In adult acute lymphoblastic leukemia (ALL) complete remission rates (CR) of 80-90% and long term survival of 35% at the best could be achieved. ALL is however not a uniform disease and outcome shows considerable variations between subtypes with LFS rates between 50% for T- and mature B-ALL and < 10% for Ph/BCR-ABL positive ALL. Table 1 gives the clinical and laboratory characteristics of subtypes in adult ALL, the relapse kinetics and localisation and the leukemia free survival (LFS).

Chemotherapy is the essential part of ALL therapy, and childhood trials have convincingly shown how by selection of cytostatic drugs, better timing and high dose therapy outcome can be substantially improved. In adult ALL optimisation of chemotherapeutic regimens is necessary as well, however it seems that new treatment options are needed to proceed further. These new options in the management of adult ALL include.

1. **Stem cell transplantation (SCT)** with extension of indications for SCT and inclusion of new modalities including allogeneic non-myoeloblatite transplants.
2. **Minimal residual disease** to guide individual treatment decisions.
3. **Molecular targeting** such as Abl-tyrosine kinase inhibitor STI571 (GLIVEC®) in Ph/BCR-ABL positive ALL.
4. **Antibody treatment.**

**Induction chemotherapy**

To improve CR rates and thereby remission quality several attempts have been or are currently explored in adult ALL, such as high dose therapy, intensification of anthracyclines and use of PEG-asparaginase. With high dose cytarabine (HdAC) administered up-front before standard induction CR rates of 75-85% were achieved, but this approach did not lead to superior LFS. Retrospective analysis of published results in adult ALL suggests that the application of dose-intensive anthracyclines during induction therapy may contribute to an improvement of CR rate and LFS.

**Postinduction therapy**

Postinduction therapy mainly consists of intensive rotational consolidation therapy, high-dose chemotherapy cycles and SCT. There is generally a superior outcome from trials implementing intensive multidrug consolidation therapy (median: 27-36%) compared to those without consolidation (median: 25%)³. High-dose chemotherapy –mainly cytarabine (HDAC) or methotrexate (HDMTX)– has been used to overcome drug resistance and to achieve therapeutic drug levels in the cerebrospinal fluid. The overall impression is that the inclusion of HdAC, HDM or both might be beneficial particularly if included in regimens with intensive rotational conventional dose chemotherapy with LFS rates of 45-55%, but all in small series.

**Stem cell transplantation**

Stem cell transplantation (SCT) from bone marrow grafts and to an increasing extent transplantation of peripheral blood stem cells (PBSCT) is an essential part of consolidation treatment in adult ALL. The optimal strategies and indications for SCT are at present explored in randomized studies.

Survival for adult ALL patients with allogeneic (allo) SCT from sibling donors in first CR is approximately 50%. LFS after allo SCT thus seems superior to that obtained with chemotherapy alone although this advantage could not be clearly demonstrated in prospective trials with adjustment for age and risk factors.

In the so far largest randomised trial allo SCT was scheduled for all patients below 40 years with sibling donor. The remaining patients were randomised (control group) to receive either autologous (auto) SCT or chemotherapy. In a recent update the survival after allo SCT was significantly superior (46%) to the control group (31%), which was predominantly due to a higher survival in HR patients with allo SCT (37%) compared to the control group (15%), whereas in SR ALL (46% versus 42%) no significant difference was observed. In the ongoing ECOG/MRC trial allo SCT is scheduled in all patients with sibling donor and compared to auto SCT randomized versus chemotherapy (control group). In an interim analysis the LFS after 3 years was 58% for patients who actually received allo SCT compared to 39% for the control group. Allo SCT yielded superior LFS for HR (57% versus 32%) and for SR
(71% versus 54%) ALL patients < 60 years. A final intent-to-treat analysis of this study is awaited.

Matched unrelated SCT (MUD) is increasingly employed in adult ALL and the LFS (39%) in patients with more advanced disease (≥ CR2) is promising. In adult poor risk ALL with a median age of 34 years the results of MUD SCT were particularly favorable for patients in CR1 (42%). Up to now the low relapse rate – most probably due to a more pronounced Graft versus Leukemia (GvL) effect – is nearly outweighed by the high TRM. With better donor selection, increasing experience, improved supportive care and management of GvHD results for MUD transplants are constantly improving and MUD is already a choice for high risk patients in CR1 such as Ph/BCR-ABL + ALL if a sibling donor is not available.

New approaches for allogeneic SCT include donor leukocyte infusions, new conditioning regimens e.g. with radiolabeled antibodies and non-myeloablative stem cell transplantation (“mini transplant”) which may lead to an extension of the upper age limit for allo SCT.

