Current Treatment Approaches in Childhood Acute Lymphoblastic Leukemia

Martin Schrappe, Martin Stanulla

Abstract
Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood and has served as a model system for clinical and basic research beyond pediatric hemato-oncology since the early 1960s. Nowadays, as a result of these prolonged and well-organized research efforts, childhood ALL can be successfully treated in about 80% of patients by the application of intensive combination chemotherapy regimens, which in specific patient subgroups may need to be supplemented with radiation therapy and/or hematopoietic stem cell transplantation. Triggered through the observation of several clinical presenting features, biological characteristics and early treatment response being associated with treatment outcome, therapy intensity on contemporary ALL protocols is adjusted according to prognostic factors predicting the risk of ALL relapse. However, although the goal of developing effective therapy for the majority of children with ALL has been achieved, significant numbers of patients still die due to recurrent disease or the toxicity of treatment applied. Thus, future research activities will have to improve our molecular understanding of leukemia and host factors underlying the differences in treatment response and outcome and to finally address the therapeutic needs of the individual child.

Introduction
Acute lymphoblastic leukemia (ALL) represents the malignant proliferation of lymphoid cells blocked at early stages of differentiation and is the most common malignancy in children (1). It accounts for approximately 25% of all childhood cancers and about 80% of childhood leukemias (1,2). The annual incidence rate of childhood ALL varies world-wide between approximately one and four new cases per 100,000 children younger than 15 years, with a peak incidence at approximately two to five years of age (2-6). More affluent countries tend to have higher incidence rates (2,3). However, incidence rates for childhood ALL vary not only between countries, but also by ethnicity within countries: in the US Hispanic children have the highest incidence and the rate is higher in white as compared to that in black children (4). More than 60% of patients diagnosed with ALL are children (1,2).

Treatment results in childhood ALL are one of the true success stories of clinical oncology with current overall cure rates of approximately 80% in developed countries (Table 1, Figure 1) (7-21).

Figure 1.
Event-free survival curves for patients treated on five consecutive ALL-BFM trials from 1981 to 2000. These results are reached by application of intensive multiagent chemotherapeutic regimens and in specific patient subgroups additional radiotherapy and/or hematopoietic stem cell transplantation (HSCT). Modern treatment regimens consist of at least four phases: (i) an induction period aiming at an initial remission induction within approximately 4 to 6 weeks through the use of multiple cancer
chemotherapeutic drugs; (ii) consolidation/ intensification and reinduction segments to eradicate residual leukemic blasts in patients who are in remission by morphologic criteria; (iii) extracompartment therapy such as central nervous system (CNS) preventive therapy, and (iv) a maintenance period to further stabilize remission by suppressing re-emergence of a drug-resistant clone through continuing reduction of residual leukemic cells (22,23). As certain clinically and biologically distinct patient subgroups with ALL have a particular poor outcome on standard ALL treatment, clinical protocols specifically addressing the potential therapeutic needs of these subgroups have been initiated in the recent past (e.g., hybrid protocols for infants, and imatinib-including regimens for BCR/ABL-positive ALL) (24,25).

Table 1: List of study groups which have recently reported long-term treatment results

