for more effective up-front therapy to prevent relapse, but also for development of therapies that can serve as effective bridging treatments between relapse and transplant. We suggest that more optimal use of minimal residual disease detection during first remission may also improve the chances for successful transplant therapy via earlier re-induction therapy, allowing transplant prior to overt relapse.
INTRODUCTION

When adults are diagnosed with acute leukemia, it is very common for the physician to discuss with them the potential role, timing, risks and impact of hematopoietic cell transplantation in the management of their disease. This often leads to recommending early transplant for those patients with high-risk disease in first remission, while delaying transplantation for those patients with lower risk of relapse until there is evidence of recurrent disease. The assumption is that following relapse or progression, patients will undergo transplantation following successful reinduction therapy to achieve a second remission.

In general, for patients with acute myeloid leukemia (AML), allogeneic related or unrelated transplantation is currently pursued for patients with intermediate- or high-risk disease, specifically those with FLT3 mutations, intermediate- or high-risk cytogenetics, complex cytogenetics, monosomy karyotypes, or for patients who did not achieve remission with the initial induction therapy. For those patients who have favorable-risk AML, transplants are not shown to be beneficial and are not generally performed in first remission.¹ These include normal cytogenetics if the leukemia cells display molecular features such as NPM1 mutations, as these patients often have comparable outcomes with standard chemotherapy. This also applies to patients with good-risk cytogenetics, such as inv(16) or t(8;21) for whom, in the absence of other concomitant risk factors such as genes associated with a stem cell phenotype, transplantation is generally delayed, in hopes that they will be cured with repeated courses of upfront cytarabine-based consolidation therapy.²⁻⁴ For such good-risk patients, transplantation is pursued in second remission after successful reinduction therapy. However, Schoch et al.⁵ find age to be an independent poor prognostic variable for de novo AML patients and that even within the good-risk cytogenetic
groups inv(16) or t(8;21), ages of 60 years and over significantly reduce overall survival. Many hematologists also do not recommend an allogeneic transplant in first remission for patients with a normal karyotype in the absence of adverse molecular phenotype, such as FLT3 mutation; once again, in the hope of curing such patients if they relapse.

For patients with acute lymphoblastic leukemia (ALL), the strategy of early transplant is still used predominantly for patients who have significant high-risk features such as the presence of the Philadelphia chromosome, a slow response to induction therapy, or high white count at the time of presentation. In 2008, the large international ALL MRC UKALL12/ECOG 2993 trial demonstrated that overall survival is significantly improved by transplantation in first remission for patients with a sibling donor, compared to those with no donor (53% vs. 45%, p=0.01). Improved overall survival is significantly better after allogeneic transplantation in standard risk patients (Ph-negative, age ≤35, or high white blood count at presentation), but not in high-risk patients. The relapse rate is improved in both standard and high-risk patients; however, TRM is increased in the high-risk patient group, likely due to the impact of older age. In practice, the idea of transplantation for standard-risk ALL in CR1 has not been uniformly accepted, and there is a lack of consensus on the indications for transplant in ALL. The LALA-87 and -94 trials find allogeneic transplantation in CR1 beneficial for high-risk patients (standard-risk patients were not studied in the larger LALA-94 trial), while the MRC/ECOG trial finds it beneficial only for standard-risk patients. Many hematologists and oncologists do not recommend an allogeneic transplantation in first remission, as the superior survival is tempered by the risk of transplant-related complications, particularly in older patients, and the risk of late effects, particularly in younger patients. The result is that many patients will
continue on with consolidation and maintenance chemotherapy regimens and pursue transplantation only at the time of relapse after successful reinduction treatment. Although data show decreases in relapse rate and modest increases in overall survival for specific risk groups of AML and ALL if transplanted in first remission, transplantation is frequently offered only after relapse.

In these discussions between patients and physicians regarding how to proceed, it is reasonable to discuss the available data and then encourage patients to enroll in a clinical trial if one is available. However, many physicians convey the idea that transplantation should appropriately be delayed and that if relapse does occur “you can be transplanted in second remission.” This approach seems a wise and practical decision to the patient. So, what are the results of this strategy; namely, in adults, how successful is the treatment of relapsed acute leukemia followed by transplantation in second remission?

