13.1 Introduction

Since 1978 more than 4500 adult ALL patients have been treated according to the protocols of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL). GMALL protocols are administered in hospitals all over Germany and the number of participating centers in Germany increased from 25 in 1981 to 120 in the most recent trial. Up to now seven consecutive trials for adult de novo ALL have been conducted. The major aim of all trials was the improvement of remission duration and survival of adult ALL patients, detailed diagnostic characterization, the development of prognostic models and the evaluation of risk-adapted, individualized and targeted treatment strategies. The time-periods and further aims of these studies are briefly summarized in Table 13.1.

Several accompanying trials of the GMALL have been initiated in parallel, such as treatment protocols for:

- Elderly patients with ALL and B-ALL
- Ph+ ALL
- B-ALL, Burkitt’s Lymphoma, and other high-grade lymphoma
- T-lymphoblastic lymphoma
- Relapsed ALL

These strategies can only partly be described in the following sections.
13.2 Therapy for Younger (15–65 Years) Patients with B-Precursor and T-Lineage ALL

13.2.1 GMALL Trials 01/81–07/03

In the earlier trials (01/81–05/93), an 8-week induction therapy with two phases was scheduled with several minor modifications [1]. All patients received reinduction therapy, and maintenance therapy with methotrexate (M) and 6-mercaptopurine (MP) was scheduled for a total treatment duration of approximately 2 1/2 years. The overall treatment outline of GMALL studies 01/81–07/03 is given in Fig. 13.1.

The results of earlier trials (01/81–04/89) have been summarized previously [1–4]. Major findings referred to identification of new prognostic factors, development of subgroup-specific and risk-adapted regimens, intensified consolidation and maintenance, and extended indications for stem cell transplantation (SCT). In study 03/87 it was shown that postponed (standard risk = SR patients) or omitted (high risk = HR patients) CNS irradiation was associated with inferior overall outcome and a higher rate of CNS relapse [1]. Complete remission (CR) rates, remission duration, and survival improved stepwise with significant differences between subgroups.
13.2.2 Study 05/93

Based on improved knowledge of clinical and biological features as prognostic factors (PF) and specific effectiveness of distinct treatment elements in subtypes of ALL, a subgroup-specific consolidation therapy was initiated in study 05/93. The trial had four treatment arms: (1) SR B-precursor ALL (patients without adverse PF); (2) HR B-precursor ALL (at least one PF); (3) T-ALL; and (4) older patients above 50 years (Elderly) (PFs of the trial are listed in Fig. 13.4). The general principle was to intensify treatment with high-dose methotrexate (HDM) in SR B-lineage ALL, with cyclophosphamide (CP) and cytarabine (AC) in T-ALL, and with HDM and HDAC followed by SCT in HR B-lineage ALL. Furthermore, there was a randomized comparison of intensified versus conventional maintenance therapy in SR and T-ALL.

Twelve hundred patients with a median age of 35 (15–65) years were included. The CR rate was 83% with a range of 70% in older patients to 87% in SR B-lineage ALL (Table 13.2). In T-ALL, immunologic subtypes had a substantial impact on outcome, with a rate of continuous complete remission (CCR) of 63% for thymic, 28% for mature, and 25% for early T-ALL, and ruled out the prognostic impact of WBC and time to CR.
In SR, high CR and CCR rates were obtained, but relapses occurred continuously up to 6 years. In HR, intensified induction/consolidation did not improve overall CR and CCR with the exception of pro-B-ALL with a reasonable CCR of 41%, whereas CCR was only 19% in other HR patients (WBC late CR as only PF). In Ph+ ALL, CCR improved slightly to 21% at 3 years (9% in study 04/89). This may be due to extended indications for SCT [5]. Based on the results in the ER group (>50 years) the GMALL study group decided to initiate a trial with dose-reduced chemotherapy for older patients (>55–65 years according to biological age).

