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Acute Lymphoid

Leukemia In acute lymphoblastic leukemia (ALL), the malignant clone arises from hematopoietic progenitors in the bone marrow or lymphatic system resulting in an increase of immature nonfunctioning leukemic cells. Infiltration of bone marrow leads to anemia, granulocytopenia, and thrombocytopenia with the clinical manifestations of fatigue, weakness, infection, and hemorrhage. These symptoms are more often the reason a patient first seeks medical advice rather than consequences of tumor bulk, such as lymph node enlargement, hepatosplenomegaly caused by leukemic infiltration, or symptoms of the central nervous system (meningeosis leukemica). ■ ■INCIDENCE AND AGE ALL is the most frequent neoplastic disease in children with an early peak at the age of 3–4 years. The incidence in adults ranges from 0.7 to 1.8/100,000 per year, being somewhat higher in adolescents and young adults (AYAs), decreasing in adults but increasing again in elderly peo ple. Thus, Philadelphia chromosome–positive ALL (Ph+ ALL; BCR/ ABL translocation) is observed in half of the elderly B-lineage patients. The frequency of immunologic, cytogenetic, and genetic subtypes changes substantially with age. PART 4 Oncology and Hematology ■ ■ETIOLOGY The etiology of acute leukemias is unknown. Internal and external factors influence the incidence of leukemia. Exposure to ionizing radiation or to chemicals, including prior chemotherapy, is associated with an increased risk of developing leukemia, more often observed in acute myeloid leukemia (AML). However, increasingly, second ary ALLs have been observed, particularly after cytostatic treatment with alkylating agents and topoisomerase inhibitors as treatment for primary tumors, most often for AML, myelodysplastic syndromes, or breast cancer. ■ ■CONGENITAL DISORDERS Patients with some rare congenital chromosomal abnormalities have a higher risk of developing acute leukemia (e.g., Klinefelter’s syndrome, Fanconi’s anemia, Bloom’s syndrome, ataxia-telangiectasia, and neuro fibromatosis). Those with Down’s syndrome have a 20-fold increased incidence of leukemia; ALL is increased in childhood and AML at an older age. ■ ■INFECTIOUS AGENTS No direct evidence implicates viruses as a major cause of human acute leukemia. However, viruses are involved in the pathogenesis of two lymphoid neoplasias. In the endemic African type of Burkitt’s lymphoma, the Epstein-Barr virus, a DNA virus of the herpes family, has been implicated as a potential causative agent (see Chap. 199). Endemic infection with human T-cell leukemia virus I in Japan and the Caribbean has been shown to be an etiologic agent for rare cases of adult T-cell leukemia/lymphoma (see Chap. 207). ■ ■DIAGNOSIS AND

CLASSIFICATION The diagnosis of acute leukemia is first made by examination of the peripheral blood and bone marrow. For further classification of the leukemic blast cells, cytochemical stains, immunologic markers, and cytogenetic and molecular analysis are required. The immunologic markers are still the major criteria to subdivide into B-cell lineage or T-cell lineage ALL leukemias. ■ ■PERIPHERAL BLOOD Peripheral blood counts and a differential count from a WrightGiemsa–stained blood smear are essential at the time of presentation.

TABLE 111-1 Laboratory Values at Diagnosis of Acute Lymphoblastic Leukemia (ALL) ALL NO.

Initial white blood cell count (× 109/L) <10 10–50

> 50–100 100 41% 31% 28% 16% Neutrophils (× 109/L) <50–100 <100,000 12% 16% Platelets (× 109/L) <20 21–40 41–100 100 22% 22% 29% 27% Hemoglobin (g/dL) <7 7–9 9 20% 33% 47% Leukemic blasts in peripheral blood 0% 25–75% 75% 8% 34% 36% Leukemic blasts in bone marrow <50% 51–90% 90% 4% 25% 71% Source: Data from three consecutive German Multicenter Trials for Adult ALL (GMALL). The white blood cell (WBC) count in ~40% of ALL patients is reduced or normal (Table 111-1). Only 16% of patients have a WBC above