<table>
<thead>
<tr>
<th>Study group</th>
<th>Period of enrollment</th>
<th>Age group eligible</th>
<th>No. of pts</th>
<th>No. of studies</th>
<th>Event-free survival at 10y*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIEOP</td>
<td>1982-2000</td>
<td>≤15 y *</td>
<td>4865</td>
<td>5</td>
<td>71.7 ± 1.3%</td>
<td>7</td>
</tr>
<tr>
<td>BFM</td>
<td>1981-2000</td>
<td>&lt; 18 y</td>
<td>6609</td>
<td>5</td>
<td>78.0 ± 1.1%</td>
<td>8</td>
</tr>
<tr>
<td>CCG</td>
<td>1983-2002</td>
<td>&lt; 21 y</td>
<td>13298</td>
<td>16</td>
<td>72.6 ± 2.9%</td>
<td>9</td>
</tr>
<tr>
<td>COALL</td>
<td>1982-2003</td>
<td>&lt; 18 y</td>
<td>1967</td>
<td>5</td>
<td>76.3 ± 3.0%</td>
<td>10</td>
</tr>
<tr>
<td>CPH</td>
<td>1990-2002</td>
<td>&lt; 18 y</td>
<td>730</td>
<td>2</td>
<td>72.1 ± 2.3%</td>
<td>11</td>
</tr>
<tr>
<td>DCOG</td>
<td>1984-2004</td>
<td>&lt; 18 y</td>
<td>1734</td>
<td>4</td>
<td>70.0 ± 2.1%</td>
<td>12</td>
</tr>
<tr>
<td>DFCI</td>
<td>1985-2000</td>
<td>&lt; 18 y</td>
<td>1457</td>
<td>4</td>
<td>80.8 ± 2.1%</td>
<td>13</td>
</tr>
<tr>
<td>INS</td>
<td>1984-2003</td>
<td>&lt; 18 y</td>
<td>786</td>
<td>3</td>
<td>76.5 ± 2.4%**</td>
<td>14</td>
</tr>
<tr>
<td>JCCLSG</td>
<td>1981-1993</td>
<td>&lt; 18 y</td>
<td>1021</td>
<td>4</td>
<td>63.4 ± 3.3%*</td>
<td>15</td>
</tr>
<tr>
<td>NOPHO</td>
<td>1992-2007</td>
<td>1-&lt;15 y</td>
<td>2668</td>
<td>2</td>
<td>75.0 ± 1.0%</td>
<td>16</td>
</tr>
<tr>
<td>POG</td>
<td>1984-2001</td>
<td>1-≤22 y</td>
<td>7393</td>
<td>12</td>
<td>73.2 ± 2.1%†</td>
<td>17</td>
</tr>
<tr>
<td>SJCRH</td>
<td>1984-1999</td>
<td>≤18 y</td>
<td>1011</td>
<td>5</td>
<td>77.6 ± 2.9%</td>
<td>18</td>
</tr>
<tr>
<td>TCCSG</td>
<td>1984-1995</td>
<td>1-&lt;15 y</td>
<td>1846</td>
<td>4</td>
<td>75.0 ± 1.8%</td>
<td>19</td>
</tr>
<tr>
<td>TPOG</td>
<td>1997-2007</td>
<td>≤18 y</td>
<td>1390</td>
<td>2</td>
<td>72.5 ± 1.3%</td>
<td>20</td>
</tr>
<tr>
<td>UK-WPCL</td>
<td>1980-2002</td>
<td>≤15 y</td>
<td>6516</td>
<td>4</td>
<td>74.1 ± 1.0%</td>
<td>21</td>
</tr>
</tbody>
</table>

* listed here are the best results reported by each study group; * < 18 y in trial AIEOP-95; ** at 8 years; † at 12 years; ‡ only in B-lineage (10y-EFS in TALL was 72.2 ± 4.7%);

AIEOP: Associazione Italiana di Ematologia ed Oncologia Pediatrica (Italy); BFM: Berlin-Frankfurt-Münster ALL Study Group (Germany, Austria, Switzerland); CCG: Children’s Cancer Group (USA); COALL: Cooperative ALL Study Group (Germany); DCOG: Dutch Childhood Oncology Group (Netherlands); DFCI: Dana-Farber Cancer Institute ALL Consortium (USA); INS: Israeli National Studies of childhood ALL; JCCLSG: Japanese Childhood Cancer and Leukemia Study Group; NOPHO: Nordic Society of Pediatric Hematology and Oncology; POG: Pediatric Oncology Group (USA); SJCRH: St. Jude Children’s Research Hospital (USA); TCCSG: Tokyo Children’s Cancer Study Group; TPOG: Taiwan Pediatric Oncology Group; UKALL: UK Medical Research Council Working Party on Childhood Leukaemia (U.K.).

