EUROPEAN HEMATOLOGY ASSOCIATION

Balancing efficacy and toxicity in the treatment of childhood acute lymphoblastic leukemia

Ajay Vora

Department of Paediatric Haematology, Great Ormond Street Hospital, London, United Kingdom

Take-home messages

- Reductions in relapse risk after first line treatment of children with acute lymphoblastic leukemia observed with intensified treatment strategies in the 1970s to 1990s have unmasked the morbidity and mortality associated with intensive therapy and revealed late treatment-related side effects on long term follow-up.
- Advances in understanding of the biological complexity of childhood acute lymphoblastic leukemia and development of sensitive methods for detecting Minimal Residual Disease (MRD) have improved molecular profiling and risk stratification models.
- Risk adapted intensification and de-escalation of treatment, drugs against specific molecular targets and immune based treatment approaches will be the basis for design of future protocols to improve efficacy while minimizing toxicity.

Introduction

The full curative potential of intensive chemotherapy in childhood acute lymphoblastic leukemia (ALL) is handicapped by treatment associated mortality and morbidity. Despite improvements in supportive care, intensive therapy carries a significant risk of mortality (4 -6 %) and morbidity (30 - 60% serious adverse event rate), especially when viewed against a low (<10%) relapse risk in recent trials[1] (Table 1). Additionally, patients remain at risk of late neurocognitive side effects and secondary cancers. It's important, therefore, to identify groups of patients who remain at high risk of relapse to direct further intensification of treatment towards them, while trying to de-escalate treatment for the remainder who achieve high rates of event-free survival with 'standard' therapy.

Current state of the art

Risk stratification

Although treatment stratification based on clinical and cytogenetic criteria have been in use for many years, risk groups identified by these variables are relatively non-specific. For example, a high-risk group with a 5 year EFS of around 50% defined by age, gender and presenting WCC identifies only 20% of patients destined for relapse, with the majority of relapses still arising out of the remaining, apparently, low risk patients.[2,3] Assessment of minimal residual disease (MRD) at post-remission time points offers a very sensitive and specific means of distinguishing between patients who will and will not relapse. Hence, most current treatment protocols use a risk stratification approach incorporating MRD assessment at one (end of induction) or two time points (and end consolidation).[4] However, although undetectable MRD at end of induction identifies a group at very low risk of relapse, a high risk group defined solely on the basis of MRD does not capture a majority of relapses[5] as these occur within the MRD intermediate risk group whose outcome can be further stratified by molecular profiling.[6,7]

De-escalation of treatment

Durable remissions of ALL were reported in roughly 50% of patients treated on St Jude total therapy V in the 1960s. Subsequently, the Berlin-Frankfurt-Munster (BFM) group showed that the event free survival could be improved to 70% by intensified induction and consolidation therapy, later confirmed by the UK MRC group in a randomised trial.[8,9] Although the BFM strategy gained wide acceptance internationally, almost without exception the original model required modification because its toxicity did not allow delivery as in Germany. Two recent trials by the UK (UKALL 2003)(1) and Dutch (DCOG 10) groups[10] have demonstrated that modest de-escalation of treatment is feasible for a MRD defined low risk group, although a contemporary European study (AIEOP-

Acute lymphoblastic leukemia - The worst and the best - Section 1

BFM 2000) found a slight increase in relapse risk associated with a reduced intensity delayed intensification course.[11] Since DS-ALL has an inferior survival due in large part to a high treatment related mortality (TRM), many groups reduce the intensity of treatment for this group of patients.[12, 13]

CNS directed therapy- is cranial radiotherapy essential?

Having been standard practice for prevention of central nervous system (CNS) relapse in older treatment protocols for children with ALL, pre-emptive cranial radiotherapy (CRT) has increasingly been replaced by other treatment strategies due to its associated high risk of late neurocognitive sequaelae, endocrinopathy and secondary cancers. A systematic review and meta-analysis of 47 randomized trials of CNS-directed therapy conducted between the 1970s and 1990s showed that CRT can generally be replaced by intrathecal therapy.[14] This observation has been confirmed in single group studies[15] and in a more recent meta-analysis of T-lineage ALL only.[16] Another recent meta-analysis demonstrated that CRT is of no benefit in prevention of relapse after contemporary first line therapy except for a small sub-group of patients with overt CNS disease at diagnosis for whom CRT reduced isolated CNS relapse, but did not affect overall survival which was poor, with or without CRT.[17]