100 × 105/L. It is noteworthy that in 8% of ALL patients, no circulating leukemic blast cells were observed. Thus, in the frequently used auto matic blood cell counting, the diagnosis may not be detected. Peripheral blood characteristically shows anemia, thrombocytope nia, and neutropenia. Nearly one-third of patients have hemoglobin levels <7–8 g/dL. A platelet count below the critical number of 20 × 109/L, associated with the risk of bleeding, and neutropenia (neutro phils <0.5 × 109/L), associated with a higher risk of infection, are each noted in one-fifth of adults with ALL. ■ ■BONE MARROW EXAMINATION Bone marrow aspirates/biopsies are important to assess immunologic, cytogenetic, and genetic markers. A biopsy of the bone marrow is essential to confirm the diagnosis of acute leukemia and to distinguish between AML and ALL. The bone marrow is usually heavily packed with leukemic blast cells with >90% in ~70% of patients, and thus, the normal hemopoietic elements are greatly reduced or absent. ■ ■LUMBAR PUNCTURE The examination of the cerebrospinal fluid is an essential routine diagnostic measure for ALL. Central nervous system (CNS) leukemia is diagnosed if ≥5 cells/μL or leukemic blast cells were observed by morphology in cerebrospinal fluid. Opinions differ as to when the first lumbar puncture should be done—i.e., either delay lumbar puncture until remission is achieved to avoid seeding of the CNS with leukemic blast cells from the peripheral blood during the spinal tap or perform the lumbar puncture before treatment starts, since early recognition of CNS disease will lead to immediate CNS-specific therapy. Lumbar puncture is restricted to patients with an adequate platelet count (>20 ×

109/L) and without manifest clinical hemorrhages. To eliminate poten tially transferred blast cells, patients should receive intrathecal metho trexate at the first lumbar puncture. ■ ■MORPHOLOGIC SUBTYPES IN ALL The French-American-British (FAB) classification distinguished three subgroups. L1 and L2 morphology has no clinical consequences. Only the L3 morphology, observed in up to 5% of adult patients, is indicative for mature B-cell lineage ALL (B-ALL) (see Chap. 65).

■ ■IMMUNOLOGIC SUBTYPES A series of monoclonal antibodies is employed to identify antigens expressed on the surface of leukemic cells, corresponding to the path ways of normal B-cell differentiation (see Fig. 113-2). The immuno logic classification aims to subdivide ALLs according to the presence or absence of B-cell or T-cell markers. A marker is considered positive if >20% of the cells are stained with the monoclonal antibody. There are different immunologic classifications, such as that of the European Group for the Immunological Characterization of Leuke mias (EGIL), with clear therapeutic implications. Table 111-2 gives a simplified correlation of immunologic subtypes, cytogenetics and molecular aberrations, and clinical characteristics. B-Cell Lineage ALL (B-ALL) More than 70% of adult ALLs are of B-cell origin, and the most frequent immunologic subtype, common ALL, is characterized by the presence of the ALL antigen CD10 with out markers of relatively mature B cells such as cytoplasmic or surface membrane immunoglobulins. Pre-B-ALL (early B-ALL) is charac terized by the expression of cytoplasmic immunoglobulin, which is negative in common ALL, but otherwise is identical with respect to all other cell markers. Pro-B-ALL corresponds to early B-cell differentia tion and was formerly termed non-T-, non-B-ALL or null ALL because neither T-cell nor B-cell features could be demonstrated. This subtype is HLA-DR, terminal deoxynucleotidyl transferase, and CD19 positive and composes ~12% of adults ALL. Mature B-ALL is seen in 3–4% of adults and is also known as Burkitt's leukemia. In mature B-ALL, blast cells express surface anti gens of mature B cells, including the sIgM. T-Cell Lineage ALL (T-ALL) Approximately 25% of adult ALLs are of T-cell lineage. All cases express the T-cell antigen CD7 and cyto plasmatic CD3 (CyCD3) or surface CD3. According to their stage of TABLE 111-2 Immunologic, Cytogenetic, Molecular, and Clinical Characteristics of Adult Acute Lymphoblastic Leukemia (ALL) FREQUENT CYTOGENETIC ABERRATIONS SUBTYPES MARKER INCIDENCE B-lineage ALL (B-ALL) HLA-DR+, TdT+, CD19+, and/or CD79a+, and/or cyCD22+ 76% Pro B-ALL No additional differentiation markers Frequent myeloid coexpression (>50%) CD10– 112% t(4;11) (q21;q23) Common ALL CD10+ 49% t(9;22)(q34;q11) del(6q) Pre-B-ALL CD10±, cyIg+ 12% t(9;22)(q34;q11) t(1;19)(q23;p13) Mature B-ALL TdT–, CD34–, sIg+ 4% t(8;14)(q24;q32) t(2;8)(p12;q24) t(8;22)(q24;q11) TdT±, cyCD3, CD7+ 24% t(10;14)(q24;q11) t(11;14)(p13;q11) T-lineage ALL (T-ALL) Early Pro/Pre T-ALL Cortical T-ALL No additional differentiation markers, mostly CD2–/(+), SCD3–, CD1a– CD1a+, sCD3± sCD3+, CD1a– 6% 12% Mature T-ALL 6% Abbreviations: BM, bone marrow; CNS, central nervous system; WBC, white blood cells.