Clinical presentation and diagnosis

The initial clinical presentation of a child with ALL largely depends on the extent of the leukemic infiltration of the bone marrow and extramedullary sites. Typical clinical signs are fever, pallor, fatigue, bruises, enlargement of liver, spleen and lymph nodes, and pain (e.g., bone pain). In most patients, complete blood cell counts show anemia, thrombocytopenia and granulocytopenia with or without concomitant leukocytosis. The diagnosis of ALL is usually made by cyt morphological and cytochemical examination of a bone marrow aspirate and in difficult cases by Jamshidi needle biopsy and is established when at least 25% lymphoblasts are present in the marrow (27). CNS involvement (CNS3 status) is diagnosed by the presence of blasts in the cerebrospinal fluid (CSF; for definition see Table 2) or if intracerebral infiltrates are detected by cross-sectional radiological imaging (28). Initial diagnostics are complemented by flow cytometry-based immunophenotyping to gain information on the blasts expression of lymphoid differentiation-
associated antigens as measured by the reactivity to specific monoclonal antibodies and to determine the cellular DNA content of leukemic cells (29, 30). In addition, a combined approach using cytogenetic and molecular genetic techniques is used for the detection of genetic aberrations, such as non-random recurrent chromosomal translocations or their molecular equivalents (e.g., the t (9;22) or the BCR/ABL fusion transcript) (31-37). Molecular-genetic techniques and/or flow cytometry are also used to monitor disease burden during therapy by measuring minimal residual disease (MRD) (38-49). A last important issue addresses the definition of what is called complete remission and relapse: complete remission is defined as the absence of leukemic blasts in blood and CSF, fewer than 5% lymphoblasts in bone marrow aspiration smears, and no evidence of localized disease. Relapse is defined as the recurrence of lymphoblasts or localized leukemic infiltrates at any site. The new MRD detection methods have required a more detailed review of these definitions (50).

**Prognostic factors and risk-adapted treatment**

Continuing research on the clinical and biological aspects of ALL has identified numerous features with prognostic potential some of which are displayed in Table 2 (26, 28, 30-67). On modern protocols, risk-adapted therapy reflecting the probability of treatment failure has become a common feature in the clinical management of childhood ALL. For this purpose, the initially assessed prognostic factors are used to estimate an individual patient’s risk of relapse and to adjust the required treatment intensity by therapy stratification into different risk groups (e.g., standard/low, intermediate, high) (1,7-21).

**Table 2. Important prognostic factors and their approximate incidences in childhood ALL.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favorable prognostic factors and their approximate incidence (%)</th>
<th>Unfavorable or less favorable prognostic factors and their approximate incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>≥ 1 and &lt; 10 years (77%)</td>
<td>&lt; 1 year (3%) or ≥ 10 years (20%)</td>
</tr>
<tr>
<td>Gender</td>
<td>female (45%)</td>
<td>male (55%)</td>
</tr>
<tr>
<td>White blood cell count at diagnosis</td>
<td>&lt; 50,000/μl (80%)</td>
<td>≥ 50,000/μl (20%)</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>CD10-positive precursor B-cell ALL (83%)</td>
<td>CD10-negative precursor B-cell ALL (4%), T-ALL (13%)</td>
</tr>
<tr>
<td>CNS diseaseb</td>
<td>CNS 1 (80%)</td>
<td>CNS 3 (3%), TLP+ (7%)</td>
</tr>
<tr>
<td>Genetic featuresc</td>
<td>hyperdiploidy (20%), TEL/AML1 positivity (20%)</td>
<td>hypodiploidy (1%), t(9;22) or BCR/ABL positivity (2%), t(4;11) or MLL/AF4 positivity (2%)</td>
</tr>
<tr>
<td>Prednisone responsed</td>
<td>&lt; 1000/μl blood blasts (90%)</td>
<td>≥ 1000/μl blood blasts (10%)</td>
</tr>
<tr>
<td>Early bone marrow response</td>
<td>&lt; 5% blasts (M1) on day 15 of induction treatment (60%)</td>
<td>≥25% blasts (M3) on day 15 of induction treatment (15%)</td>
</tr>
<tr>
<td>Remission status after induction therapy in the bone marrow (morphologically assessed)</td>
<td>&lt; 5% blasts (M1) after 4 to 5 weeks of induction treatment (98%)</td>
<td>≥5% blasts (M2 or M3) after 4 to 5 weeks of induction therapy (2%)</td>
</tr>
<tr>
<td>Minimal residual disease in the bone marrow (molecularly assessed)</td>
<td>&lt; 10^4 blasts after 5 weeks of induction treatment (40%)</td>
<td>≥10^3 blasts after 12 weeks of treatment (induction and consolidation) (10%)</td>
</tr>
</tbody>
</table>