**Transplantation for AML and ALL in second remission**

Most studies analyze the results of transplantation in patients with varying disease status (first remission, second and subsequent remission, early relapse, refractory relapse, induction failure). It is generally agreed that relapsed leukemia in the adult is a fatal condition that cannot be cured by therapy other than allogeneic transplantation. Single institution trials of full-intensity transplantation suggest that patients with AML or ALL who are transplanted after achieving a second remission have a disease-free survival of approximately 40-50%, a number that is often utilized in the discussion with the patient, implying that the possibility of cure remains even after the failure of up-front therapy to cure the patient. Figure 1 shows data from the CIBMTR for patients with AML or ALL who underwent transplantation in second remission.
from related or unrelated donors following an ablative conditioning regimen, demonstrating that approximately 40-50% of patients are cured of leukemia with this approach (Dr. Mary Horowitz, personal communication). These data imply the potential curability of the patient if they are not cured by the initial upfront chemotherapy and then undergo transplantation in second remission. What is not always considered when discussing this theoretical 40-50% cure rate is the inherent bias in evaluating the success of second remission transplantation only as it applies to those select patients who are able to attain second remission, and who are suitable candidates for allogeneic transplantation based on age, medical, financial, and psychological criteria.

What is the likelihood of achieving a second remission after relapse in adult patients with acute leukemia?

Most induction regimens utilize intensive chemotherapy to achieve a remission, followed by consolidation treatments, and in the case of ALL, maintenance therapy. For AML, induction is still built around an anthracycline/cytarabine treatment regimen. Multiple regimens have been suggested for treatment of relapse.10-14 Depending upon the duration of remission, these same drugs may still be effective in achieving a second remission, particularly if the initial remission lasted more than a year or two. For instance, in patients undergoing reinduction therapy, one of the most important factors predictive of reinduction success is the length of the first remission; 1-year OS for relapse-free interval from first CR of ≤6 months is 14%, 7-18 months is 36%, and >18 months is 57%.15 For patients with ALL, often the same induction chemotherapy drug regimen that achieved a first remission is utilized to attempt a second remission and the same prognostic features, namely duration of the first
remission, have an impact on the success of this strategy (Table 1). For patients whose remission has lasted longer than a year, the second remission can be achieved in approximately 50%, while those patients whose duration of remission was shorter have a lower likelihood of achieving remission with the same drugs and should be considered for alternative investigational therapy. Thus, the ability to achieve a second remission is contingent upon a number of clinical and biological factors, including the duration of response to the first treatment, the nature of that treatment and the overall condition of the patient at the time of relapse. Although patients who relapse typically have a reduction in their leukemic burden with additional treatment, it is the very rare patient who is cured by this approach. Among 547 patients who relapsed in the German ALL study, no patient without a transplant survived more than one year after relapse. Therefore, these salvage therapies in transplantation-eligible patients are best considered as bridges to transplant, performed with curative intent.

As noted above, for those patients who achieve a second remission without any limiting organ toxicities that would preclude proceeding to transplant, and who have an identified HLA-matched sibling, unrelated or potentially cord blood donor, the cure rate can approach 50%. It is these patients who have had a successful reinduction therapy and who can proceed to transplantation before another relapse, that represent the best-case scenario for patient outcomes after relapsed ALL (Figure 1B).

However, most patients do not achieve a second remission and proceed to a curative therapy, thus raising the question, “what is the overall effectiveness of a strategy that reserves transplantation until after achievement of a second remission?” Recent studies suggest that the overall outcome of such an approach is really not so optimistic. The investigators who conducted the MRC ECOG trial to determine the
role of transplantation in the management of ALL, followed not only those patients who underwent transplantation in first remission, but also those who did not, in order to determine the outcome of treatment. In a follow-up study of 609 patients who relapsed on the MRC UKALL12/ECOG 2993 study, the overall survival at 5 years after first relapse was only 7%, 8% for males and 3% for females (Figure 2A). Figure 2B shows the outcomes for patients in this MRC/ECOG relapse study who did not receive a sibling donor transplant in first remission, and later relapsed and survived at least 100 days post-relapse, based on the therapy they received after relapse. In fact, the percentage of patients who proceeded to allogeneic transplant after relapse was relatively small, less than 20% of study population. The study design is partially responsible for this low rate of 2nd remission transplants because most patients with sibling donors had already been transplanted in CR1.