After autologous (auto) SCT in CR1 in adult ALL the survival at 3 years is approximately 42%; again the LFS shows a wide range from 15-65%. There is apparently no significant difference in LFS whether peripheral blood stem cells (PBSCT) (41%) or bone marrow (35%) is used as stem cell source, as evidenced by a preliminary evaluation of the EBMT data. Overall these data seem somewhat optimistic.

### Prognostic factors and risk stratification

Prognostic factors in ALL include age, white blood cell count, cytogenetics, molecular genetics and response to treatment which is time to achieve CR and minimal residual disease during the course of treatment. Table 2 summarizes low risk and high risk features derived from the GMALL studies. These risk factors emerge in a similar pattern also in other adult ALL trials. The consequences in terms of clinical studies are however different. In the GMALL trials they are used to define a standard, a high and a very high risk group (exclusively Ph/BCR-ABL positive ALL). These patients are treated differently according to their risk profile e.g. standard risk patients are not candidates for SCT in first CR whereas in other studies all patients are treated uniformly, including allogeneic SCT in first CR.

### Table 1. Characteristics of subgroups of adult ALL*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Clinical/Laboratory characteristics</th>
<th>Relapse kinetics and localisation</th>
<th>LFS</th>
</tr>
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<tbody>
<tr>
<td><strong>B-Lineage</strong></td>
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<tr>
<td>Pro-B-ALL</td>
<td>t(4;11)/ALL1-AF4 (70%) High WBC (&gt; 100/ml) (26%) Myeloid coexpression (&gt; 50%)</td>
<td>Mainly BM (&gt; 90%)</td>
<td>~ 40-50%</td>
</tr>
<tr>
<td>c-ALL/pre-B-ALL</td>
<td>Higher age (24% &gt; 50 yrs) Ph/BCR-ABL (40-50%) m-BCR (70%), M-BCR (30%)</td>
<td>Mainly BM (90%) Up to 5-7 yrs</td>
<td>~ 30%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>Orgin involvement (32%) CNS involvement (13%) Higher age (27% &gt; 50 yrs)</td>
<td>Frequent CNS (10%) Up to 1-1 – yrs</td>
<td>~ 40-50%</td>
</tr>
<tr>
<td><strong>T-Lineage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymic ALL</td>
<td>Mediastinal tumor (60%) CNS involvement (8%)</td>
<td>Frequent CNS (10%) Extramedullary (6%)</td>
<td>~ 50-60%</td>
</tr>
<tr>
<td>Early T-ALL</td>
<td>High WBC (&gt; 50/ml) (46%)</td>
<td>Up to 3-4 yrs</td>
<td>~ 20-30%</td>
</tr>
<tr>
<td>Mature T-ALL</td>
<td>Younger age (11% &gt; 50 yrs)</td>
<td></td>
<td>~ 20%</td>
</tr>
</tbody>
</table>

*Data based on German multicenter trials of adult ALL.

### Table 2. Prognostic factors for LFS in adult ALL

<table>
<thead>
<tr>
<th></th>
<th>Low risk features</th>
<th>High risk features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Adolescents (15-20 yrs) Higher age (&gt; 50 yrs)</td>
<td></td>
</tr>
<tr>
<td><strong>WBC</strong> (B-lineage)</td>
<td>&lt; 30000/μl &gt; 30000/μl</td>
<td></td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>Thymic T-ALL Pro B-ALL Early T-ALL Mature T-ALL</td>
<td></td>
</tr>
<tr>
<td><strong>Cytogenetics/ Molecular genetics</strong></td>
<td>Normal diploid karyotype (?) t(9;22)/ BCR-ABL</td>
<td></td>
</tr>
<tr>
<td>Hyperdiploid karyotype (?) t(4;11)/ ALL1-AF4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time to CR</strong></td>
<td>CR &lt; 2-4 wks CR &gt; 2-4 wks</td>
<td></td>
</tr>
<tr>
<td><strong>MRD after induction during consol.</strong></td>
<td>&lt; 10⁻³-10⁻⁴ &gt; 10⁻³-10⁻⁴ or increasing</td>
<td></td>
</tr>
</tbody>
</table>