* prognostic factors are treatment dependent and, therefore, the selection presented in the table above cannot be entirely comprehensive; it reflects the current recommendations of the German BFM study group.
* CNS1 (puncture nontraumatic, no leukemic blasts in the cerebrospinal fluid (CSF) after cytocentrifugation); CNS3 (puncture nontraumatic, ≥5 leukocytes/μL CSF with identifiable blasts); TLP+ (traumatic lumbar puncture with identifiable leukemic blasts); a TLP with no identifiable blasts is not an adverse factor; the prognostic impact of CNS2 status (puncture nontraumatic, ≥5 leukocytes/μL CSF with identifiable blasts) is debated. For cytomorphological examination, CSF samples should be analyzed after cytocentrifugation, a method through which cellular components within the CSF are concentrated by centrifugation.
* hyperdiploidy defined as the presence of more than 50 chromosomes or a DNA index (the ratio of DNA content in leukemic G0/G1 cells to that of normal diploid lymphocytes) ≥1.16; hypodiploidy defined by <45 chromosomes; the prognostic value of MLL gene rearrangements other than MLL/AF4 and presence of the E2A/PBX1 fusion transcript are debated.
* after 7 days induction with daily prednisone and a single intrathecal dose of methotrexate on treatment day 1.
* assessed by molecular genetic techniques or flow cytometry; markers required to have a sensitivity of at least 10^-9.

27
The prognostic significance of an inadequate early reduction of leukemic blasts in the peripheral blood was first described by the BFM study group and confirmed by several other study groups (62, 65, 68). Of importance, the specificity of response evaluation might vary with the composition of the induction regimen and the time point of response evaluation (63, 64, 66, 67). Although a poor early response to induction therapy as described above is highly predictive of treatment failure, the majority of recurrences occurs in the large group of patients with an adequate morphological response to treatment. Of advantage in this context, the sub-microscopic assessment of MRD is approximately 1,000 to 10,000-fold more sensitive compared to methods based on morphological detection and provides excellent prognostic information (38-50). Although most of the experience on MRD in clinical settings was gained through DNA-PCR-based detection of leukemic clone-specific immunoglobulin and/or T-cell receptor gene rearrangements, flow-cytometry-based analyses by detection of specific antigen patterns of the leukemic clone also produced sensitive and reliable results comparable to PCR-based methods (41-43, 46, 47).

Remission induction

Contemporary treatment approaches for childhood ALL aim at an initial remission induction to restore normal hematopoiesis within approximately 4 to 6 weeks. In most study groups this goal is achieved in approximately 98% of patients through the systemic application of three drugs (glucocorticoid, vincristine, L-asparaginase) to which an anthracycline may be added as a fourth drug (1, 7-21). On ALL-BFM protocols, remission induction is initiated by a 7-day monotherapy with orally administered prednisone (and one intrathecal dose of intrathecal methotrexate on day 1), which is particularly useful in avoiding complications related to extensive tumor cell lysis. Undoubtedly, the dose intensity of the induction phase can have a major impact on the overall treatment outcome (1, 26, 69, 70, 76). Nevertheless, in specific subgroups of childhood ALL, the necessity of a four-drug induction regimen is subject to debate and it is, for example, unclear if addition of an anthracycline to a three-drug induction regimen is of real benefit to certain low- or intermediate-risk patients (71-73). The clinical anti-leukemic benefit of effective asparagine depletion in induction has been demonstrated (74).

