PROCEEDINGS ARTICLE

Modern therapy of young and adult Ph-ALL

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Acute lymphoblastic leukemia (ALL) in adults is currently associated with an overall survival rate of around 40% at 5 years. This is an unsatisfactory result that makes it imperative to dissect further the biology of the disease in order to identify highly specific therapeutic targets to implement selectively the cure rate. The recognition of discrete ALL subsets followed by the application of risk-oriented therapies has been a major achievement over the past 30 years.

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Keywords: acute lymphoblastic leukemia; treatment strategy; risk classification

TREATMENT OBJECTIVES

Major prognostic subgroups are now identified: patients with survival probabilities of 60–70% in low-risk T-acute lymphoblastic leukemia (T-ALL); selected patients with B-lineage ALL and early clearing of minimal residual disease (MRD); and young adults with all favourable characteristics when treated on pediatric protocols. The primary clinical end point is the identification of an individual prognostic profile allowing the application of a subset/risk-oriented therapeutic strategy, where risks and benefits of different treatment options including hematopoietic stem cell transplantation (HSCT) are optimally balanced.¹ Progress is expected with the use of chemotherapy programs increasingly inspired to the pediatric experience for induction and early consolidation, HSCT when indicated and targeted therapy when possible, with a concurrent view to prevent toxic side effects and limit the incidence of treatment-related mortality (Figure 1). The final goal is to bring the overall survival rate to at least 50% at 5 years in unselected adults aged 60 years and less.

DIAGNOSIS AND CLASSIFICATION

EGIL and WHO classifications provide a framework to identify ALL subsets associated with distinct clinico-prognostic, immunophenotypic and genetic/cytogenetic features. Pro-B and pro/pre-mature-T ALL are considered high risk, although most recent and aggressive treatment regimens have sensibly modified this pattern. The cytogenetic/genetic study is fundamental to exclude Philadelphia chromosome-positive (Ph+) ALL and to identify MLL-AF4+ ALL, the latter still considered a poor-risk situation. Other high-risk subsets exhibit trisomy 8, monosomy 7, t(8;14), low hypodiploidy and complex karyotype. The prognostic significance of t(1;19)/E2A-PBX1 is debated. Several genetic lesions carrying a pejorative prognostic effect were described, such as IKZF1 deletion.

RISK STRATIFICATION

ALL patients respond with substantial heterogeneity to induction-consolidation therapy. Groups at different risk of relapse, with variable survival probabilities, were identified by risk models combining age (worse outcome >35–55 years), white cell count (WBC, worse >30–100 × 10⁹/l), immunophenotype, cytogenetics/genetics and time to complete remission (CR) or speed of

response to early treatment (that is, circulating blasts after prephase with steroids, bone marrow blasts on day 14 of induction). The classic distinction is between standard-risk (SR) and high-risk (HR) patients, whose survival ranges from about 50% to 30% or less, respectively. Such a purely clinical risk classification is inadequate, because up to 50% of SR patients ultimately relapse.

COMPLETE REMISSION AND BEYOND: MRD

To prolong survival and achieve cure, it is mandatory to obtain a CR first and then act to prevent systemic or local recurrence. The central nervous system is the extramedullary site at greater risk of recurrence (≤5%), and hence the need to adopt a specific central nervous system prophylaxis program. The concept of hematological CR can be improved by the assessment of MRD. This analysis is performed by either flow cytometry or a molecular biology technique (RQ-PCR). MRD studies allow to detect with accuracy and a sensitivity of 10^{−4} and greater very small amounts of ALL cells in remission marrows, at selected treatment timepoints, thereby defining exactly whether, when and how rapidly the ALL clone declines in response to chemotherapy. With PCR, achieving a complete MRD response at weeks 10–16 or even earlier is regarded as truly indicative of SR behavior (molecular CR). Prospective studies confirmed MRD to represent the most reliable single prognostic indicator in both SR and HR groups,^{2–4} largely overcoming traditional risk factors in multivariable analyses. A study indicated persistent MRD, and not simply CD20 expression, to confer a worse outlook in CD20+ ALL, a disease subset once considered HR.⁵ The information provided by MRD assessment is crucial to decide for allografting in SR patients who are MRD positive, or alternatively not to transplant selected HR patients when found to be MRD negative.

