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Deferring allogeneic transplantation for adult acute lymphoblastic leukemia: is there a second chance?

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Chemotherapy to induce remission in patients with adult acute lymphoblastic leukemia (ALL) yields complete remission rates 75–90% using either adult protocols or pediatric-inspired multiagent regimens.[1] The choice of consolidation therapy is risk directed and consideration for allogeneic hematopoietic cell transplantation (HCT) in the first complete remission (CR1) is guided by the presence of high risk factors at diagnosis and achievement of complete remission with no detectable minimal residual leukemia.

In this issue, Cassaday and colleagues analyzed single-center outcomes of adult ALL patients treated with adult type protocols who achieved complete remission without minimal residual disease (MRD).[2] HyperCVAD was the most commonly used induction regimen. In this retrospective analysis, authors compared three consolidation strategies for patients in MRD-negative CR1: continued treatment with consolidation/maintenance chemotherapy or allogeneic donor transplantation using either myeloablative conditioning (MAC) or reduced intensity conditioning (RIC). Nearly identical 3-year overall survival was observed in these three cohorts and the authors suggested that deferred HCT constitutes a viable strategy for adult ALL treated with adult-type regimen.

Several observations from this report are worth closer for examination. First, it has to be noted that a highly selected group of patients is examined. Of the 152 patients with available MRD data, less than 60% were free of MRD after induction and the definition of MRD varied over time. Lagging long-term efficacy of adult induction regimens for ALL is clearly revealed by the fact that over 80% of MRD-negative patients in CR1 who continued on consolidation chemotherapy-only approach experienced relapse at a median time of ~2 years after achieving remission. Remarkably, half of relapsed patients attained second complete remission (CR2), and 70% of them proceeded with deferred HCT in MRD-negative CR2. Notably, most patients in CR2 did not have high-risk features at diagnoses and their median age was 30 years, which was significantly younger than the CR1 patients. The main conclusion of this report highlights that survival after allograft in MRD-negative CR2 was similar compared to MRD-negative CR1. These results are better than any prior experience with relapsed adult ALL,[3,4] and suggest that more favorable prognosis can be expected in adults with ALL who demonstrated upfront chemosensitivity, long duration of CR1 and HCT in MRD-negative CR2. Additionally, while the event-free survival and overall survival

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rates were comparable between RIC and MAC HCT, the relapse rate was significantly higher with RIC. Previous results of RIC in ALL support its use in older and frail patients, however, relapse was higher in most series and RIC may not overcome MRD, particularly in those with Ph + ALL.[5,6] Higher risk of relapse with Ph + ALL after RIC allogeneic HCT, even in patients who are MRD negative as reported by Cassaday et al., supports the need to incorporate tyrosine-kinase inhibitors (TKI) or other ALL-directed therapy post-transplant to reduce relapse.

This study needs to be interpreted in the context of a changing landscape in the management of adult ALL. Recent key studies demonstrated that young adults/adolescents (AYA) with ALL benefitted when treated on pediatric multiagent intensified protocols as compared to adult protocols.[7] Higher doses of non-myelosupressive agents and intensified L-asparaginase in pediatric protocols inspired development of several adult prospective clinical trials using pediatric multiagent regimens for adult ALL. Prospective protocols reported by GRALL, PETHEMA and others groups demonstrated improved (up to 55–65%) 5-year leukemia-free survival rates for adult ALL and emphasized that intensive chemotherapy protocols are feasible up to age 60 years.[8–10] Usually, patient age and institutional preference determines the choice of a pediatric-style versus adult ALL induction protocol. While pediatric inspired regimens may be more challenging to deliver due to the drug dose frequency and intensity and have the potential for increased morbidity, recent experience showed low mortality and manageable toxicity.[9–11] As a result, the strategy for adult ALL therapy has changed, and many centers offer chemotherapy-only consolidation and maintenance for those with standard risk. Prospective studies in adult ALL demonstrated that while allogeneic donor HCT performed in CR1 reduced relapse by at least 50%, high non-relapse mortality (NRM) abrogated the survival benefit in patients above age 35 years, resulting in 5-year overall survival of ~40%.[12] Recent comparison of pediatric-type regimen with allogeneic donor HCT in CR1 showed similar relapse but worse NRM leading to better CR1 survival without HCT.[13] These outcomes challenge the use of allogeneic donor HCT in CR1 for patients with standard risk ALL, at least those who achieve MRD-negative CR and suggest reserving allograft for high-risk disease.

Persistent MRD clearly portends a highly adverse prognosis superseding many classical high-risk features such as high WBC, age, cytogenetics and time to CR. MRD negativity has become the most important goal of induction chemotherapy. While the choice of post-remission consolidation strategy such as allograft versus chemotherapy is determined by MRD, the specific kinetics and sensitivity of MRD measurement remains to be established. The strength of the study by Cassaday et al. is in incorporating pre-transplant MRD assessment for patients treated with salvage therapies who achieved CR2. The outcomes of patients in CR2, which have mostly been studied in pediatric series, suggest that duration of CR1 >3 years was associated with less relapse and leukemia-free survival approaching 40–50%. As many institutions now defer HCT for adults with standard risk ALL, the outcomes and prognostic factors affecting allogeneic HCT in CR2 need to be rigorously studied. Differences in the kinetics and the biology of ALL relapse in high risk and standard risk disease can inform on risk-adapted relapse preventing strategies. Success of allograft in CR2 thus could be enhanced by early disease detection and effective novel therapies. Examination of novel prognostic factors in CR2 patients may reveal additional insights.

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