Chemotherapy vs, allogeneic HSCT for Philadelphia chromosome–negative adult lymphoblastic leukemia

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Therapy outcome in adults with acute lymphoblastic leukemia (ALL) has substantially improved in the last decade, with complete remission (CR) and long-term overall survival (OS) rates of around 90% and 40%-50%, respectively. Treatment of Philadelphia chromosome-negative (Ph-neg) ALL in adults is still based on conventional multidrug chemotherapy followed or not by (usually allogeneic) hematopoietic stem cell transplantation (allo-HSCT). Significant improvements have been achieved in recent years from the use of improved targeted therapy and immunotherapy in CR patients with positive measurable residual disease (MRD) and even in newly diagnosed patients with ALL. If these approaches will reduce (or eliminate in some cases) the need of allo-HSCT is still a matter of research.
There is clear evidence that adult patients with standard-risk (SR) ALL at baseline and end-of-induction and/or end-of-consolidation MRD levels <0.01%, are best managed with conventional chemotherapy, whereas patients with poor MRD clearance are best treated with allo-HSCT. However, is not clear whether this same principle can be applied to patients with high-risk (HR) features at diagnosis, for whom allo-HSCT has been classically considered as the standard post-consolidation therapy. In this sense, it is important to note that allo-HSCT only benefitted MRD-positive patients in two studies from the French GRAALL Group.
The allocation of adult patients with Ph-negative ALL to chemotherapy or to allo-HSCT as post-consolidation therapy according to MRD levels has been addressed in some prospective trials, two of them from the Italian NILG Group and two from the Spanish PETHEMA group. All trials showed that there was a subset of Ph-neg adult patients with good MRD clearance after induction and/or after consolidation that achieve OS rates of 60-70% without allo-HSCT. The last trial of the PETHEMA Group showed a clear relationship between the early deep clearance of MRD and OS, with OS over 80% in HR patients who showed a MRD level <0.01% at mid induction treatment. The GMALL Group is currently conducting a randomized trial evaluating the allo-HSCT vs. standard therapy in Ph-negative ALL patients with HR features and molecular CR after induction.
Apart of MRD level, some studies have shown that genetic features of ALL have independent prognostic significance, with differences in these features for BCP-ALL and for T-ALL. Other studies have shown that the absolute relapse rate associated with a specific MRD value varied significantly according to the genetic subtype of ALL. Thus, integration of genetic subtype/subclone-specific MRD might potentially allow for more refined risk stratification.
There are some unanswered questions on the role of allo-HSCT in first complete remission in adults with Ph-neg ALL. Will MRD clearance with immunotherapy avoid allo-HSCT in CR1? Will CAR T therapy administered in early phases in patients with HR features and positive MRD avoid the need for HSCT in CR1? Will prophylactic therapy after allo-HCST be necessary in HR ALL patients to decrease the 20-30% relapse after transplant?
In summary, it is highly probable that the incorporation of targeted therapies and immunotherapy in frontline therapy of ALL, combined with genetic and MRD-based stratification of therapy, will contribute to best define the role of allo-HSCT in ALL management and will improve the outcome of adult patients with ALL.