T-cell differentiation, they may express other T-cell antigens (e.g., the E-rosette receptor CD2 and/or the cortical thymocyte antigen CD1a). Early pro/pre-T-ALL (also termed early T precursor ALL [ETP-ALL]), cortical or thymic T-ALL, and mature T-ALL can be distinguished with these markers. ETP-ALL is characterized by lack of CD1a and CD8, weak CD5 expression, and at least one myeloid/stem cell marker.

Biphenotypic or Mixed Leukemias Biphenotypic leukemias are defined as those expressing markers of both lymphoid and myeloid lineages on the same leukemic cells. Bilineage leukemias are those with two populations of blast cells with either lymphoid or myeloid antigens. It is not clear whether these patients should receive an ALL or AML treatment protocol. In pediatric studies, starting with a pediatric ALL protocol seemed preferable, which was then followed by AML consoli dation elements.
■ ■CYTOGENETIC AND MOLECULAR ANALYSIS Cytogenetic and molecular analyses should be performed in all cases. They are important to define ALL subtypes, can identify independent prognostic markers of disease-free survival, and may determine spe cific targeted therapies. The diagnostic techniques for ALL are standard cytogenetics, fluo rescence in situ hybridization, and

reverse transcriptase polymerase chain reaction. These methods allow the detection of Ph+ ALL, with the chromosomal translocation t(9;22)(q34;q11) and the detection of the corresponding BCR-ABL1 gene rearrangement. Further ALL entities that have been identified are t(4;11)(q21;q23)/MLL-AFA4, abn11q23/MLL, and t(1;19)(q23;p13)/PBX-E2A. CHAPTER 111 Gene expression profiling, single nucleotide polymorphism array analysis, array-comparative genomic hybridization, and next-generation sequencing recognize the newly defined ALL entities: ETP-ALL and Ph-like ALL. Acute Lymphoid Leukemia GENETIC ABERRATIONS AND FUSION TRANSCRIPTS CLINICAL CHARACTERISTICS RELAPSE KINETICS AND LOCALIZATION 70% ALL1-AF4 (20% Flt3 in MLL+) High WBC (>100,000/μL) (26%) Mainly BM (>90%) 33% BCR::ABL1 with 54% IKFZ1 del