13.2.3 Study 06/99 and 07/03

The GMALL study 06/99 was initiated as a pilot trial. One major aim was to develop a new, shortened, and intensified induction regimen based on the following new principles compared to previous GMALL trials: (1) Dexamethasone (DEXA) instead of prednisone to improve antileukemic activity and prophylaxis of CNS relapse; (2) prephase with CP; (3) G-CSF parallel to chemotherapy; (4) intensified daunorubicin with two 2-day cycles (DNR) vs. 4 weekly applications; and (5) one dose PEG-L-ASP instead of 14 days conventional ASP. Induction I was followed by GMALL induction phase II as previously reported (Fig. 13.2) and a uniform consolidation I. Thereafter treatment was risk adapted. Patients with HR features and with very HR ALL (Ph+) were transferred to SCT in first CR including allogeneic sibling, matched-unrelated, and autologous SCT. Patients with SR ALL received six consolidation cycles and a reinduction therapy. Maintenance therapy was stratified according to the course of minimal residual disease (MRD) (see below). Figure 13.3 gives an overview on the study design.

Overall, 843 patients with a median age of 36 years were included. The CR rate was 83%, with 12% failure/PR and 7% early death (ED). The CR rate improved after

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**Table 13.2. Results of the GMALL Trial 05/93 [5]**

<table>
<thead>
<tr>
<th></th>
<th>SR</th>
<th>HR</th>
<th>Elderly</th>
<th>T-ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable</td>
<td>291</td>
<td>352</td>
<td>216</td>
<td>304</td>
</tr>
<tr>
<td>CR</td>
<td>87%</td>
<td>85%</td>
<td>70%</td>
<td>86%</td>
</tr>
<tr>
<td>Early death &lt;56 days</td>
<td>3%</td>
<td>3%</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Continuous CR at 5 years (CCR)</td>
<td>47%</td>
<td>27%</td>
<td>16%</td>
<td>51%</td>
</tr>
</tbody>
</table>

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**Fig. 13.3.** Overall outline of GMALL Trial 07/03. BM, bone marrow evaluation; MRD, evaluation for minimal residual disease; CNS Gy, 24 Gy CNS irradiation; SC, stem cell; SR, standard risk; HR, high risk; VHR, very high risk; SCT, stem cell transplantation; auto, autologous; allo, allogeneic; MUD, matched unrelated.
modifications of the DEXA regimen. With lower doses of DEXA, the rate of ED and severe infections decreased significantly. The earlier application of G-CSF during phase I of induction contributed to a significant decrease of grade III/IV granulocytopenias and probably also mucositis [6]. The optimized regimen for induction (Fig. 13.2) was used in the ongoing study 07/03. Interim results confirmed the high antileukemic activity with CR rates of 89% and the feasibility with 4% ED. Beside the optimized induction, the use of Imatinib in Ph+ ALL parallel to induction (see below) contributed to the improvement. Further progress is attempted by additional use of rituximab in CD20-positive patients. The aim of this trial is to improve overall survival (OS) to above 50%, and according to interim results this goal seems to be achievable.

13.2.4 Results of Stem Cell Transplantation

The general principle was to administer allogeneic SCT in CR1 only for HR patients (definition Fig. 13.4) starting with study 04/89. Patients with Ph+ ALL were also eligible for matched, unrelated BMT (starting with study 05/93). Starting with study 06/99 sibling and unrelated SCT were used on an equal footing.

In GMALL study 05/93 survival after SCT in CR1 was 54% for sibling (n = 68) and 51% for unrelated donors (n = 31). The most favorable results for sibling SCT were obtained in pro-BALL (59%). In Ph+ ALL, unrelated SCT improved survival (50%) compared to sibling SCT (25%) [7]. Equal survival rates for matched related (45%) or unrelated (42%) SCT in 1st CR were also reported from an overview analysis of nine German SCT centers [8].

