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Acute Lymphoblastic Leukemia (ALL)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

SSMO SSOM SGMO

SGH+SSH

Publisher

DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
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Source

www.onkopedia-guidelines.info

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Date of document: February 2012

Compliance rules:

- Guideline
- Conflict of interests

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1 Introduction

Acute lymphoblastic leukemia (ALL) is a life-threatening malignant disease. Due to the sophisticated diagnostics, the complex therapy, its life-threatening course, and the rarity of the disease, the emergency admission to a specialized hematological center is urgently recommended.

Outside of clinical studies, there is no standard therapy generally applicable to adult patients with ALL. In order to assure state-of-the-art therapy and to further development of therapy concepts, all patients should be treated in the context of clinical trials. For patients who don't fit into the trials, for example, because of existing exclusion criteria or a lack of studies offered, therapy should proceed in accordance with the prospectively elaborated therapy recommendations issued by the respective study groups. In Germany, these are the GMALL therapy recommendations. These recommendations are connected to the GMALL Registry and include patient information and documentation. Recently, therapy recommendations have also been compiled by the European Working Group for Adult ALL and published in book form. The book gives an updated and detailed overview of all essential topics related to ALL management [1].

2 Definition and Basic Information

Acute leukemias are characterized by the proliferation and accumulation of malignant, transformed, immature, hematopoietic cells, so-called blasts, in the blood and the bone marrow. All other lymphatic organs (e.g. lymph nodes, spleen) and non-lymphatic organs (e.g. liver, CNS, skin, bone, etc.) can also be affected. The leukemic blasts displace the normal hematopoietic bone marrow and cause cytopenias in all three cell lineages (anemia, thrombocytopenia, granulocytopenia).

2.1 Epidemiology

The overall incidence rate of ALL amounts to 1.1/100,000 per year. The peak incidence lies in childhood at an age of less than 5 years (5.3/100.00). Thereafter the incidence rate declines continually. In patients over 50 years it rises a second time and reaches a peak at the age of over 80 years (2.3/100.000). There is a slight predominance of males (1.4:1.0).

2.2 Risk Factors

In the majority of cases the pathogenetic causes of ALL remain unknown. In general, endogenous and exogenous factors may be associated with the development of ALL. Among these factors are congenital defects of DNA repair mechanisms, e.g. the ataxia-telangiectasia syndrome. The risk of acquiring an acute leukemia is also 18-times higher in children with trisomy 21 than in reference groups. Chromosomal damages of the kind which are induced by

exposure to radioactivity favor the development of acute leukemias similar to an exposure to myelotoxic chemicals such as benzene, chloramphenicol, etc. Acute leukemias (especially AML) are also being increasingly observed as secondary neoplasias after chemotherapy with alkylating agents, epipodophyllotoxins, and topoisomerase inhibitors.

2.3 Pathogenesis

ALL is characterized by an uncontrolled proliferation of early lymphoblastic progenitor cells in the bone marrow, whose maturation is blocked at a distinct level of differentiation. The leukemic blasts of a given patient in general display individually specific genetic markers. These so-called clonal markers indicate that the origin of ALL is to be found in one transformed lymphatic stem cell. The transformation might occur on various levels of lymphoid cell maturation. As a result the leukemia cells of ALL subgroups display a variety of phenotypic features, for example, a set of cell surface markers which are correlated with the stage of maturation and also with the disease's clinical manifestation.

More than 60% of all adult ALL have cytogenetic aberrations which are also often characteristic of certain phenotypic and clinical manifestations and, in part, are also of prognostic relevance. In addition, they give indications to genes connected to the pathogenesis of the disease. Genes affected by aberrations, and/or their gene products, are involved in signal transduction, regulation of transcription, cell-cycle control, and/or the regulation of apoptosis. The alteration of single genes has impact on the transcription of downstream genes and subsequent regulatory mechanisms. It must be assumed that several genetic aberrations are necessary for the malignant transformation of lymphoid progenitor cells. They result in differentiation disorders increase of proliferative functions, and/or a loss of mechanisms which lead to apoptosis. These alterations ultimately lead to a survival advantage of the malignant clone and result in a differentiation block on a certain level of maturation, in analogy to regular lymphoid progenitor cells. The most important example of the pathogenetic and prognostic significance of a single aberration is the translocation t(9;22) (Philadelphia chromosome), which is associated with the formation of the BCR-ABL fusion gene. In this case a protein with aberrant tyrosine kinase activity is expressed, which is responsible for the development of Ph/BCR-ABL-positive ALL.