> 25% CDKN2A/B Higher age >50 years (24%) Mainly BM (>90%) Prolonged relapse kinetics (up to 5–7 years) 4% t(1;19)/PBX-E2A Higher age >55 years (27%) Frequent organ involvement (32%) and CNS involvement (13%) Frequent CNS (10%) Short relapse kinetics (up to 1–1.5 years) 50% NOTCH1B 33% HOX11b 5% HOX11L2b 4% NUP213-ABL1 Younger age (90% <50 years) Frequent mediastinal tumors (60%) Frequent CNS involvement (8%) High WBC (>50/μL) (46%) Frequent CNS (up to 10%) Extramedullary (6%) Intermediate relapse kinetics (up to 3–4 years) When relapsed, fast progression

TABLE 111-3 Response Parameters According to Minimal Residual Disease (MRD) TERMINOLOGY DEFINITION Complete hematologic remission (CHR) Leukemic cells not detectable by light microscopy (<5% blast cells in bone marrow [BM]) Complete molecular remission/MRD negativity Patient in complete remission, MRD not detectable, ≤0.01% = ≤1 leukemia cell in 10,000 BM cells Molecular failure/MRD positivity Patient in complete hematologic remission, but not in molecular complete remission >0.01% Molecular relapse/MRD positivity Patient still in complete remission, had prior molecular complete remission, leukemic blast cells in BM not detectable (<5%) Hematologic relapse

> 5% blast cells in BM/blood Ph-like ALL, also known as BCR-ABL1-like ALL, is characterized by genetic lesions similar to Ph+ ALL, associated with IKZF1 (Ikaros) gene deletion, CLRF2 (gene for cytokine-like receptor-2) overexpres sion, and tyrosine kinase activating rearrangements involving ABL1, JAK2, PDGFRB, and several other genes; however, it is BCR-ABL1 negative. The frequency is 10% in children and 25–30% in young adults but does not increase further with age like Ph+ ALL. Treatment based on the underlying genetic lesion with BCR-ABL inhibitors (e.g., dasatinib) or JAK2 inhibitors (e.g., ruxolitinib) has so far had limited success in adults. PART 4 Oncology and Hematology ■ ■MINIMAL RESIDUAL DISEASE Minimal residual disease (MRD) is the detection of residual leuke mic cells that are not recognizable by light microscopy. Methods for determining MRD are based on the detection of leukemia-specific aberrant immunophenotypes by flow cytometry, the evaluation of leukemia-specific rearranged immunoglobulin or T-cell receptor sequences by real-time

quantitative polymerase chain reaction, or the Frequent Chemotherapy Regimens in Adult ALL BFM-like Regimen Pre Induction Consolidation Re-Induction Consolidation Maintenance HDMTX Asp Pred Vind Adria Asp HDMTX HDAraC Vind VP16 Asp Dexa/Pred Vincristine Dauno/Ida Cyclo AraC VP16 6MP Asp Hyper-CVAD Regimen POMP ± other Dexa Vincristine Doxo Cyclo HDMTX HD AraC MRD evaluation • Prophylactic CNS treatment; intrathecal monotherapy; MTX or intratecal triple MTX, AraC, Dexa/Pred, +/– cranial irradiation (24 Gy) • MRD evaluation; material collection at diagnosis, evaluation after Induction I, Induction II, Consolidation I, then every 3 months. • Rituximab in B-lineage, nelarabine in T-lineage • Maintenance therapy, ~2 years in all subtypes (except Burkitt) FIGURE 111-1 A schematic treatment algorithm in acute lymphoblastic leukemia (ALL). 6-MP, 6-mercaptopurine; Adria, Adriamycin (doxorubicin); AraC, cytarabine; Asp, asparaginase; BFM, Berlin-Frankfurt-Münster; CNS, central nervous system; CR1, first complete remission; Cyclo, cyclophosphamide; Dauno, daunorubicin; Dexa, dexamethasone; Doxo, doxorubicin; HD, high-dose; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; Ida, idarubicin; MRD, minimal residual disease; MTX, methotrexate; POMP, mercaptopurine, vincristine, methotrexate, and prednisolone; Pred, prednisolone; Vind, vindesine; VP16, etoposide.