CR (< 10⁻³-10⁻⁴) and negative > 10⁻⁴ or increasing
Minimal residual disease

ALL is an “ideal” disease for detection and monitoring of minimal residual disease (MRD) and for the development of MRD adapted treatment strategies since > 90 % of the patients have individual markers. MRD refers to residual leukemic blast cells which cannot be detected by microscopic examination of the bone marrow smear. With conventional microscopic examination the detection limit for residual blast cells is 1-5 % and after achievement of hematologic CR further evaluation of the individual course is not possible. With new methods the detection of leukemia by specific phenotypes (flow cytometry), translocation breakpoints e.g. BCR-ABL, E2A-PBX1, MLL-AF4, and TEL-AML1 (Fluorescence-in-situ-hybridization, polymerase chain reaction [PCR]) or rearrangements of immunoglobuline heavy chain (IGH) or T-cell-receptor (TCR-β, -δ, -γ, -γ) genes (PCR, real-time PCR) a sensitivity of \(10^{-3}-10^{-6}\) can be reached. A prerequisite for longitudinal MRD evaluation is the identification of individual rearrangements or leukemia-specific phenotype at the time of diagnosis in each patient. In childhood ALL it has been shown that positive MRD is correlated with a very poor outcome, whereas children without detectable MRD have a high chance of cure. In a pilot study of the GMALL study group a strong correlation between MRD level and relapse risk also could be shown. Further prospective trials are needed to establish the value of MRD based treatment decisions for adult ALL.

Ph/BCR-ABL positive ALL – Molecular targeting

Ph/BCR-ABL positive ALL has an overall incidence in adult ALL of 20-25 %, increasing with age to > 40 % in patients above 50 years, and is the worst prognostic subgroup with a survival of only 10 %. Ph/BCR-ABL nearly exclusively occurs in B-precursor (common/pre-B-ALL). Diagnosis is made by cytogenetic analysis of the translocation t(9;22) and with a higher sensitivity – by detection of the BCR-ABL rearrangement with PCR analysis. The CR rate for this group is 70 % and thus somewhat lower than the 80-90 % achieved for Ph/BCR-ABL negative common/pre-BALL patients. However, only 10-30 % of the CR patients are in molecular remission after intensive induction therapy. At present the best results can be achieved with allo SCT from sibling donors where the survival rate is 30-35 %, thus lower than allo SCT in CR1 in B-lineage Ph/BCR-ABL negative ALL. The tendency for the outcome of MUD transplants in small patient cohorts is even better (35-40 %) and the outcome of auto transplants is somewhere between 20-30 %.

Abl-tyrosine kinase inhibitor STI571

The BCR-ABL fusion gene leads to an upregulation of tyrosine kinase (TK) activity which plays a crucial role in pathogenesis and disease progression of BCR-ABL positive leukemias. With a selective inhibitor of the Abl tyrosine kinase (STI571) cellular proliferation of BCR-ABL positive CML and ALL cells can be inhibited selectively. Promising results have also been achieved in a phase II study in heavily pretreated patients with relapsed or refractory Ph/BCR-ABL positive ALL with haematological response in 19 out of 32 patients. Clinical responses were correlated to MRD levels in bone marrow and peripheral blood. Thus quantitative PCR provides an option for continuous monitoring of the therapeutic effects of STI571. Oral treatment with STI571 is generally well tolerated and feasible also in elderly patients. Based on these promising results phase II studies in patients with de novo Ph/BCR-ABL positive ALL have been started. Several approaches such as treatment with STI571 in patients with MRD after induction therapy or after BMT or parallel to induction chemotherapy will be evaluated.

Antibody treatment

ALL blast cells express a variety of specific antigens such as CD20, CD19 and leukemia-specific combinations of antigens which may serve as targets for treatment with monoclonal antibodies (MoAbs). A prerequisite for Ab therapy is the presence of the target antigen on at least 20-30 %, preferably > 50 % of the blast cells. The largest experience exists with Rituximab, a MoAb to CD20, which is expressed on normal and malignant B-cells. It exerted significant antitumor activity in Non-Hodgkin’s lymphoma. CD20 (> 30 % of the cells) is also expressed on 1/3 of B-precursor ALL blasts, particularly in the elderly patients (40-50 %), and the majority of mature B-ALL blast cells (70-80 %). This provides a rationale to explore the potential role of treatment with Rituximab in B-precursor ALL, mature B-ALL and Burkitt’s lymphoma. Further Abs [B43(Anti-CD19)-Genistein, B43(Anti-CD19)-PAP, Anti-B4-bR (Anti-CD19) in B-Lineage ALL and Anti-CD52 antibodies (Campath-1H) and Anti-CD7-Ricin in T-lineage ALL] have been investigated in phase I-II pilot trials in ALL. Antibody treatment could have a potential role in the treatment of elderly ALL patients in whom intensive chemotherapy is limited and could be administered as single agents or in combination with chemotherapy, for purging and as post-transplant therapy.

References