MAXIMIZING RESPONSE, WITH OR WITHOUT HSCT

Modern regimens derived from the pediatric world allow a 90% or greater CR rate in patients aged up to 45–55 years, with a survival rate close to 50% at 3 years.⁶ Therefore, the incorporation of any new drug into these programs requires MRD as additional end point to demonstrate an adjunctive early therapeutic benefit. As regards to post-remission phase, debate persists as to the exact role of allogeneic HSCT in the different risk and disease subsets. HSCT is more effective than chemotherapy against recurrence but

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Figure 1. Conceptual sequence of the modern treatment strategy for adult ALL.

carries a risk of treatment-related mortality of about 15% or higher, particularly in older age groups. In an intention-to-treat analysis (donor vs no donor), the MRC–ECOG-randomized trial demonstrated the superiority of SCT in SR patients but not in HR patients;⁷ however, the margin of improvement was narrow and the cost in terms of treatment-related mortality was high. Several European groups adopt a risk-/MRD-oriented policy to avoid unnecessary treatment-related mortality and to define which patients can be cured by chemotherapy or require SCT, and which ones fail either modality and should be shifted to experimental therapy. Because 20–30% of HSCT-treated patients will relapse, therapeutic progress can arise only from real breakthroughs in this area and not from an endless chemotherapy vs HSCT competition. Recently, blinatumomab, a new bispecific anti-CD19 monoclonal antibody engaging CD3+ T cells as anti-CD19 effectors, was shown capable of inducing a high rate of molecular or clinical CR in most patients treated at the time of molecular or clinical relapse, respectively.⁸ In T-ALL, nelarabine proved effective in the setting of relapsed disease.⁹ These drugs share the potential to improve significantly current treatment results once brought to firstline therapy.

CONCLUSIONS

Ph-ALL in adults must be regarded as a curable disease as long as we can demonstrate therapeutic progress, albeit slowly, through a correct design and interpretation of clinical trials. Intergroup collaboration such as that promoted by the European Working Group on Adult ALL¹⁰ is essential to provide rapid exchange of data and warrant early access to therapeutic innovations to as many patients as possible.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. *J Clin Oncol* 2011; **29**: 532–543.
- Bruggemann M, Raff T, Flohr T, Gokbuget N, Nakao M, Droege J et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood* 2006; **107**: 1116–1123.
- Bassan R, Spinelli O, Oldani E, Intermesoli T, Tosi M, Peruta B 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; **113**: 4153–4162.
- Bruggemann M, Schrauder A, Raff T, Pfeifer H, Dworzak M, Ottmann OG 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; **24**: 521–535.
- Mannelli F, Gianfaldoni G, Intermesoli T, Cattaneo C, Borlenghi E, Cortelazzo S et al. CD20 expression has no prognostic role in Philadelphia-negative B-precursor acute lymphoblastic leukemia: new insights from the molecular study of minimal residual disease. *Haematologica* 2011; **97**: 568–571.
- Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol* 2009; **27**: 911–918.
- Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK 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; **111**: 1827–1833.
- Topp MS, Kufer P, Gokbuget N, Goebeler M, Klinger M, Neumann S et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol* 2011; **29**: 2493–2498.
- Gokbuget N, Basara N, Baurmann H, Beck J, Bruggemann M, Diedrich H et al. High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. *Blood* 2011; **118**: 3504–3511.
- Goekbuget N (ed). *Recommendations of the European Working Group for Adult ALL*. UNI-MED Verlag AG: Bremen, London, Boston, 2011.