detection of fusion genes associated with chromosomal abnormalities (e.g., BCR-ABL, MLL-AF4). The detection limit with these methods is 10−3–10−5 (0.1–0.001%). With new techniques such as next-generation sequencing (NGS) or digital droplet polymerase chain reaction (ddPCR), the sensitivity may increase to 10−5–10−6. The phenotypic aberrations are unique to each patient with ALL and can be detected in up to 95% of individuals. Collection of bone marrow at diagno sis for identification of patients' individual markers is essential for follow-up of MRD. ■ ■MOLECULAR RESPONSE AFTER INDUCTION THERAPY AND IMPACT ON OUTCOME Achievement of molecular complete response/molecular remission is the most relevant independent prognostic factor for disease-free and overall survival in pediatric and adult ALL (Table 111-3). Patients with molecular complete remission after induction therapy have sig nificantly superior outcomes in several studies, with a disease-free survival rate of ~70% compared to <40% for MRD-positive patients. Patients with molecular failure after induction should proceed to a targeted therapy to reduce the tumor load, followed by allogeneic stem cell transplantation (SCT), if possible. ■ ■PROGNOSTIC FACTORS, RISK STRATIFICATION, AND MRD The aim of identification of prognostic parameters at diagnosis, which include age, WBC count, immunophenotype, and cytogenetic and genetic aberrations, is to stratify patients into risk groups: standardrisk patients are patients without any risk factors, and high-risk patients are those with one or more risk factors. High-risk patients are most often candidates for SCT in first complete remission (CR). MRD is thus the most important prognostic factor during therapy (Fig. 111-1); 20–30% of adult ALL patients who are MRD negative after induction will relapse. Potential reasons include loss of sensitivity, evolution of leukemic subclones, and extramedullary origin of disease. If the MRD status of a patient is not available, risk stratification should rely on clinical and laboratory risk factors evaluated at diagnosis. 6-MP MTX ± other Stem Cell Transplantation in CR1 according to risk factors/MRD

■ ■TREATMENT PRINCIPLES Treatment of ALL consists usually of pre-phase therapy, induction therapy, consolidation cycles, and maintenance treatment. Treatment should start immediately when the diagnosis of ALL is established and can later be specified or adapted when ALL subtype is known (e.g., Ph+). Pre-Phase Therapy Pre-phase therapy consisting of glucocorti coids (prednisone 20–60 mg/d or dexamethasone 6–16 mg/d, both IV or PO) alone or in combination with another drug (e.g., vincris tine, cyclophosphamide) is usually given for ~5–7 days. It allows