3 Clinical Presentation

The clinical symptoms of ALL patients results from the increasing hematopoietic insufficiency and the infiltration of lymphoid organs. Symptoms of hematological deficiency are:

- Anemia: pallor of skin and mucous membranes, tachycardia, dyspnea, vertigo, decreased physical fitness
- Granulocytopenia in patients with leukocytopenia, leukocytosis, or regular total leukocyte counts in the blood cell count: fever, increased susceptibility to infection
- Thrombocytopenia: susceptibility to bleeding and hematomas, petechiae.

One-third of all patients suffer from infections or hemorrhages at the time of the initial diagnosis. Almost 60% display lymph-node enlargement. Splenomegaly is just as common. A mediastinal mass is found in 14% of ALL cases, but in 60% of all patients with T-ALL. 7% of the patients exhibit an initial CNS involvement. The involvement of the CNS is mostly diagnosed by the routine liquor diagnostics; however, if the medulla is affected clinical symptoms may appear, ranging from headaches, vomiting, lethargy, neck stiffness up to neurological deficits (especially of cerebral nerves). Affection of extramedullary organs is seen in 9% of ALL cases, whereas leukocytosis is encountered in 60% of ALL patients. The absence of leukocytosis or blasts in the blood does not rule out the diagnosis of ALL. The symptoms of the disease usually develop within days and are accompanied by a rapid loss of physical fitness.

4 Diagnosis

A bone-marrow analysis is mandatory whenever ALL is suspected. This procedure will not always be successful, particularly not in patients with a massive infiltration or fibrosis of the bone marrow (punctio sicca). In this case a bone marrow biopsy will have to be performed, or diagnostics must be carried out on blasts from the peripheral blood. In 97% of the patients the bone marrow exhibits a massive leukemic infiltration of more than 50%, with impairment of erythropoiesis, thrombopoiesis, and granulopoiesis.

4.1 General Diagnostics and Preparation for Therapy

Confirmation of the diagnosis, staging, and the assessment of potential accompanying diseases will require at least the following procedures:

- Medical case history and physical examination
- General health condition and evaluation of comorbidities
- Complete blood cell count, including leukocyte count with differential cell counts, reticulocytes, clinical chemistry including coagulation diagnostics and urine analysis
- HLA typing in patients who are potentially eligible for allogeneic stem cell transplantation
- Infectiological analyses including hepatitis B and C as well as HIV serology
- Pregnancy test, if applicable
- Lumbar puncture with cytological liquor diagnostics and i.th. therapy
- Imaging diagnostics (chest X-rays, sonography of the abdomen; if possible, computer tomography of the chest and the abdomen, and further examinations depending on the prevailing symptoms)
- ECG and echocardiography
- Information about fertility-preserving measures and the necessity of conception control.

4.2 Special Diagnostics

Bone-marrow aspirates should be analyzed by cytology and by immunophenotyping in the treating hospital. The following analyses should be additionally carried out in a reference laboratory, if possible:

- Morphology /cytochemistry
- Immunophenotyping
- Molecular genetics (Ph/BCR-ABL, t(4;11)/ALL1-AF4)
- Minimal residual disease (see chapter 5.4.)
- Cytogenetics

Essential is the differentiation of B and T precursor ALL as well as additional immunological subtyping. Furthermore, potential therapeutic targets must be identified. At present, they consist of the expression of CD20 and the presence of a BCR-ABL translocation. Complete diagnostic work-up is also mandatory in elderly patients, particularly because the incidence of BCR-ABL translocations increases with age.