Limiting exposure to toxic drugs

UK and US COG groups limit exposure to anthracyclines in induction to NCI high risk patients only (age >10 years or WCC >50x10^9/L) to reduce the depth and duration of marrow failure, severity of mucositis and risk of late cardiotoxicity. In view of excess infection related induction mortality in Down syndrome patients, in the UK, even NCI HR patients start 3 drug induction without anthracycline which is added at day 15 for those with a slow early response (day 15 M3 marrow). Although thioguanine is more effective than mercaptopurine at preventing CNS relapses, its association with an increased risk of death in remission and veno-occlusive disease (VOD) of the liver[18] precludes its use for the maintenance phase of treatment. The risk of osteonecrosis might be reduced by using an alternate week schedule of dexamethasone during delayed intensification,[19] but appears not to be higher in patients who receive steroid pulses in maintenance.[20]

Limiting the proportion of patients receiving Hemopoietic Stem Cell Transplant (HSCT)

The proportion of patients transplanted in first remission varies by study group from <5% to 15%. Some groups have reported a benefit of matched related donor HSCT compared

Table 1. Outcomes with contemporary childhood ALL protocols.

Trial	Group	Region	Years	Subgroup (n)	EFS (yrs)	OS (yrs)
Several	COGUS, Canada, Australia, New Zealand		2000-05	All patients (6994)	N/A	91.3% (5-yr)
				B-ALL (5845)	N/A	92.0% (5-yr)
				T-ALL (457)	N/A	81.5% (5-yr)
Total XV (age 1-18)	SJCRH	US	2000-07	All patients (498)	85.6% (5-yr)	93.5% (5-yr)
				B-ALL (422)	86.9% (5-yr)	94.6% (5-yr)
				T-ALL (76)	78.4% (5-yr)	87.6% (5-yr)
00-01(age 1-18	DFCI	US, Canada	2000-04	All patients (492)	80.0% (5-yr)	91.0% (5-yr)
				B-ALL (443)	82.0% (5-yr)	N/A
				T-ALL (49)	69.0% (5-yr)	N/A
AIEOP-BFM 2000 (age 1-18)	BFM	Western Europe	2000-06	All patients	N/A	N/A
				B-ALL (4016)	80.4% (7-yr)	91.8% (7-yr)
				T-ALL (464)	75.9% (7-yr)	80.7% (7-yr)
ALL-10 (age 1-18)	DCOG	Netherlands	1997-2004	All patients (865)	87% (5-yr)	92% (5-yr)
				B-ALL (661)	88% (5-yr)	93.3%(5-yr)
				T-ALL (116)	80% (5-yr)	88%(5-yr)
UKALL 2003 (age 1-25)	MRC/NCRI	UK	2003-11	All patients (3126)	87.3% (5-yr)	91.6%
				B-ALL (2733)	88% (5-yr)	92.3%
				T-ALL (386)	82% (5-yr)	86.4%

*AIEOP-BFM: Association of Italian Pediatric Oncology and Berlin Frankfurt-Munster; COG: Children's Oncology Group; SJCRH: St. Jude Children's Research Hospital; DFCI: Dana Farber Cancer Institute Consortium; MRC/NCRI: Medical Research Council/National Cancer Research Institute; *infants <1-year-old excluded.*

with chemotherapy in high risk sub-groups,[21] but a transplant related mortality (TRM) of 5-20% associated with unrelated and mismatched donor transplant limits the benefit of HSCT. Although TRM has improved with the incorporation of standardized donor matching and conditioning therapy,[22] it remains a significant concern as does acute and late HSCT-related toxicity especially that associated with total body irradiation (TBI) based conditioning. An on-going randomized international study (FORUM) is testing whether radiation free conditioning is associated with reduced toxicity without compromising efficacy. Most groups have also narrowed the indications for CR1 HSCT with a focus on MRD response based criteria rather than solely clinical or genetic features.

Future perspectives

As cure rates improve, greater attention should focus on reducing treatment related deaths which make up an increasing proportion of treatment failures. Identification of groups at high risk of toxicity (e.g., Down syndrome) and pharmacogenomic analysis will guide targeted supportive care and individualized drug dosing to reduce toxic deaths. There is evidence that gene expression signatures of leukemic blasts can predict in-vitro and *in vivo* chemosensitivity and treatment in future could be customized to a patient's pharmacogenomic and leukemia genotype. Translation of recent advances in understanding of the molecular biology of ALL and its influence on phenotype and clinical outcome will help define specific sub-groups that might benefit from such an approach. Targeted and immune based treatment could replace elements of conventional chemotherapy regimens responsible for some of the major toxicities, thereby reducing toxicity whilst retaining overall efficacy of treatment. These include tyrosine kinase inhibitors for Philadelphia chromosome negative ABL class fusions, antibodies such as blinatumomab and cellular therapy with autologous and universal chimeric antigen T cells (CART). The efficacy and toxicity of these interventions as single agents or in combination with chemotherapy will need to be tested in controlled clinical trials with long term follow-up.