safe tumor reduction to avoid tumor lysis syndrome, to initiate sup portive therapy, such as substitution of platelets/erythrocytes, or to treat infections. The time required for pre-phase therapy will also allow time to obtain results of the diagnostic workup (e.g., cytogenetics, molecular genetics). Induction Therapy The goal of induction therapy is the achieve ment of a CR or, even better, a molecular CR. With current regimens, the CR rate has increased to 80–90% and is higher for standard-risk patients (>90%) and lower for high-risk patients (~60%). Induction regimens are centered around vincristine, glucocorti coids, and anthracyclines with or without cyclophosphamide or cyta rabine. L-Asparaginase is the only ALL-specific drug and is now more intensively used in adults. Pegylated asparaginase has the advantage of a significantly longer period of asparagine depletion. Dexamethasone is often preferred to prednisone because it penetrates the blood-brain barrier and also acts on resting leukemic blast cells. Two chemotherapy regimens are widespread (Fig. 111-1). One is patterned after the pediatric BFM (Berlin-Frankfurt-Münster) pro tocol, which is mostly used in European adult ALL trials. Another approach is to repeat two different alternating intensive chemotherapy cycles, identical for induction and consolidation, for eight cycles, such as Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) protocol, which is preferentially used in the United States but also in many other parts of the world. Postremission Consolidation Usual protocols use six to eight courses and often contain systemic high-dose (HD) therapy to reach sufficient drug levels in sanctuary sites such as the CNS. Most often HD methotrexate (1–1.5 g/m2 and up to 3–5 g/m2) and/or HD cytara bine (4–12 doses at 1–3 g/m2) are administered. Maintenance Therapy Maintenance therapy, a strategy trans ferred from childhood ALL, is mandatory. It consists of 6-mercapto purine and methotrexate plus intrathecal therapy. The potential effect of further intensification cycles during maintenance remains unclear. The duration of maintenance therapy for T-ALL and B-ALL is 2–2.5 years, except for Burkitt’s leukemia, for which a half year to 1 year is sufficient. In Ph+ ALL, patients also require maintenance therapy that should include a tyrosine kinase inhibitor (TKI), most likely the TKI that has been used during induction and consolidation therapy. It is also standard to give a TKI after allogeneic SCT. The duration of main tenance therapy with a TKI is also 2–2.5 years and should be guided by MRD evaluation. TKI use is often interrupted or switched to another TKI if toxicity occurs. ■ ■TREATMENT OF ALL PATIENTS ACCORDING TO AGE The outcome of ALL is strictly related to the age of a patient, with cure rates of ~90% in children, decreasing to <10% in elderly or frail patients. Thus, age-adapted protocols have emerged, where the age limits are directed by the hematologic and nonhematologic toxicities. Table 111-4 provides a summary of the best results obtained in adult ALL according to ALL subtype, age, and treatment. The major risk of relapse is in the first 2 years and is less likely after 5 years. ■ ■PROPHYLAXIS AND TREATMENT OF CENTRAL NERVOUS SYSTEM LEUKEMIA Prophylactic CNS therapy in ALL is essential in order to prevent CNS leukemia and to avoid spread of leukemic cells from the CNS back

TABLE 111-4 Best Results in Recent Studies for Adult Acute Lymphoblastic Leukemia (ALL)
SUBTYPE TREATMENT OVERALL SURVIVAL Burkitt’s leukemia Short intensive chemotherapy

- rituximab; no SCT; no maintenance 80–90% B-lineage ALL, Ph– AYA 15–35/45 years Pediatric inspired, few/no SCT ≥70–80% Adults 45–55 years Intensive chemotherapy +/– SCT 50–60% Elderly 55–70 years Less intensive chemotherapy + immunotherapy ~30% Frail >70/75 years Various ≤10% B-lineage ALL, Ph+ Ph BCR-ABL Intensive chemotherapy +

TKI +/– SCT 60–70% Ph-like ALL Chemotherapy + dasatinib/JAK inhibitors ≤50% T-lineage ALL Early (ETP) Intensive chemotherapy + nelarabine + SCT 40–50% Cortical/thymic Intensive chemotherapy + nelarabine, no SCT 70–84% CHAPTER 111 Mature Intensive chemotherapy + nelarabine + SCT 30–50% Abbreviations: AYA, adolescent and young adult; ETP, early T precursor; Ph, Philadelphia chromosome; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor. Acute Lymphoid Leukemia to the periphery. Treatment options include intrathecal therapy, sys temic HD chemotherapy, and cranial radiation therapy (CRT). Wide variations exist in CNS prophylaxis regimens. Intrathecal therapy mostly consists of methotrexate as a single drug or in combination with cytosine arabinoside (AC) with or without glucocorticoids. The route of intrathecal therapy application is generally lumbar puncture. Systemic HD chemotherapy may comprise HDAC or HD methotrexate since both drugs reach cytotoxic drug levels in the cerebrospinal fluid and show effectiveness in overt CNS leukemia. CRT (18–24 Gy in 12 fractions over 16 days) is also effective as preventive treatment of CNS leukemia. Using combined modalities for CNS prophylaxis, the CNS relapse rate has decreased to 2–5%. Particular attention to CNS prophylaxis is required for targeted therapies. In Ph+ ALL, not all TKIs cross the blood-brain barrier equally such as imatinib and nilotinib but dasatinib and probably ponatinib do. In immunotherapies, intrathecal therapy is required because most antibodies do not enter the CNS. CNS involvement at diagnosis is observed in 5–10% of adult patients and is higher in mature B-ALL (up to 10–15%) and T-ALL (up to 10%). Treatment consists of the standard chemotherapy with additional intrathecal applications 3–5 times per week until blast cells are cleared in the spinal fluid. Patients with initial CNS involvement have a similar overall survival as CNS-negative patients. Relapse in CNS is usually accompanied by bone marrow involve ment, and if blast cells are not seen morphologically, MRD as a sign of discrete infiltration is positive in nearly all cases. CNS relapse requires local as well as systemic therapy. The outcome after CNS relapse is dis mal, and salvage chemotherapy followed by allogeneic SCT is the most effective option. Chimeric antigen receptor (CAR) T cells (most often targeting CD19) can cross the blood-brain barrier and achieve CRs in patients with CNS relapse. Extramedullary manifestation and relapses in ALL are often observed. Patients should have the general treatment and, if required, local intervention (e.g., local radiation if residual mediastinal mass). ■ ■STEM CELL TRANSPLANTATION SCT is an essential part of the treatment strategy for adult ALL. Peripheral blood cells are more often being used as a stem cell source, instead of bone marrow. If no matched sibling stem cell donors are available,