4.3 Classification

The WHO classification (2008) of ALL is summarized in Table 1. ALL is classified along with the lymphoblastic lymphomas as a precursor lymphoid neoplasm of the B or T cell type. It will be referred to as lymphoblastic lymphoma if bone-marrow involvement is below 25%, and as leukemia if the infiltration rate exceeds 25%. The further distinction between cytogenetically and molecular biologically defined subgroups is only of limited relevance for risk-adapted treatment selection.

In clinical practice it makes more sense to use the classification of the GMALL studies, which is based on the immunophenotype of the leukemic blasts, see Table 2. The majority of ALL cases in adults (75%) are B lineage, further classified based on the status of differentiation as pro-B, common, pre-B, and mature B-cell ALL; whereas 25% of all ALL cases in adults belong to the T lineage, classified according to the differentiation status as either 'early', thymic, or 'mature' T-ALL. Specific clinical and cytogenetic and/or molecular genetic aberrations are associated with the various immunological subtypes, see Table 2.

The morphological FAB classification is nowadays only important for the identification of L3 morphology. This morphological subtype corresponds to the mature B-cell ALL or Burkitt's leukemia/lymphoma. The diagnosis of mature B-cell ALL should be confirmed by immunophenotyping (surface immunoglobulins) and molecular genetics (C-MYC aberration). The distinction between B cell precursors and mature B ALL is essential for treatment selection.

Table 1: WHO Classification of ALL (2008)

Precursor lymphoid neoplasms
B-lymphoblastic leukemia/lymphoma, NOS (not otherwise specified)
B-lymphoblastic leukemia/lymphoma, with recurrent genetic abnormalities
B-lymphoblastic leukemia /lymphoma, with t(9;22)(q34;q11.2);BCR-ABL
B-lymphoblastic leukemia /lymphoma, with t(v;11q23); MLL rearranged
B-lymphoblastic leukemia /lymphoma, with t(12;21)(p13;q22);TEL-AML1 (ETV6-RUNX1)
B-lymphoblastic leukemia /lymphoma, with hyperdiploidy
B-lymphoblastic leukemia /lymphoma, with hypodiploidy
B-lymphoblastic leukemia /lymphoma, with t(5;14)(q31;q32);IL3-IGH
B-lymphoblastic leukemia/lymphoma, with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)
T-lymphoblastic leukemia/lymphoma
Mature B-cell neoplasms
Burkitt's lymphoma (including the mature-cell "Burkitt's" B-ALL, which is not listed as a distinct entity)

Table 2: Classification of ALL in GMALL Studies

Subgroup	**Immunophenotyping**		**Cyto/Molecular Genetics**	
Designation	Characteristic markers	Incidence	Frequent aberrations	Genes involved
B- Lineage ALL	HLA-DR+, TdT+, CD19+ a/o CD79a+ a/o CD22+	76%		
B-Precursor ALL				
Pro-B	CD10-	11%	t(4;11)	ALL1-AF4
c- (common)	CD10+	49%	t(9;22)	BCR-ABL
Pre-B	CyIgM+	12%	t(1;19) t(9;22)	E2A-PBX1 BCR-ABL
Mature B	SIgM+	4%	t(8;14)	CMYC
T- Lineage ALL	TdT+, cyCD3+, CD7+	24%		
"Early" T	CD2-, sCD3-, CD1a-	6%		
Thymic	sCD3±, CD1a+	12%		
"Mature" T	sCD3+, CD1a-	6%		

4.4 Minimal Residual Disease

The threshold for microscopic detection of leukemic blasts in the evaluation of bone-marrow aspirates is 1-5%. Much more sensitive is the monitoring of therapy responses by applying methods which permit the detection of leukemic blasts far below the cytological detection limit, the so-called "minimal residual disease" (MRD). The sensitivity of these methods should reach a level of at least 10^{-4} (which is equivalent to the detection of one leukemic cell among 10,000 regular cells), allowing us to study leukemic cells and examine their dynamics in patients who are clinically and cytologically in a state of complete remission.