In the GMALL study 06/99, also high-risk T-lineage ALL patients were candidates for SCT in CR1. The OS after sibling SCT (n = 50) was 53% and after unrelated SCT (n = 71) 44%. Results of SCT differed significantly between the subgroups ranging from 74% in ProB and 64% in HR-T-ALL to 44% in Ph+ALL and 18% in HR-B-lineage ALL. Thus it could be demonstrated that pro B-ALL and HR T-ALL profit substantially from allogeneic SCT. The results for Ph+ALL were promising and underlined the value of MUD SCT. HR-B-lineage ALL did poorly with chemotherapy alone as well as with SCT [9].

13.3 Therapy of Ph/BCR-ABL-Positive (Ph+) ALL

Treatment of this formerly most unfavorable subtype was revolutionized by the invention of imatinib as the first therapy targeted to the increased tyrosine-kinase (TK) activity induced by the bcr-abl rearrangement. An early phase II trial in relapsed/refractory Ph+ ALL demonstrated a CR rate of 29% [10]. Resistance and relapse developed rapidly in the majority of patients, although a proportion of patients could be transferred to allogeneic SCT [11]. It could be demonstrated furthermore that treatment response was significantly correlated to the quantitative course of BCR-ABL levels in
bone marrow and blood [12] and thereby MRD evaluation provided an excellent method for response evaluation.

In younger patients (<55 years), the GMALL group therefore integrated imatinib in front-line therapy of Ph+ ALL – first in the interval after induction therapy. With this schedule, no molecular remissions could be achieved. In the next step imatinib was administered parallel to chemotherapy in phase II of induction. With this schedule, the CR rate increased to 96% and half of the patients achieved molecular remissions [13]. More than 70% of the patients were transferred to SCT, and OS of Ph+ ALL improved significantly. Neither toxicity of chemotherapy nor mortality after SCT increased. Therefore, in the most recent trial imatinib is given parallel to phase I of induction to increase the number of molecular remissions and the risk of resistance.

The application of imatinib after SCT proved to be very promising due to synergisms with graft-versus-leukemia effects. These effects, however, depend on molecular response. The majority of patients, who obtained a molecular remission with SCT and imatinib, achieved a long-term survival, whereas most of the patients who did not respond to imatinib relapsed eventually [14]. In an ongoing trial, the GMALL evaluates now whether prophylactic use of imatinib after SCT is superior to the application in patients with positive MRD status.

In older patients (>55 years), a GMALL pilot trial for elderly ALL showed a very poor response rate in Ph+ ALL (19%) [15]. Therefore, the GMALL group started a randomized trial for elderly Ph+ ALL comparing induction chemotherapy with imatinib only (600 mg) with a dose-reduced chemotherapy induction. After induction all patients received imatinib together with consolidation chemotherapy. The CR rate was 93% for the imatinib induction compared to 54% with chemotherapy. However, LFS and survival were similar in both arms due to a high rate of relapse [16], and only one third of the patients achieved a molecular CR.

Most probably pre-existing or developing resistance to imatinib is a major problem. With gene expression analysis it was demonstrated that resistance to imatinib is associated with a set of 56 differentially expressed genes [17]. A high proportion of patients develop resistance mutations in the TK domain at relapse (90%) and in a considerable proportion these mutations are already present at diagnosis (40%) [18]. These results may help to predict response to imatinib and other TK inhibitors. Also a less genotoxic chemotherapy in combination with imatinib or other TK-inhibitors will be evaluated in the next GMALL studies for Ph+ ALL.

13.4 Studies for Mature B-ALL and High-Grade B-Cell Non-Hodgkin’s Lymphomas

Major advances in the treatment of mature B-ALL were achieved by innovative childhood B-ALL studies with short, intensive cycles including high doses of fractionated CP and HDM in combination with conventional drugs. The GMALL study group developed such a regimen in two consecutive trials as described previously. Both protocols were based on six short, intensive and alternating cycles at 21-day intervals (ABABAB) with differences in the dose of HDM (0.5 g/m² in study B-NHL83 and 1.5 g/m² in study B-NHL86) [19]. A significant improvement with a CR rate of 63% and 74%, respectively, was obtained and the CCR rate increased from 53% in study B-NHL83 to 71% in study B-NHL86 [19].