increasingly matched unrelated donors or haploidentical donors are used. Indications for SCT in first CR are controversial. However, in most studies, SCT is recommended for high-risk patients defined either by conventional prognostic factors or by MRD positivity. High-risk patients transplanted in first CR have a survival rate of 50% or greater. Decreasing transplant-related mortality from 20–30% to 10–15% has contributed substantially to better outcomes. For standard-risk patients with sustained molecular remission, allogeneic SCT in first CR is not recommended. Autologous SCT should be restricted to MRD-negative patients, BCR-ABL–negative patients and older patients because it is less toxic but associated with a substantially higher relapse rate. For all

relapsed adult ALL patients, an allogeneic SCT is thus far the only curative option.

■ ■PEDIATRIC-INSPIRED THERAPIES FOR ADOLESCENTS AND YOUNG ADULTS The principle of pediatric-inspired therapies is to have higher doses and more applications of ALL-specific drugs such as glucocorticoids, vincristine, and L-asparaginase and fewer myeloablative anthracyclines or alkylating agents, with strict adherence to time-dose intensity, thereby reducing the role of SCT. The overall survival rates for AYAs are 70–80%. ■ ■ADULT ALL The treatment results for adult ALL patients have greatly improved with more intensive chemotherapy, optimized SCT, and better sup portive care. In several recent multicenter prospective trials, the overall survival rate for standard-risk patients was >70% with chemotherapy alone, and for high-risk patients, the overall survival rate has increased from 20–30% to >50%. PART 4 Oncology and Hematology ■ ■ALL IN THE ELDERLY Palliative treatment regimens for elderly patients have failed, with CR rates of ~40%, a high early death rate of 24%, and a poor overall survival of only a few months. Intensive chemotherapy has also failed, with a higher CR rate of 56%, but still an early death rate of 23%, and only moderate improvement of overall survival to 14 months. Specific elderly ALL protocols with less intensive therapy based on glucocor ticoids, vincristine, and asparaginase, largely avoiding anthracyclines and alkylating agents, have improved outcomes. The early treatmentrelated death rate decreased to <10%, CR rates improved to ~90%, and overall survival of ~30 months was noted. Frail patients above the age of 70–75 years have very poor survival of <10%. Hopefully, this will improve with ongoing targeted therapies with either TKIs in Ph+ ALL or immunotherapies. ■ ■TARGETED THERAPIES Substantial progress in adult ALL has been made in the past decade by the introduction of new targeted therapies, including TKIs and immu notherapeutic approaches (Table 111-5). ■ ■TYROSINE KINASE INHIBITORS IN PHILADELPHIA-POSITIVE ALL Patients with Ph+ ALL constitute ~25% of adult B-ALL patients, with the frequency increasing to ~50% among elderly patients. In the preimatinib era, CR rates were 60–70%; survival with chemotherapy was ~10%, and after allogeneic SCT, it was ~30%. With the first-generation TKI imatinib, CR rates increased to 80–90%, the rate of BCR-ABL negativity increased from 5 to 50%, and the 5- to 10-year overall sur vival improved to 50–70%. Faster and deeper molecular responses are achieved with secondgeneration TKIs (dasatinib, nilotinib), and these responses apparently translate into a survival benefit. The third-generation TKI ponatinib is also effective in tumors bearing mutations (particularly T315I) that convey resistance to earlier-generation TKIs. Treating adult Ph+ ALL with an allogeneic SCT in first CR is still a good treatment option for adult patients, with a 5-year overall sur vival of 60–70%. In elderly patients, when low-intensity chemotherapy was combined with dasatinib, the CR rate was >90%. In a next step, by combining mini-chemotherapy with a TKI and adding immuno therapy with inotuzumab (an anti-CD22 antibody), the CR rate was