Various methods can be used to quantify minimal residual disease, e.g. PCR analyses of defined fusion genes or flow cytometry for leukemia-associated immunophenotype. The highest degree of standardization, concomitantly combined with the widest applicability and sensitivity, is reached by the detection of individual, clonal gene rearrangements of immunoglobulins (IgH, IgK) or T-cell receptors (TCR-β, -δ, -γ) by means of real-time PCR [2]. For therapeutic decisions, the GMALL study group currently only accepts MRD measurements based on clonal gene rearrangements by quantitative PCR in patients with Ph-negative ALL, or of BCR-ABL transcripts by quantitative PCR in Ph-positive ALL. Both tests must be performed in reference laboratories [3, 4].

Minimal residual disease is now also being used to obtain a more refined definition of therapy responses. Molecular CR, defined as a negative MRD status subsequent to induction, is an important endpoint used for measuring the efficacy of induction or consolidation therapies. Molecular relapse, defined as new evidence of MRD after molecular remission had been reached, is associated in 90 % of the cases with a subsequent cytological relapse and should therefore be treated as such in clinical trials. The new terminology has been confirmed in a recently published consensus paper [4].

The MRD represents at all times, while therapy is in progress and thereafter, a highly significant prognostic factor. The early achievement of a molecular CR characterizes a subgroup of patients with very good prognosis, whereas patients with persistent MRD display a high relapse rate [5]. This even holds true after subsequent stem cell transplantation.

At present, the persistence of MRD is the most unfavorable prognostic factor in adult ALL. The analysis of MRD must be therefore performed in all patients. The quantitative determination of minimal residual disease can only be based on material (leukemic blasts) taken at the time of initial diagnosis. For this reason material of each patient has to be sent to a reference laboratory. In case of *punctio sicca* another puncture must be performed after prephase therapy in order to obtain a bone-marrow aspirate. Alternatively a bone-marrow trephine biopsy (unfixed native material) must be sent in.

4.5 Differential Diagnosis

Diagnostic problems will not occur in the majority of patients if all the special tests mentioned in Chapter 4.1 and Chapter 4.2 are performed. The immunological and morphological identification of lymphoid blasts permits differentiating the disease from an acute myeloid leukemia (AML), a myelodysplastic syndrome (MDS), chronic lymphocytic leukemia, a lymphoid blast crisis in cases of CML or other forms of chronic or acute leukemias as well as reactive lymphocytosis, e.g. in case of infectious mononucleosis. Differentiation of ALL from a lymphoblastic T-cell or B-cell NHL is based on the quantification of blasts in the bone marrow.

In about 29% of the patients the typical ALL blasts display a coexpression of myeloid surface markers such as CD13, CD33 (>20%). Certain ALL subgroups are associated with a higher incidence of myeloid coexpression, e.g. "early" T-ALL, pro-B-ALL, Ph/BCR-ABL-positive ALL,

however, myeloid coexpression is not relevant to the prognosis of the disease. Treatment is selected according to the lymphoid differentiation status, see Table 2.

4.6 Risk Stratification

Prognostic factors were established for adults ALL many years ago [6, 7] and are internationally accepted. Yet, there are some notable differences among the different study groups, especially with regard to the therapeutic consequences. The currently valid prognostic factors of the GMALL studies are shown in Table 3.

Table 3: Unfavorable Prognostic Factors of ALL in Adults (GMALL Study 07/2003)

High leukocyte count	**> 30,000/µl in case of B-precursor-ALL**
Subtype	pro B, early T , mature T
Late CR	> 3 weeks (after induction II)
Cytogenetic / molecular aberrations	t(9;22) - BCR-ABL t(4;11) - ALL1-AF4
	Complex aberrant karyotype
Minimal Residual Disease	High MRD level after early consolidation* MRD increase under therapy*

Legend:
** Detailed definition according to therapy protocol*

The GMALL therapy recommendations currently pursue a risk-adapted therapy strategy for younger patients (in analogy to GMALL Study 07/2003). The risk factors listed in Table 3 result in the definition of a standard (without unfavorable prognostic factors) and a high-risk group (at least one unfavorable prognostic factor). Patients with Ph/BCR-ABL-positive ALL are additionally treated with imatinib. Therapy proceeds risk-adapted, subsequent to a uniform induction and first consolidation therapy. High-risk and very-high-risk patients are scheduled for stem cell transplantation, whereas chemotherapy with alternating consolidation cycles is continued over one year in patients with standard risk. Standard-risk patients who respond poorly to therapy, and in whom treatment intensification with stem cell transplantation appears to be a reasonable procedure, are identified by MRD monitoring.