Similarly, the 5-year overall survival of 263 relapsed ALL patients reported by the PETHEMA Study Group, was only 10%, and among 314 relapsed and refractory patients reported by the M.D. Anderson Cancer Center, it was only 3%. An exception to these data was recently reported by the German ALL Group who described a 3-year overall survival of 24% in a group of patients who relapsed, among whom, remarkably, 75% actually proceeded to allogeneic transplantation.

Contributing to the poor overall survivals typically seen after first relapse is the inability to attain second remission, the inability to maintain sufficient performance status to undergo transplant, and the inability to find an acceptable donor before disease progression.

A similar trend is seen for patients with AML, as reported by the Eastern Cooperative Oncology Group (ECOG). The 5-year overall survival for patients following first relapse is approximately 10%, echoing the problem facing the patient with relapsed
leukemia whose disease, in general, is less chemosensitive and, thus, less likely to achieve a remission (Figure 3). Another study of relapsed AML by the Dutch-Belgian Hematology-Oncology Cooperative Group (HOVON) and the Swiss Clinical Cancer Research Collaborative Group (SAKK), reports that the survival rate after first relapse for patients who have not been transplanted previously is 12% (Figure 4). Of all the patients treated with allogeneic transplant post-relapse, the second remission rate is only 18%.22 Although a few patients may still be able to proceed to transplantation after having failed to achieve a remission, or proceed to transplantation without a reinduction attempt, the overall cure rate remains quite low.

Transplant regimens in the management of relapsed leukemia

In addition to the limitations in the efficacy of reinduction therapies to achieve a remission for patients with relapsed leukemia, the problem of effective treatment is not restricted to non-transplant therapeutics. There has been little progress in the development of transplant regimens that could be more efficacious in treating patients with relapsed disease, i.e. not in remission at time of transplantation. The biggest growth in transplant therapy has been in the use of the reduced intensity regimen to treat older patients with leukemia and other hematologic disorders. In general, these studies have shown that patients with leukemia who can be cured were those who are transplanted in first remission when they have a low disease burden. This strategy is generally not effective for the patient with advanced disease (relapse, induction failure). Most programs do not transplant patients who are not in remission, while others are exploring new treatment approaches that might improve the outcome, even for patients with active disease. These non-remission transplantation approaches include regimens incorporating radio-immunotherapy to leukemia-related antigens
(anti-CD45, anti-CD33)\textsuperscript{23,24}; helical tomotherapy,\textsuperscript{25,26} which seeks to increase the radiation dose to the diseased marrow without increasing the toxicity to surrounding organs; novel-agent-based regimens that replace fludarabine with clofarabine; post-transplant hypomethylating agents or histone deacetylase (HDAC) inhibitors to reduce the chances of relapse; and genetically modified leukemia-specific T cells. These are important avenues of study, all of which are designed to reduce relapse after transplant, especially for patients at high risk because they were not in remission at the time of transplant.

**What are new approaches that could provide a more effective bridge to transplant?**

As noted above, most reinduction regimens for AML utilize the same medications that were used to achieve a first remission, although some will use an alternative regimen, including agents such as etoposide and mitoxantrone that are not generally part of primary induction or consolidation therapies. In some patients, particularly those with an early relapse or where the disease kinetics are relatively slow, use of hypomethylating-based therapy, combined with HDAC inhibitors, can achieve a remission with less toxicity to the patient, thus facilitating a transition to transplant. There is ongoing interest in the use of FLT3 inhibitors to achieve a remission, although these agents have not yet demonstrated efficacy consistently enough to rely upon them as bridges to transplant. Recent progress in the sequencing of an individual patient’s leukemia cells may also provide a means of more intelligently determining the most appropriate and effective therapy to achieve a second remission.\textsuperscript{27,28} A promising bi-specific CD33/CD3 T-cell engager is currently in pre-clinical
development for an AML BiTE therapy analogous to the CD19/CD3 BiTE therapy, currently in human trials for ALL.\textsuperscript{30}