References

*1. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol 2013;14:199-209.

First and only randomised trial demonstrating that treatment intensity can be tailored to MRD response.

2. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 2008;111:4477-89.

3. Mitchell C, Payne J, Wade R, et al. The impact of risk stratification by early bone-marrow response in childhood lymphoblastic leukaemia: results from the United Kingdom Medical Research Council trial ALL97 and ALL97/99. Br J Haematol 2009;146:424-36.

*4. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010;115:3206-14.

Largest prospective study confirming MRD as the single most important predictor of outcome in chilhood ALL.

*5. van Dongen JJ, Seriu T, Panzer-Grumayer ER, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. Lancet 1998;352:1731-8.

First large study that found MRD is the single most important predictor of outcome in childhood ALL.

*6. Moorman AV, Enshaei A, Schwab C, Wade R, Chilton L, Elliott A, et al. A novel integrated cytogenetic and genomic classification refines risk stratification in pediatric acute lymphoblastic leukemia. Blood. 2014;124(9):1434-44.

Integration of cytogenetics and molecular abnormalities with MRD improves precision of risk stratification in childhood ALL.

7. Clappier E, Grardel N, Bakkus M, et al. IKZF1 deletion is an independent prognostic marker in childhood B-cell precursor acute lymphoblastic leukemia, and distinguishes patients benefiting from pulses during maintenance therapy: results of the EORTC Children's Leukemia Group study 58951. Leukemia 2015;29:2154-61.

8. Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children with lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. Medical Research Council Working Party on Childhood Leukaemia. Lancet 1995;345:143-8.

9. Tubergen DG, Gilchrist GS, O'Brien RT, Coccia PF, Sather HN, Waskerwitz MJ, et al. Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: a Childrens Cancer Group phase III trial. J Clin Oncol 1993;11:527-37.

10. Pieters R, de Groot-Kruseman H, Van der Velden V, et al. Successful therapy reduction and intensification for childhood acute lymphoblastic leukemia based on minimal residual disease monitoring: Study ALL10 from the Dutch Childhood Oncology Group. J Clin Oncol 2016;34:2591-601.

11. Schrappe M, Zimmermann M, Möricke A, et al. Reduced intensity delayed intensification in standard-risk patients defined by minimal residual disease in childhood acute lymphoblastic leukemia: Results of an international randomized trial in 1164 patients (Trial AIEOP-BFM ALL 2000). Blood 2016;128:4.

12. Patrick K, Wade R, Goulden N, et al. Outcome of Down syndrome associated acute lymphoblastic leukaemia treated on a contemporary protocol. Br J Haematol 2014;165:552-5.

13. Buitenkamp TD, Izraeli S, Zimmermann M, et al. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. Blood 2014;123:70-7.

14. Richards S, Pui CH, Gayon P. Systematic review and meta-analysis of randomized trials of central nervous system directed therapy for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2013;60:185-95.

15. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblas-

tic leukemia without cranial irradiation. N Engl J Med 2009;360:2730-41.

16. Kelly MJ, Trikalinos TA, Dahabreh IJ, et al. Cranial radiation for pediatric T-lineage acute lymphoblastic leukemia: a systematic review and meta-analysis. Am J Hemato. 2014;89:992-7.

*17. Vora A, Andreano A, Pui CH, et al. Influence of cranial radiotherapy on outcome in children with acute lymphoblastic leukemia treated with contemporary therapy. J Clin Oncol 2016;34:919-26.

A recent meta-analysis confirming that cranial radiotherapy is not essential for first line treatment of childhood ALL.

18. Vora A, Mitchell CD, Lennard L, et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. Lancet 2006;368:1339-48.

19. Mattano LA Jr., Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. Lancet Oncol 2012;13:906-15.

20. De Moerloose B, Suciu S, Bertrand Y, et al. Improved outcome with pulses of vincristine and corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL) and lymphoblastic non-Hodgkin lymphoma (NHL): report of the EORTC randomized phase 3 trial 58951. Blood 2010;116:36-44.

21. Balduzzi A, Valsecchi MG, Uderzo C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. Lancet 2005;366:635-42.

22. Peters C, Schrappe M, von Stackelberg A, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: A prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. J Clin Oncol 2015;33:1265-74.