5 Therapy

Therapy of ALL is divided in several stages: induction, consolidation and maintenance. The aim of induction therapy is the achievement of a complete remission (CR). Attaining a CR is an essential requirement for long-term survival or cure. The following therapeutic phases which are referred to as consolidation and maintenance serve the purpose of maintaining the complete remission, and are summarized by the term of post-remission therapy. The term consolidation therapy also includes bone marrow and blood stem cell transplantation (SCT).

5.1 Induction

A prephase therapy (dexamethasone, cyclophosphamide) should be given to all patients in order to prevent a tumor lysis syndrome. In patients with hyperleukocytosis, prephase therapy will be sufficiently effective to induce a mild cell reduction.

Standard medication for the induction therapy is vincristine and dexamethasone in combination with an anthracycline derivative (in most cases dauno- or doxorubicin). In addition, asparaginase is applied in induction therapy. This substance is particularly effective in ALL and differs from other cytostatic agents by its specific mechanism of action, resistance, and the spectrum

of adverse effects. In the GMALL trials, the pegylated form of asparaginase was applied, except in elderly patients. Pegylated asparaginase has a duration of action of 10-20 days, depending on the dose. Asparaginase activity should be measured on a weekly basis. In addition, special supportive measures are required under asparaginase therapy, including monitoring of liver parameters, pancreatic enzymes, glucose, coagulation factors, substitution of coagulation factors, if necessary, and thrombosis prophylaxis. Remission control is mandatory subsequent to induction phase I. If complete remission has not been achieved according to the cytological evaluation of bone marrow smears (percentage of blasts <5%) the patient will have to be allocated to the high-risk group.

More drugs are added in induction phase II – cyclophosphamide, cytosine-arabinoside, 6-mercaptopurine, methotrexate.

Important new elements of induction therapy consist of intensification of asparaginase therapy by means of a increased dosage, the combined administration of antiCD20-antibodies in CD20-positive ALL, and imatinib in Ph-positive ALL (see below).

5.2 Consolidation

Intensive consolidation is a standard procedure in ALL therapy. There are various consolidation therapy concepts in use all over the world. The efficacy of single elements can hardly be evidenced. However, available data indicate that a cyclic consolidation therapy with alternating substances and particularly the application of high-dose methotrexate, high-dose cytarabine, the increased dose intensity of asparaginase, as well as the repetition of induction therapy (re-induction) are effective. The timely application of the treatment blocks is essential in the consolidation phase.

5.3 Maintenance

After completion of the consolidation and intensification cycles maintenance therapy is a standard therapy for all ALL patients (with the exception of mature B-cell ALL patients), who do not receive SCT and in whom no MRD monitoring has been conducted. Clinical trials which left out maintenance therapy resulted in distinctly lower overall survival rates. Ongoing studies are currently investigating the question whether intensification cycles under conventional maintenance therapy with mercaptopurine and methotrexate can further improve the outcome. In the GMALL studies duration and intensity of maintenance therapy is guided by the results of MRD monitoring. The final evaluation of these results is still pending.

5.4 Stem-Cell Transplantation (SCT)

Allogenic SCT is an essential component of post-remission therapy of ALL in adults, using related and unrelated donors. By now, twice as many unrelated stem cell transplantations are performed due to the high efficiency of the donor registries. Long-term results are comparable. Autologous SCT is applied in rare cases subsequent to a further consolidation therapy, only if a compatible allogenic donor is not available and a negative MRD status has been reached, or if no other form of salvage therapy is applicable. For elderly high-risk patients, and patients with contraindications to conventional SCT, the non-myeloablative SCT (NMSCT) presents a therapeutic alternative.