Another frequently discussed issue addresses the choice of the glucocorticoid for optimal induction. Despite some debate on a truly equivalent dose, compared to prednisolone, dexamethasone appears to have a stronger antileukemic effect in vitro and has been shown to provide better leukemic CNS control and lower relapse rates (75-83). However, dexamethasone was also associated with increased side-effects including severe infectious complications (81-83). Table 3 summarizes some of the experiences gained through studies comparing prednisolone with dexamethasone in the treatment of childhood ALL. A comparison of dexamethasone at 10 mg/m²/d vs. 60 mg/m²/d prednisolone in induction is currently evaluated in a large international trial (47-49).

The 2% of patients not in remission after induction therapy will either have died of treatment- or disease-related complications or display nonresponsive disease. The latter group includes patients that will achieve only delayed remission or show resistant disease. Because of the poor prognosis of this minor non-responsive patient population, alternative therapeutic approaches should be considered early during the disease process (84, 85).
Table 3. Selected studies comparing prednisolone (pred) with dexamethasone (dexam) in the treatment of childhood ALL.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years</th>
<th>Study design</th>
<th>Study population</th>
<th>Glucocorticoid dose*</th>
<th>Dexa vs. pred administration in induction</th>
<th>Dexa vs. pred administration elsewhere</th>
<th>Outcome†</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 7111</td>
<td>1971-1974</td>
<td>randomized</td>
<td>all risk groups</td>
<td>pred 40 mg/m²/d vs. dexam 6 mg/m²/d</td>
<td>days 1-28 or days 1-21 or days 11-31</td>
<td>7-day pulses in maintenance</td>
<td>Isolated CNS relapse rates: pred 25.5%; dexam 14.3%</td>
<td>76</td>
</tr>
<tr>
<td>DCLSG ALL VI</td>
<td>1984-1985</td>
<td>historical control</td>
<td>non-HR patients (n=190)</td>
<td>dexam 6 mg/m²/d</td>
<td>14-day pulses in maintenance</td>
<td>EFS at 10 years on DCLSG ALL VI (82±3) was almost 30% better compared to ALL V</td>
<td>Isolated CNS relapse rates: ALL V 1.1%; ALL V 12.9%</td>
<td>77</td>
</tr>
<tr>
<td>DFCI 91-01</td>
<td>1991-1995</td>
<td>historical control</td>
<td>all risk groups (n=377)</td>
<td>SR patients: dexam 6 mg/m²/d</td>
<td>5-day pulses in intensification and maintenance</td>
<td>EFS at 5 years DFCI 91-01 83±2%; DFCI 97-01 76±2%</td>
<td>Isolated CNS relapse rates: DFCI 91-01 1.1%; DFCI 97-01 4.1%</td>
<td>78</td>
</tr>
<tr>
<td>CCQ 1922</td>
<td>1993-1995</td>
<td>randomized</td>
<td>all risk groups (n=1760)</td>
<td>pred 40 mg/m²/d vs. dexam 6 mg/m²/d</td>
<td>days 1-28</td>
<td>5-day pulses in intensification and maintenance</td>
<td>EFS at 6 years pred 77±2%; dexam 82±2%</td>
<td>Isolated CNS relapse rates: pred 7.1%; dexam 3.7%</td>
</tr>
<tr>
<td>UK MRC ALL97 and ALL97/99</td>
<td>1997-2002</td>
<td>randomized</td>
<td>all risk groups (n=1603)</td>
<td>pred 40 mg/m²/d vs. dexam 6,5 mg/m²/d</td>
<td>days 1-28 in ALL97 and days 1-29 in ALL97/99</td>
<td>5-day pulses in intensification and maintenance</td>
<td>EFS at 5 years pred 76±3%; dexam 84±3%</td>
<td>Isolated CNS relapse rates: pred 5.0%; dexam 2.6%</td>
</tr>
<tr>
<td>ECOG L96-14</td>
<td>1995-1999</td>
<td>randomized</td>
<td>only SR and HR patients (n=359)</td>
<td>pred 40 mg/m²/d vs. dexam 8 mg/m²/d</td>
<td>days 1-31</td>
<td>days 1-14 in four intensification elements for SR and three elements for IR patients</td>
<td>No differences in EFS at 6 years*: no statistically significant difference with regard to site of relapse or toxicity; a tendency towards less CNS relapses with dexam was set off by an increase in bone marrow relapses in SR; tendency towards higher incidence of complications with dexam</td>
<td>80</td>
</tr>
</tbody>
</table>