TABLE 111-5 Targeted Therapies in Adult Acute Lymphoblastic Leukemia (ALL) Tyrosine Kinase Inhibitors (TKIs) Ph/BCR-ABL+ ALL TKIs Imatinib, dasatinib, nilotinib, bosutinib, ponatinib, asciminib Ph/BCR-ABL-like ALL ABL1, ABL2: dasatinib, ponatinib; JAK2: ruxolitinib Immunologic Approaches Antibodies directed against leukemia surface antigens Monovalent antibodies Bivalent antibodies against the tumor and CD3 (e.g., blinatumomab) Adoptive cellular therapy T cells engineered to kill leukemic cells Checkpoint Inhibitors PD-1 inhibitors: pembrolizumab, nivolumab CTLA-4 inhibitors: ipilimumab Targeted Agents Proteasome inhibitors: bortezomib, ixazomib BCL-2 inhibitors: venetoclax, navitoclax

90% and the overall survival improved further. A pilot experience with a chemotherapy-free regimen composed of dexamethasone, the TKI dasatinib, and the bispecific antibody blinatumomab (anti-CD19 and anti-CD3) demonstrated a CR rate of 98% and 2-year overall and disease-free survival rates of 95% and 88%, respectively. Blinatumomab eliminates Ph+ leukemic cells with resistant mutations. ■ ■IMMUNOTHERAPEUTIC APPROACHES Treatments involving monoclonal antibodies or activated T cells are currently changing the treatment paradigm of ALL. The prerequisite is that B-lineage blast cells express a variety of specific antigens, such as CD19, CD20, and CD22 (Table 111-6) that are targetable with a wide variety of monoclonal antibodies. A new treatment principle is the acti vation of the patient's T cells to destroy their CD19+ leukemic blasts. Anti-CD20 The anti-CD20 monoclonal antibody rituximab has improved the outcome of patients with de novo Burkitt's leukemia/ lymphoma. With repeated short cycles of intensive chemotherapy combined with rituximab, the overall survival increased to >80%. Rituximab is now included in most B-ALL regimens and is given at the usual dose of 375 mg/m2 on day –1 before chemotherapy for at TABLE 111-6 Expression of Antigens in B-Cell Lineage Acute Lymphoblastic Leukemia (ALL) for Potential Antibody Therapy SURFACE ANTIGEN ALL SUBTYPES EXPRESSION ON LBCa MONOCLONAL ANTIBODY CD20 Burkitt's lymphoma/ leukemia B-precursor 86–100% 30–40% Rituximab Ofatumumab CD22 B-precursor Mature B-ALL 93–98% ~100% Inotuzumab Epratuzumab Moxetumomab pasudotox CD19 B-precursor Mature B-ALL 95–<100% 94–<100% T cell–activating therapies Blinatumomab Bispecific CD3/CD19 Chimeric antigen receptor modified T cells (CAR T cells) aDefined as ≥20% positive blast cells. Abbreviation: LBC, leukemic blast count. Source: Reproduced with permission from D Hoelzer: Novel antibody-based therapies for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2011:243, 2011.

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