The indication for SCT in first remission varies from country to country. Like the GMALL study group, the majority of study groups pursue a risk-adapted indication for SCT in first remission [8]. Transplantation in first CR is recommended for all patients with high-risk features. In the GMALL studies, this applies to almost 50% of the patients. Transplantation in first remission is not recommended for standard-risk patients, as these patients have an overall survival chance

of more than 50% with conventional chemotherapy as well. The indication of SCT for standard-risk patients is based on the MRD status

The GMALL study group has issued an expert recommendation for stem cell transplantations in ALL. This recommendation is available from the study group. The objective is standardization of conditioning, GvHD prophylaxis, and other transplantation-associated processes, in order to improve the outcome and data quality for evaluation.

5.5 CNS Prophylaxis

An effective prophylaxis of CNS relapses is crucial in ALL. Risk factors for the development of CNS relapses are T-ALL, mature B-cell ALL, and a high leukocyte count at the time of diagnosis. Therapeutic options include intrathecal therapy with methotrexate, a triple combination (methotrexate, cytarabine, corticosteroid), systemic high-dose therapy with methotrexate and/or cytarabine, as well as prophylactic cranial irradiation (24Gy). The best results with regard to the rate of CNS relapses (<5%) is obtained with a combination of all modalities, which is also part of the current GMALL recommendations.

In case of initial CNS involvement an intensified intrathecal therapy with 2-3 weekly applications is recommended until blast clearance is reached, followed by 1-2 consolidating applications. In patients with frequent intrathecal methotrexate instillations a leucovorin rescue should be applied for the purpose of mucositis prophylaxis.

5.6 Ph/BCR-ABL-Positive ALL

The Philadelphia-(Ph-)chromosome and/or the corresponding fusion BCR-ABL transcript is the most frequent aberration in ALL with an incidence of 30–40% in B-precursor ALL. The prognosis of this subgroup has been markedly improved by the application of tyrosine kinase (TK) inhibitors, especially imatinib [9].

In younger patients imatinib is given in combination with intensive chemotherapy. This therapy results in remission rates of more than 90%. The molecular remission rate exceeds 50%. The percentage of patients who were able to undergo allogenic stem cell transplantation could also be distinctly increased this way. At present, the GMALL study group recommends imatinib in combination with a reduced induction therapy (no daunorubicin). A study with dasatinib applied in the same combination is concomitantly conducted in several centers.

Due to the development of resistances and relapses under chemotherapy in combination with TK inhibitors, stem cell transplantation continues to be the only possibility to achieve long-term remissions in Ph+ ALL. A further improvement seems to be possible by an administration of imatinib after transplantation. At present, results of a randomized GMALL study are still pending, in which imatinib treatment in all patients was compared to treatment only in patients with a positive MRD status.

In elderly patients with Ph-positive ALL, studies predominantly tested the concept of imatinib monotherapy as induction. This therapy which can often be applied under outpatient conditions achieves a CR in 90 % of the patients and is superior to a dose-reduced induction chemotherapy in combination with imatinib, as was also shown in a randomized study by the GMALL [10]. At present, induction with imatinib monotherapy is recommended in elderly patients. A study with nilotinib combined with a dose-reduced induction and a moderately intensive consolidation is being concomitantly conducted at several centers.

Various possibilities to optimize the therapy of Ph+ ALL are currently being tested in the scope of clinical trials, among which is a study of a moderately intensive induction chemotherapy with TK inhibitors, a trial focusing on monotherapies with second-generation TK inhibitors, e.g. dasa-

tinib and nilotinib, the combination or the sequential application of various TK inhibitors, the application of dose-reduced conditioning also in elderly patients, and testing maintenance therapies after chemotherapy but also after transplantation. Therapy control based on resistance-associated BCR-ABL mutations and MRD is also being tested. New kinase inhibitors are being studied for the benefit of patients with a T315I mutation, a mutation which induces a resistance to all currently available TK inhibitors.