In ALL, the focus has been on both the development of new drugs, as well as immunologic therapies that might be effective in achieving a second remission. These include nelarabine for treatment of T-cell ALL as an alternative to reinduction therapy with the same drugs,\textsuperscript{31} and clofarabine-based reinduction regimens for treatment of relapsed ALL have also proven effective.\textsuperscript{32} Despite the use of novel drugs for reinduction, the achievement of a second remission is still only approximately 30-50\%.\textsuperscript{15,33} Recent data on a novel therapeutic, the bi-specific T cell engager (BiTE), has shown an 80\% response rate in patients with relapsed ALL. This approach utilizes an antibody fragment recognizing the CD19 antigen on pre-B ALL, fused to an anti-CD3 antibody fragment, which “engages” a local T cell response, to enlist the patient’s immune system in tumor cell killing and increase the remission rate. These studies have shown an impressive rate of response and, importantly, acted as a bridge to transplant in patients with relapsed ALL; 100\% of the 8 patients who proceeded to transplantation were alive and in hematologic remission at analysis (Figure 5).\textsuperscript{30} These data, if confirmed, also offer the possibility that in the future, cure may be achieved for a much higher proportion of patients with relapsed disease without transplantation, thus providing not only an effective bridge to transplant, but hope for those who are transplant-ineligible. The use of CD19-specific chimeric antigen transduced T cells is also showing strong anti-leukemic activity in patients with CD-19-positive CLL, and is now being explored in patients with CD19+ALL.\textsuperscript{27,28} Antibody-targeted drug delivery is also being explored with CD19 antibody-drug conjugates.\textsuperscript{34}
In addition to development of novel agents that can be used to bridge a patient from relapse to transplant, and improved conditioning regimens that reduce the chances of relapse post-transplant, there are additional measures that can be taken to optimize the chances that a patient will actually be able to receive a transplant after detection of relapse. The first, and simplest, is to identify a donor early on in the course of treatment of the disease. Family typing, we believe, should be done in all patients with acute leukemia, not so much to plan transplants for everyone, but to know what the options are. Then, if necessary plans can be made in an expeditious way including performing searches through the National Marrow Donor Program and cord blood registries to know what the possibilities might be for a patient. Furthermore, with the development of haploidentical transplants, there are increased donor options that improve the chances of moving quickly to transplant without a reinduction attempt, in patients with low disease burden, i.e. detectable by MRD or morphologically as <10% blasts.35

The United States lags far behind Europe in performing appropriate molecular disease assessments that would enable determination of the depth of the remission and the likelihood of relapse in patients who achieve a remission. Many practitioners still rely on morphology and cytogenetics, including FISH, to document remission and follow blood counts and marrow results over time. For AML, the predictive value of minimal residual disease (MRD) detection is less well supported than for ALL, and MRD assessment is not routinely used for clinical decision-making.36-38 Multiple studies in ALL have shown that the detection by flow cytometry or PCR of MRD after completion of induction therapy predicts relapse-free survival and that the detection of an increasing leukemia signal is a harbinger of relapse, often by a period of months.39-43 In fact, MRD monitoring in select centers appears to have superseded
other prognostic factors in adult ALL.\textsuperscript{44} Thus, the incorporation of MRD assessment strategies into the overall treatment of ALL improves the interpretation of depth of the remission, and patients with AML could also benefit from the clinical application of reliable, highly-predictive MRD assays. Regular assessments of the marrow in first-remission patients could either confirm that the remission is stable or alert physicians and patients to the need to consider alternative therapies or transplant, as an MRD signal is an indication of incurability and chemoresistance of the leukemia. Moreover, pre-transplant MRD may also predict for increased risk of relapse following an allogeneic transplant, indicating a possible need for post-transplantation therapies.\textsuperscript{45}