13.4.1 B-NHL90 Protocol

In the protocol B-NHL90 the dose level for M was doubled to 3 g/m² (patients <50 years). The protocol was also opened for patients with Burkitt’s lymphoma and other high-grade B-cell NHL. Overall 270 patients were included. The CR-rate was 83% in Burkitt NHL (n=118), 75% in B-ALL (n=89), 70% in B-lymphoblastic lymphoma (n=10), 76% in large cell anaplastic NHL (n=21), and 66% in diffuse large cell B-NHL (n=32) with survival rates of 70, 38, 64, 80, and 61%, respectively. Despite substantial hematotoxicity and mucositis, the ED rate of overall 4% (mostly B-ALL: 11%) and death in CR of 3% were low. Higher age had no impact on CCR in Burkitt’s NHL. It was concluded that dose intensification for HDM did not lead to a further improvement of outcome in B-ALL. On the other hand, results in Burkitt’s NHL were very promising with less toxicity than in B-ALL [20].
13.4.2 B-ALL/NHL 2002 Protocol

More than 80% of patients with mature B-ALL show a CD20-positive phenotype. Therefore, in the subsequent trial two major changes of the protocol were implemented: (1) introduction of rituximab before each of the six chemotherapy cycles followed by two consolidation doses of rituximab, and (2) implementation of a HDAC- and HDM-based cycle C in younger patients (<55 years) changing the schedule to ABCABC. The dose of M was reduced to 1.5 g/m². Older patients received a dose-reduced version of the schedule without cycle C.

According to an interim analysis in 53 patients who had completed the first two cycles, CR was achieved after only two cycles (AB) in 10/11 B-ALL patients (91%). In 26 Burkitt’s NHL patients, the response rate (15 CR/10 PR) after two cycles was 96%. Fifty out of 53 patients were alive after a median follow-up of 137 days. Rituximab was administered without excess toxicity. The survival rate was improved significantly to approximately 90% in younger patients with B-ALL, in BuNHL, and other B-NHL. In older patients with B-ALL, mortality is not negligible, and more frequent relapses are observed [21]. It was also demonstrated that the protocol is applicable in HIV-positive patients with B-ALL or Burkitt’s lymphoma [22]. In the future, the reduction of toxicity, namely mucositis, and further improvement of outcome in older patients with mature B-ALL will be the focus of the study group.

13.5 Prognostic Factors

Central diagnostic review in all patients including morphology/cytochemistry, immunophenotyping, cytogenetics, molecular genetics, and eventually MRD made a major contribution to the identification of prognostic factors in the GMALL studies.

13.5.1 Immunophenotyping

The refined classification according to surface and intracytoplasmatic markers of ALL blasts by flow cytometry contributed to a better characterization of ALL subtypes, their specific clinical and biologic features, and revealed their prognostic relevance [4, 23–25]. In the GMALL, immunophenotype contributes substantially to the prognostic model and also to treatment stratification, e.g., application of rituximab in all CD20-positive patients. In an early paper, prethymic phenotype (cyCD3+, CD2–, sCD3–) was identified as a poor prognostic feature [26] and the unfavorable outcome of mature T-ALL was detected later [5, 27]. Therefore, early and mature T-ALL is now considered a high-risk subgroup and patients are candidates for SCT in first CR. The prognostic relevance of phenotype rules out all other prognostic factors including WBC >100 000/μl.

Similar observations have been made for early B-lineage ALL (also referred to as pro B-ALL, CD10-negative ALL). This subtype was associated with an inferior prognosis in GMALL studies [4]. In study 04/89, an improved outcome was observed for early B-lineage ALL patients treated according to the high-risk protocol with either HDAC consolidation or allogeneic SCT [28]. More recently it was demonstrated that CD10-negative pre-B-ALL has a similarly unfavorable outcome as pro-B-ALL [29].