Treatment is guided by MRD monitoring (BCR-ABL level). In case of MRD persistence after 1-2 consolidation cycles a revision of therapy should be discussed with the GMALL Study Center, unless a stem cell transplantation is planned.

5.7 Elderly ALL Patients

Remission rates decrease with increasing age of the patients due to increased induction mortality. In >65-year-olds the remission rates amount to 60-80% [11]. The overall survival rates are at 20-40% in published studies using moderately intensive, age-adapted therapy. One important therapeutic decision concerns the application of moderately intensive chemotherapy to the individual patient despite his biological age, or whether palliative therapy should be preferred instead. The chances of cure are better and early mortality will be lower if therapy involves at least moderately intensive chemotherapy [12]. For this reason, elderly patients should also be included in controlled prospective clinical trials.

Currently, several treatment protocols are available for elderly ALL patients. These protocols have been adapted to subgroups and encompass, apart from dose-reduced chemotherapy, molecular (imatinib) and antibody therapy (e.g. anti-CD20). Dose-reduced allogenic transplantations may also be taken into consideration under the condition that complete, high-quality initial diagnostics are applied to the elderly patients as well.

In patients, in whom a moderately intensive chemotherapy cannot be applied because of existing comorbidities, treatment may proceed in conformity with the GMALL therapy recommendation for frail patientsl. Long-term remission and good quality of life can often also be achieved in elderly patients with Ph/BCR-ABL-positive ALL with imatinib, dasatinib or nilotinib monotherapy. In case of therapy failure, the conversion to dasatinib might be temporarily successful. In these patients, analysis of resistance-associated mutations of the BCR-ABL kinase domain should be initiated.

5.8 Lymphoblastic Lymphomas

The phenotype of T-lymphoblastic lymphomas is similar to that of T-ALL, however, bone-marrow involvement lies below 25%. The disease occurs typically in younger males is associated with a mediastinal mass in over 90% of the cases it. T-LBL can be very successfully treated by applying adapted ALL regimes [13]. The GMALL study group has published a therapy recommendation for T-lymphoblastic lymphomas which is based on chemotherapy applied in analogy to that of the GMALL Study 07/2003, but additionally integrates PET control of residual mediastinal mass in remission.

5.9 Mature B-Cell ALL

According to the new WHO classification the mature B-cell ALL is allocated to the group of Burkitt's leukemias/lymphomas. It is characterized by rapid progression, and frequently a large tumor mass, along with an increased incidence of CNS (12%) and organ (34%) involvement [14]. The treatment results were distinctly improved with therapy regimes derived from pediatric oncology, including a rapid sequence of short intensive chemotherapy blocks; essential elements are high-dose methotrexate and fractionated cyclophosphamide or ifosfamide. Ther-

apy only lasts 21 weeks. Recently monoclonal antibodies against CD20 have been introduced into the treatment of B-ALL and Burkitt's lymphomas. In 80-90% of patients these leukemias/ lymphomas express CD20. The early administration of rituximab prior to the chemotherapy cycles has significantly improved the treatment results [15].

5.10 Relapse

Risk of relapse is highest in the first two years after achievement of CR. Patients with early relapse (first remission <18 months) have an unfavorable prognosis. The overall survival rate after relapse is below 10% [16].

The primary objective in the management of relapse patients is to obtain a second complete remission and subsequently carry out the stem cell transplantation. Important for therapy selection are the previous therapy, the duration of the first remission, the patient's age, the availability of a stem cell donor, the leukemic subtype, and the availability of cellular structures for targeted therapeutic approaches. In patients with early relapse, a subgroup-adapted procedure, including clinical trials with new substances, should be pursued. In patients with late relapse, retreatment with the initially effective induction therapy is the first therapeutic option. Extramedullary relapses of ALL (e.g. CNS, testes) are treated with intensive systemic therapy followed by SCT. Salvage and stem cell therapy are also recommended for patients with molecular relapse. The GMALL study group is currently running a project on the optimization of relapse therapy and advises individuals.