* taper not indicated; † EFS = event-free survival
* depending on asparaginase randomization in induction (no asparaginase: days 1-28; 10 days asparaginase before (days 11-31), concurrent with or after glucocorticoid and vincristine induction (days 1-21).
* age 0 to 15 years, initial white blood cell counts lower than 50,000/μL, and absence of a mediastinal mass and/or cerebromeningeal leukemia at diagnosis, no B-ALL.
* age 1 to less than 10 years with white blood cell counts lower than 50,000/μL, no lymphoma syndrome, no B-ALL.
* SR, non-T phenotype, age 1 to 6 years, white blood cell count less than 20,000/μL at diagnosis; IR, age 1 to 6 years and a white blood cell count between 20 and 100,000/μL at diagnosis; patients with T-cell markers. Patients positive cytogenetics for t(9;22), 11q23 aberrations or a t(1;19), a mediastinal mass or meningeal infiltration were excluded from both groups and stratified into the SR group.
* SR pred 84±5%; SR dexam 81±4%; IR pred 80±5%; IR dexam 86±5%.
Consolidation/intensification and reinduction treatment

Eradication of residual leukemic blasts in patients who are in remission by morphologic criteria is the primary aim of consolidation/intensification treatment. Consolidation/intensification treatment is necessary as patients successfully induced into remission, but not given additional treatment, usually relapse within months. A so-called reinduction or delayed intensification treatment can further enhance the effect of previous consolidation/intensification therapy both in low and high risk patients (86-88). The consolidation/intensification phases administered in protocols of the large study groups on treatment of childhood ALL may differ, for example, with regard to amounts, timing, and number of drug doses, drug composition and overall treatment context. Thus, the direct impact of most of these consolidation/intensification strategies and/or their individual components is difficult to assess. Today, most protocols use high-dose methotrexate (combined with folinic acid rescue) together with 6-mercaptopurine (6-MP) and/or prolonged administrations of asparaginase in consolidation/intensification (7-21, 69, 70, 89, 90). Reinduction treatment mainly consists of a late repetition of the initial remission induction and early intensification phases (71, 88). A randomized trial by the Children’s Cancer Group applying an augmented BFM protocol showed that intensified consolidation and double-delayed intensification can further improve the outcome of high-risk patients with a slow initial treatment response (91). Of interest, a recent subsequent trial on higher-risk patients with a rapid marrow response to induction therapy by the same group, demonstrated an improved event-free survival with more intensive but not with longer postinduction intensification treatment (92). Unfortunately, further intensification of treatment including higher doses of glucocorticoids have been associated with a high incidence of osteonecrosis, especially in older children (93). Consequently, some investigators suggest glucocorticoid administration in intensification/consolidation on alternate weeks for children older than 10 years to reduce the complication rates (92).