This commentary does not mean to imply that the difficulty of achieving a second remission and getting a patient to transplant is justification, in and of itself, for exposing all patients to the risks of transplantation during first remission. It is simply intended to encourage transplantation in first remission for all patients with acute leukemia in whom this is deemed appropriate, such as poor prognosis AML or ALL and, to point out the many flaws and inadequacies in our therapeutic strategy related to bridging therapy from relapse to transplant, and the impact of such clinical situations on overall outcomes. The development of more effective drugs and immune approaches to achieve a second remission, more effective transplant regimens for patients who do not achieve a second remission, implementation of rigorous assessment of MRD, and preemptive planning of transplant will hopefully change the outcome of these therapies, bringing the probability of cure for patients with relapsed acute leukemia from a myth to reality.
ACKNOWLEDGMENTS

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AUTHORSHIP CONTRIBUTIONS

S.F. and J.R. conceptualized and wrote this manuscript.

CONFLICT-OF-INTEREST DISCLOSURE

The authors have no conflicts to disclose.
REFERENCES


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Patients with evaluable information on the type of salvage therapy, without CNS involvement and with Ph/BCR–ABL-negative ALL. HDAC indicates high-dose cytarabine; HDMTX, high-dose methotrexate; and Mitox, mitoxantrone.

* No percentage was calculated in subgroups with total number of cases less than 10.

†‡ Patients received SCT as their salvage treatment; and CR rate indicates the remission rate after SCT.

FIGURE LEGENDS

Figure 1. Acute Leukemia overall survival following second remission transplant. (Courtesy of CIBMTR). Probability of Survival After Allogeneic Hematopoietic Stem Cell Transplantation with Myeloablative Conditioning for AML (Panel A) or ALL (Panel B) in CR2 in adults 18-50 years of age in the US, 2005-2007.

Figure 2. Probability of survival from first relapse. Panel A. Overall survival in years from date of first relapse based on sex. Panel B. Survival post-relapse is stratified according to therapy given in relapse. Patients who died within 100 days of relapse and those who were transplanted in CR1 were excluded from this analysis for better comparison of the different therapeutic modalities. This research was originally published in Blood. Fielding et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109:944-950. © the American Society of Hematology.

Figure 3. OS for AML following first relapse. Data are from 8 consecutive ECOG studies for newly diagnosed AML patients. Presented at the American Society of Hematology Meeting, 2005 in Atlanta, Georgia

Figure 4. OS for Patients with AML after first relapse based on previous transplantation. SCT refers to both autologous and allogeneic hematopoietic stem cell transplantation. OS for the No SCT group is 12% and for the previous SCT group is 5%. Reprinted with permission. © (2005) American Society of Clinical Oncology. All rights reserved. Breems et al: J Clin Oncol 23(9), 2005:1969-1978.

Figure 5. Time to clinical relapse. (from Topp et al. JCO 2011;29:2493, Figure 1) The probability of relapse-free survival after initiation of blinatumomab treatment in all 20 evaluable
patients is shown in blue. Median follow-up for relapse-free survival is 405 days (range, 78 to 655 days). The probability of relapse-free survival after initiation of blinatumomab treatment in all 12 evaluable patients who have not undergone allogeneic transplantation after completion of blinatumomab treatment is shown in yellow. Median follow-up for relapse-free survival is 276 days (range, 78 to 655 days). HSCT, hematopoietic stem-cell transplantation. Reprinted with permission. © (2011) American Society of Clinical Oncology. All rights reserved. Topp et al: J Clin Oncol 29(18), 2011:2493-2498.
Figure 1

A.  AML: OS for Transplant in CR2

B.  ALL: OS for Transplant in CR2
AML OS from First Relapse
ECOG DATA

5-yr OS = 11% for ≤55
6% for >55
Figure 4

Breems D A et al. JCO 2005;23:1969-1978, Figure 1D
Figure 5

No Hematologic Relapse (probability)

Duration of Disease-Free Survival (days)

- All patients
- Patients without HSCT

Topp M S et al. JCO 2011;29:2493-2498
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