6 Follow-Up

Relapses may occur up to 5 years after initial diagnosis. Afterwards the likelihood of a relapse strongly decreases. Continued regular differential blood cell counts and bone-marrow checks will therefore be necessary. MRD monitoring should be performed every three months in the first year after termination of therapy, and every six months in the following year, in order to detect any potential molecular relapses.

Follow-up examinations also serve the purpose of identifying the late effects of therapy. This may concern aseptic bone-marrow necroses after corticosteroid administration, MDS, secondary malignant neoplasms e.g. AML, infertility, endocrine disorders, psychosocial deficiencies etc. However, the great majority of ALL patients in long-term remission are to be considered as cured and do not suffer from any late complications.

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8 Active Studies

8.1 Current Studies and Management of ALL Patients in Germany

In rare diseases such as ALL the only way to optimize therapy consists in the combination of healthcare provision and clinical research conducted in the context of therapy optimization studies. In Germany, the majority of adult ALL patients are treated in clinical studies or according to therapy recommendations issued by the GMALL, the German Multicentric Study Group for ALL in Adults. Over 140 hospitals all over Germany contribute to this study group which is the largest of its kind worldwide. The studies comprise numerous innovative therapy approaches, including new drugs, with a special focus on the development of risk-adapted individualized therapies. In the latest study of 07/2003 an overall survival rate of more than 50% has been achieved in adult ALL patients for the first time.

Currently it is suggested that the data of all adult ALL patients are entered into the GMALL registry. This also includes biological materials to be sent in. If the inclusion criteria for a clinical trial are fulfilled, inclusion into the study may then ensue. If study inclusion is not possible, the patients should be treated and documented in analogy to the GMALL recommendations. Registration makes it possible that all patients can be monitored nationwide, also with regard to their respective long-term therapy outcome.

Therapy studies and recommendations of the GMALL study group are currently obtainable from the competence network "Acute and Chronic Leukemias" (www.kompetenznetz-leukaemie.de) where inclusion/ exclusion criteria, therapy protocols, and the addresses of study centers are listed.

8.2 Current Studies and Management of ALL Patients in Austria

The clinical trials and the recommendations of the GMALL study group have been supported and are being applied at most centers all over Austria for many years.

At present, a registry (AGMT-ALL Registry) is being established to collect diagnostic and therapeutic data pertaining to patients with acute lymphoblastic leukemia and/or highly aggressive lymphomas such as Burkitt's lymphoma or lymphomas of the T-lymphoblastic type. Most recently, the highly specific MRD diagnostics (PCR), which have been developed in Germany, are now also available in Austria, so that the recommended prognostic factors canbe used in therapy decision-making in this country as well. Both MRD diagnostics and cerebrospinal liquid (liquor) diagnostics by means of flow cytometry are in a state of development.

In summary, due to the close long-term cooperation with the GMALL study group all therapies mentioned above as well as the diagnostics are available in Austria and can thus be passed on to our patients.

8.3 Current Studies and Management of ALL Patients in Switzerland

In Switzerland, all centers treating acute lymphoblastic leukemias work according to protocols issued by the Group for Research on Adult Acute Lymphoblastic Leukemia GRAALL Intergroup (LALA-GOELAMS-SAKK). Two protocols, i.e. GRAALL 2005 (Randomization between Conventional and Increased Cyclophosphamide Dosage in Induction and Late Intensification) and GRAAPH 2005 (Therapy of Ph-Positive ALL), have just reached their intended inclusion numbers and have been closed. The GRAALL 2005-R (Randomized Therapy of CD20-Positive ALL with or without Rituximab®) protocol is still open until September 2012. Participation in subsequent protocols in preparation is intended.

8.4 Contact Data

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9 Links

Leukemia Competence Network – German Leukemia Study Registry: Acute Lymphoblastic Leukemia
http://www.kompetenznetz-leukaemie.de/content/studien/studienregister/

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11 Disclosure

according to the rules of the German Association of Hematology and Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.