Central nervous system-directed therapy

CNS-directed therapy has become a prerequisite for successful treatment of childhood ALL. Before its introduction in the 1960s, more than 50% of children with ALL suffered from disease recurrence originating in the CNS (1, 22). This high rate could be reduced to less than 5% through the introduction of cranial irradiation, intrathecal chemotherapy with methotrexate alone or in combination with other drugs (cytarabine, hydrocortisone), and systemic application of chemotherapeutics with adequate penetration into the CNS (high-dose methotrexate, dexamethasone, high-dose cytarabine) (1,7-21). The intensity of CNS-directed treatment is adjusted according to the risk of ALL relapse in the CNS, the most important risk factor being overt CNS involvement at diagnosis (CNS3) (28, 99-101). Additional risk factors include a high initial white blood cell count, pro-B or precursor T-cell immunophenotype, t (9;22) or t (4;11), and a traumatic lumbar puncture with identifiable blast cells present at diagnosis (66, 101). CNS-directed therapy may differ in the number of intrathecal injections and/or intrathecally applied drugs, as well as in the inclusion of cranial irradiation at different doses (7-21, 94-96). Excluding infants, most clinical protocols administering intensive systemic therapy still recommend preventive cranial irradiation (12 or 18 Gy) for high-risk patients and/or those with a precursor T-cell immunophenotype - at least for those with white blood cell counts of 100.000/μl or more at diagnosis. In T-ALL with high WBC, elimination of preventive cranial radiation has caused a significant increase of systemic recurrences (95). Patients with CNS2 status or a traumatic lumbar puncture are recommended to receive additional therapeutic doses of intrathecal chemotherapy. Also CNS3 patients receive more intense intrathecal chemotherapy and, in addition, are subject to therapeutic cranial irradiation (18 or 24 Gy when ≥ two years of age; younger children should receive reduced
doses). All other patients (precursor B-cell ALL, CNS1, non HR) should receive preventive intrathecal chemotherapy. More recently, the best-balanced strategy for CNS prophylaxis in ALL treatment has been debated (97, 98). New molecular marker may define the risk of CNS involvement and recurrence more precisely than the blast count in the CSF (102).

**Allogeneic hematopoietic stem cell transplantation**

Results of frontline and relapse protocols have improved over time. At the same time, the experience gained also led to advances in HSCT procedures. The continuous parallel developments in both fields complicate the description of the exact role of HSCT in childhood ALL and elucidate the strong need for prospective clinical trials (103). In 2003, the ALL-BFM and the ALL-REZ BFM study groups initiated a prospective, international, multicenter trial (ALL-SCT-BFM 2003) which will now be extended to a larger international consortium (104). This trial exactly defined procedures on HLA-typing, donor selection, conditioning regimen, graft versus host disease prophylaxis and therapy as well as standards of supportive care ensure a high degree of standardization with regard to all relevant components potentially associated with the heterogeneity in outcome observed in the context of HSCT. It is expected that the results of such prospective trials will more precisely determine the indication of the different HSCT procedures in high-risk or relapsed childhood ALL. Meanwhile, HSCT in children with ALL in first remission should be confined to patients whose disease is associated with poor prognostic features such as the t (9;22) or a poor response to remission induction therapy (105-107).