13.5.2 Cytogenetic and Molecular Analysis

t(9;22) or the corresponding BCR-ABL fusion transcript is the most frequent aberration in adult ALL. In the GMALL trials, initial detection and follow-up for MRD are performed by central laboratories [30], and prospective analysis of MRD has a major impact on treatment decisions. Recently, the presence of a fusion gene NUP214-ABL1 also conferring increased TK activity was also detected in 4% of the T-ALL patients. This may represent a target for therapy with TK-inhibitors [31]. Quantitative analysis of MRD is also established for t(4;11) and the corresponding fusion gene ALL1-AF4 [32].

More recently, the GMALL group has focussed on the application of gene expression analysis in T-ALL. For the GMALL studies, the most important question is whether new adverse prognostic factors can be identified within the favorable subgroup of thymic T-ALL in order to select additional patients who could benefit from SCT in first CR. It was demonstrated that overexpression of the HOX11 oncogene confers a favorable prognosis but is mostly confined to thymic T-ALL. Within thymic T-ALL it did not show prognostic relevance. HOX11L2 overexpression is a rare feature that is observed in 10% of T-ALL cases and identifies within thymic T-ALL patients with poor prognosis [33]. Furthermore, it was demonstrated that high expression
of the ETS transcription factor ERG, which has an incidence of 50% within T-ALL, is associated with an inferior survival in T-ALL. The prognostic relevance was confirmed in a multivariate analysis together with immunophenotype (early/mature), presence of HOX11L2 and absence of HOX11. Most importantly, within thymic T-ALL high ERG and HOX11L2 were confirmed as adverse prognostic factors [34]. The overexpression of ERG was then correlated to the overexpression of the BAALC gene, which is present in 25% of adult T-ALL cases. The latter is also correlated with inferior prognosis. The prognostic significance of BAALC increased if combined with ERG. Patients with low BAALC/low ERG had a favorable prognosis compared to an unfavorable prognosis in patients with high BAALC/high ERG [35].

13.5.3 MRD Analysis

The GMALL central laboratory for MRD analysis has demonstrated in a large patient cohort that persistence of MRD above $10^{-4}$ until week 16 (after consolidation 1), which is observed in 25% of the patients, confers a very poor prognosis with a relapse rate above 90%. On the other hand, there is a small proportion of patients (10%) who decline rapidly below $10^{-4}$ at day 11 and day 24 (after induction 1). These patients have an excellent prognosis. In the remaining patients the relapse rate was nearly 50% [36].

Thanks to the frequent MRD analyses during first year of therapy, it was possible to identify molecular relapses in patients who had already achieved a molecular remission. If the MRD level increased during the second year to more than $10^{-4}$, 89% of the patients relapsed. As a result of this study molecular relapse is treated in the GMALL trials similarly to cytologic relapse and identifies patients for salvage therapy and SCT [37].

Based on these findings, the ongoing GMALL trial 07/2003 comprises a risk stratification based on MRD analysis in patients with SR according to conventional factors. Patients with high level of MRD after consolidation I ($>10^{-4}$) were allocated to a MRD-HR group and to SCT in first CR. Patients with low level of MRD after induction and consolidation I were defined as MRD low risk and received no maintenance therapy. The remaining patients (MRD intermediate risk) with inconclusive course of MRD or technical problems were scheduled for intensified maintenance (Table 13.3).

According to an interim analysis of MRD risk stratification at month 12 in 98 SR patients, the risk groups according to MRD were distributed as follows: MRD-LR 36%, MRD-HR 9%, and MRD-IMR 55%. The major reasons for allocation to MRD-IMR were lack of a second marker (58%), insufficient sensitivity (51%), and inconclusive course of MRD (28%). Most patients in the MRD-IMR group had, however, combinations of several reasons. Further treatment after MRD risk stratification was evaluable in 88 patients. In nearly all MRD-LR patients therapy was stopped. The relapse risk (RR) in this cohort was so far 20–30%. In MRD-HR less than half of the patients could receive SCT. In several cases the relapses occurred shortly after the end of the first year of therapy and before the MRD results were available.

