Acute lymphoblastic leukemia - Section 3

New concepts in acute lymphoblastic leukemia frontline trials

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Take Home Messages
- Treatment is so successful that improvements are difficult to show for reasons of statistical power. There is call for even wider collaborations.
- There is considerable over-treatment. We should aim to identify groups and test de-escalated therapy for patients who would potentially benefit from less therapy.
- Translational research gives us new prognostic markers and potential new targets for intervention, but proving the effect of targeted therapy is difficult.
- Innovative immunotherapy is currently one of the most promising new modalities.

Introduction
Contemporary treatment of acute lymphoblastic leukemia (ALL) cures >90% of children and >70% of young adults. However, some patients still relapse and die of ALL while others die from complications or suffer from toxicity and long-term sequelae as survivors. For children, the risk of dying from therapy is approaching the risk of dying from ALL. Thus, despite its curability, the potential therapeutic window for improvement is paradoxically narrowing. Further intensification risks causing the death of curable patients whereas de-intensification may result in increased risk of relapse and death from disease. Increasing knowledge of the pathogenesis provides markers for improved stratification as well as new targets for therapy. Manipulation of the immune-system and the use of immunological targets provide additional therapeutic possibilities (Table 1).

Current state-of-the-art
Power
Designing trials for rare diseases with good prognosis, such as ALL, is challenging. Statistical power is a major issue. In standard risk ALL with >95% survival, studies need to recruit immense numbers to detect differences between both intensification and de-escalation interventions. Smaller subsets with worse prognosis need smaller numbers, but recruitment takes longer because of the low incidence. This frequently necessitates the expansion of the recruitment base to international and inter-group collaborations. The formation of the ALLTogether consortium by European study-groups, the Interfant-collaboration for infants, the EsPhALL-COG protocol for Ph+ALL and the expansion of the BFM and ALLIC-groups are such examples.

Children and adults
Recent improvements have come from the adoption of “pediatric-style” treatment for young adults, in protocols for adults, or by collaborations including both age groups. Such integration has clarified some reasons for the age-difference in prognosis: Immunophenotype, genetics and MRD-response work in concert to produce a worse risk-profile with age. Out of 47 open or recently closed optimization-trials listed at www.clinicaltrials.gov only 15 were exclusive to adults, 9 included a wide range of ages, 11 included children and younger adults and 12 were pediatric studies with 18 as the upper age-limit.

De-intensification
Treatment for ALL is associated with severe toxicity, partly related to the treatment intensity. However, treatment-related death, second malignancies and serious long-term side effects occur even in standard risk patients. To identify patients, who may be cured with less therapy without increasing deaths from relapse, is one of the major challenges in ALL trials. One de-intensification successfully carried out for most children, is the removal of CNS-irradiation. Modest MRD-directed de-intensifications have been tried by several pediatric groups, but take a long time to evaluate and the conclusions drawn may have limited external validity. Subgroups with an elevated toxicity risk have been described, e.g. osteonecrosis in adolescents, thrombosis in adults and severe myelotoxicity in patients with low TPMT/NUDT15 activity. Both clinical risk-groups and patients with genetic susceptibility may be candidates for targeted de-intensification. To facilitate the comparison across treatment protocols common toxicity definitions as suggested by the Ponte di Legno group and the international pediatric classification of treatment-related mortality should be used.
New markers and targets

Modern genetic technology may help both in stratifying patients into known sub-groups as well as identifying new genetic aberrations, forming both the basis for new risk-groups and targets for directed therapy. Novel potentially prognostic and in some protocols stratifying genetic markers include Ph-like ALL,12 IKZF1-mutations and connected copy-number alteration patterns,13 TCF3-HLF fusion transcripts,14 ETV6-RUNX1-like ALL, DUX-4-, MEF2D- and ZNF384 rearrangements.15 Tyrosine kinase inhibitors (TKIs) are used in Ph+ALL. Similar therapy has been shown to have effect on “ABL-class”-kinases (ABL1, ABL2, PDGFRB and CSF1R)16 with alternative partners or JAK-STAT pathway activation (involving CRLF2, JAK2 and EPOR).17 A COG phase III trial adds the TKI dasatinib to chemotherapy in patients with Ph-like mutations. St.Jude’s Total Therapy XVII incorporates dasatinib, ruxolitinib or bortezomib based on molecular targets and treatment response. The upcoming European ALLTogether trial will also test TKIs in patients with ABL-class fusions.

Immunotherapy

Allogeneic hematopoietic stem-cell transplantation (HSCT), the traditional general immunotherapy for ALL is burdened with treatment related mortality and permanent side effects. The ongoing FORUM-trial is attempting to omit irradiation to children to reduce long-term effects. Targeted immunotherapy with monoclonal antibodies use activation/modulation of immune responses. Targets under current study include CD20 and CD22. Epratuzumab (anti-CD22) is tested in the IntReALL-trial for relapsed BCP-ALL. Anti-CD38 antibodies are starting early phase trials in relapsed/refractory patients. Bi-specific antibodies (BITEs) elicit autologous T-cell responses against leukemic cells by docking the T-cell receptor with a target antigen on the leukemic cells.18 Similarly, autologous T-cells can be genetically engineered to express a chimeric T-cell receptor directed against a leukemic cell antigen (CAR-T cells). The most common target for both therapies is CD19, but several others are under development. Both BITEs and CAR-T cells have shown remarkable effects with successful eradication of bulky, refractory disease. Side-effects include cytokine-release syndrome, CNS-toxicity and B-cell aplasia. One CAR-T (Tsagenlecleucel) and one BITE (Blinatumomab) have recently received a label for treatment of refractory ALL.19 The appropriate place in the therapy for these agents is currently under intense study. There are >50 ongoing trials using CAR-T cells and >10 studies including BITEs worldwide. Antibodies linked to chemotherapeutic agents should probably be considered targeted chemotherapy rather than immunotherapy. Antigen-targets include CD22, 19, 20 and 123. Inotuzumab ozogamicin (CD22) linked to the toxin calicheamicin, has recently been approved for relapsed and refractory B-lineage ALL.20 Trials including modulation of T-cell responses by the use of checkpoint-inhibitors targeting PDL-1, its receptor or CTLA-4 are also ongoing.

Table 1 Moving towards personalized medicine in ALL. Summary of main categories and interventions.

| Examples                                                                 | Intervention                      |
|------------------------------------------------------------------------|-----------------------------------|
| Clinical factors, e.g. T-cell immunophenotype, CNS3-status             | Stratification                    |
| Genetic aberrations, e.g.                                             | Stratification                    |
| IKZF1 mutations, CNA-profile, TCF3-HLF fusion transcript, JAM21        | Dose-Intensification              |
| Minimal residual disease                                              | Stratification                    |
| Pharmacodynamics                                                       | Therapeutic drug monitoring        |
| Pharmacogenomics                                                       | Dose-adjustment TPM7/NUDT15        |
| TYK-fusions                                                           | Tyrosine kinase inhibitors         |
| JAK-STAT pathway activation                                            | JAK kinase inhibitors              |
| NOTCH pathway activation                                              | NOTCH1 inhibitors                 |
| CD20-expression                                                       | Monoclonal antibodies              |
| CD38-expression                                                       | Bi-specific antibodies             |
| CD19-expression                                                       | Chimeric antigen receptor (CAR) T-cells |
| CD22-expression                                                       | Antibody-drug conjugates           |
| PDL1-expression                                                       | Checkpoint Inhibitors              |

CNA: copy number alterations.
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