**Maintenance therapy**

Hypothetically, maintenance treatment aims at a further stabilization of remission by suppressing the re-emergence of a drug-resistant clone through consistently reducing the pool of residual leukemic cells. The current standard of maintenance therapy consists of up to two or three years of treatment (from initial time of diagnosis) with daily oral 6-MP and weekly oral methotrexate (7-21). The combination of 6-MP with methotrexate acts synergistically as methotrexate inhibits purine de novo synthesis, leading to a higher intracellular availability and increased incorporation of phosphorylated thiopurines in DNA and RNA (108-110). During maintenance treatment, 6-MP and methotrexate doses are adjusted according to absolute leukocyte or neutrophil and platelet counts. Important to note and a potential source of heterogeneity with regard to outcome analyses, the starting dose as well as dose adjustment guidelines while on therapy may differ between the different study groups. As several reports suggested an improved outcome with bedtime administration, 6-MP is commonly administered in the evening hours (110, 111). Also, 6-MP should not be given in combination with milk since the xanthine oxidase activity contained in milk decreases the bioavailability of 6-MP (112). Of utmost clinical importance, at St Jude Children’s Research Hospital researchers have demonstrated that maintaining the highest tolerable dose of daily 6-MP in maintenance therapy is an important prognostic factor in childhood ALL (113). Intensification of maintenance treatment by the administration of vincristine/dexamethasone pulses was recently shown to provide no extra benefit (114). The reduction of maintenance therapy to less than 2 years (from the time point of initial diagnosis) was associated with an increased frequency of leukemic relapses (115). Although it was proven disadvantageous to shorten maintenance treatment, whether or not extended maintenance of up to 3 years is offering any beneficial effect for particular subgroups in the context of different treatment strategies is not completely evaluated. With regard to the debate on the better thiopurine, three randomized studies compared the toxicity and efficacy of 6-thioguanine with 6-MP in interim maintenance and maintenance therapy of childhood ALL (Table 4) (116-118). However, due to the observation of dose-dependent high rates of severe hepatotoxic side-effects associated with the application of 6-thioguanine, the current thiopurine drug of choice for maintenance treatment remains 6-MP.
During the last decades, prospective attempts on the treatment of children with relapsed ALL have been conducted (119-124). Similarly to frontline ALL therapy, treatment outcome after first relapse depends on clinical and biological characteristics of the leukemia. A short duration of first clinical remission, bone marrow involvement, a precursor T-cell immunophenotype, and unfavorable chromosomal aberrations [e.g., a t (9;22)] have been identified as the most important poor prognostic factors at time of relapse of ALL. In addition, MRD levels during the initial course of relapse treatment were shown to be of prognostic value (125). Roughly, conventional intensive chemotherapy and radiotherapy can cure up to one third of children with relapsed ALL, with percentages ranging from 0 to 70% depending on the pattern of prognostic factors present at relapse. For patients with early systemic relapse (within 18 months of achieving first complete remission), HSCT from an HLA-identical sibling is currently thought to be the treatment of choice. In the situation of a HSCT from an unrelated donor, due to potentially higher toxicity, beneficial effects may be restricted to high-risk patients. For other subgroups of relapsed ALL (e.g., late relapses, extramedullary disease), the role of allogeneic HSCT remains controversial and prospective trials are needed (103, 104).

**Late effects of treatment**

Quality of treatment has become more important since the major study groups have reached relatively comparable rates of long-term event-free survival. Unfortunately, with overall improvements in survival, the long-term adverse effects of treatment have become apparent, as well. These include cardiac late effects (anthracycline therapy-associated cardiomyopathy), neuropsychologic (e.g., methotrexate therapy-associated) and endocrinologic deficits, as well as secondary neoplasms such as acute myeloid leukemia associated with topoisomerase II inhibitor treatment and brain tumors associated with radiotherapy (126-128). The long-term adverse effects differ according to many factors including individual’s health status and the treatment received. Therefore, it is important that leukemia survivors receive regular exams by health care professionals who are familiar with leukemia treatment and the associated risks and who are able to recognize the early signs of late effects. Meanwhile, some study groups provide extensive recommendations for screening and treatment of late effects.
management of late effects after treatment for childhood ALL (128). These long-term follow-up approaches will not only improve the health and quality of life for survivors, but also provide an improved infrastructure for systematic studies on long-term consequences of childhood ALL treatment and, hopefully, their future prevention.

Perspective

Conventional methods of risk classification in childhood ALL including standard MRD analyses provide excellent tools for clinical treatment stratification of childhood ALL. In addition, MRD analysis for “phenotypic” characterization offers the ability to molecularly discern clinically relevant differences that may be of importance for developing a better understanding of leukemias and advancing therapeutic strategies. Thus, MRD analysis in combination with a comprehensive evaluation of leukemia and host characteristics holds the potential to further improve treatment by leading to an even more exact and earlier characterization of patients at true risk of relapse. Both comprehensive molecular characterization and early identification of these patients will be essential in future clinical trials in order to utilize the optimal therapy in the first treatment cycles and, for those in need of it, to secure the timely introduction of potential targeted treatment based on individual molecular characteristics of leukemic cells. Of importance, all future approaches should be evaluated in close context with “classical” risk-adapted treatment strategies and molecular monitoring of treatment response.

References

18. Pui CH, Pei D, Sandlund JT, Ribeiro RC, Rubnitz JE,


S E C T I O N A


109. Rivard GE, Infante-Rivard C, Dresse MF, Leclerc JM,