<table>
<thead>
<tr>
<th>Table 13.3. MRD-based stratification in GMALL study 07/03</th>
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<tbody>
<tr>
<td>MRD risk group</td>
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<tr>
<td>MRD low risk (MRD-LR)</td>
</tr>
<tr>
<td>MRD high risk (MRD-HR)</td>
</tr>
<tr>
<td>MRD intermediate risk (MRD-IMR)</td>
</tr>
<tr>
<td>Molecular relapse</td>
</tr>
<tr>
<td>Day 71 $^a$</td>
</tr>
<tr>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>$&gt;10^{-4}$</td>
</tr>
<tr>
<td>MRD evaluation not possible</td>
</tr>
<tr>
<td>Technical prerequisites not fulfilled $^c$</td>
</tr>
<tr>
<td>Inconclusive course of MRD</td>
</tr>
<tr>
<td>Increase of MRD above $10^{-4}$ later than week 16 after</td>
</tr>
<tr>
<td>previous negative status</td>
</tr>
<tr>
<td>Week 16 until week 52 $^b$</td>
</tr>
<tr>
<td>and</td>
</tr>
<tr>
<td>and</td>
</tr>
<tr>
<td>Always $&lt;10^{-4}$</td>
</tr>
<tr>
<td>Negative in week 52</td>
</tr>
<tr>
<td>$&gt;10^{-4}$</td>
</tr>
</tbody>
</table>

$^a$ after induction, before first consolidation
$^b$ during consolidation
$^c$ Technical prerequisites: At least 2 clone-specific markers, minimum sensitivity of $10^{-4}$ material from decisive time-points available
Only patients with immediate SCT remained relapse free in the MRD-HR group. In MRD-IMR half of the patients received intensified maintenance. In this group the RR was overall also around 20–30% with lowest RR for intensified maintenance and highest RR for premature stop of therapy. Unexpectedly the MRD-IMR group was large (>50%) partly due to strict quality standards for MRD evaluation as mandatory for a prospective study. Further characterization of this subgroup also by other means e.g. gene profiling is attempted. Overall the interim results demonstrate that the treatment recommendations for the MRD risk groups are reasonable although the relapse rate was higher than expected. Nevertheless the major question is still whether the intermediate risk group can be reduced and whether any type of treatment de-escalation is justified in adult ALL [38].

### 13.5.4 Development of Risk Models in the GMALL Studies

The risk model for adult ALL first described for study 01/81 [2] was continuously developed in subsequent trials (Fig. 13.4). It is important to note that in the meantime prognostic factors are different for B-precur sor and T-ALL and individualized factors such as course of MRD are added. Furthermore, although increasing age is one of the most significant adverse prognostic features, it is not included in the risk stratification. The aim of risk stratification is to identify patients who could benefit from SCT and since outcome of SCT also decreases with age, it is not an adequate feature for this purpose.

### 13.6 Future Risk Stratification and Treatment Concepts for Adult ALL

Risk and subtype adjusted treatment strategies led in the GMALL studies to considerable improvement of outcome in mature B-ALL, T-ALL and Ph-positive ALL but to a lesser extent in B-precursor ALL. Future concepts will integrate a variety of additional factors thereby resulting in a more complex, flexible and patient specific treatment approach [39]. These approaches include:

- Subgroup adjusted treatment e.g. for mature B-ALL and Burkitt’s NHL
- Age adapted treatment e.g. specific protocols for elderly fit, elderly frail and adolescent patients.
- Individualized treatment e.g. according to MRD, drug resistance or TK domain mutations
- Risk adapted indications for SCT
- Targeted therapies e.g. with kinase inhibitors in Ph+ ALL, monoclonal antibodies and other new drugs e.g. subtype specific therapy in T-ALL
- Evaluation of new cytostatic drugs

Beside these sophisticated approaches a better adherence to protocols, support of patients to improve their compliance and documentation of compliance would be warranted. Treatment should be done at experienced centers and closer cooperation between internal medicine and pediatrics including cooperative studies is attempted.

### References


