Lecture

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MANAGEMENT OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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The lecture presents modern data on acute lymphoblastic leukemia as the one of the most common malignant disease of children, youth and the elderly. The data on the major risk factors, causes, pathogenesis, clinical manifestations, as well as the main approaches to the diagnosis and treatment of this disease and possible predictions for patients in different clinical situations are described.

KEY WORDS: acute lymphoblastic leukemia, etiology, pathogenesis, clinical manifestations, diagnosis, treatment, prognosis

ВЕДЕННЯ ПАЦІЄНТІВ З ГОСТРИМ ЛІМФОБЛАСТНИМ ЛЕЙКОЗОМ

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У лекції представлені сучасні дані про гострий лімфобластний лейкоз як один з найбільш поширених злоякісних захворювань дитячого, юнацького та похилого віку. Наведено дані про основні фактори ризику, причини виникнення, патогенез, клінічні прояви, а також основні підходи до діагностики та лікування цього захворювання і можливі прогнози для пацієнтів в різних клінічних ситуаціях.

КЛЮЧОВІ СЛОВА: гострий лімфобластний лейкоз, етіологія, патогенез, клініка, діагностика, лікування, прогноз

ВЕДЕНИЕ ПАЦИЕНТОВ С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ

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В лекции представлены современные данные об остром лимфобластном лейкозе как одном из самых распространённых злокачественных заболеваний детского, юношеского и пожилого возрастов. Приведены данные об основных факторах риска, причинах возникновения, патогенезе, клинических проявлениях, а также основные подходы к диагностике и лечению этого заболевания и возможные прогнозы для пациентов в разных клинических ситуациях.

КЛЮЧЕВЫЕ СЛОВА: острый лимфобластный лейкоз, этиология, патогенез, клиника, диагностика, лечение, прогноз

DEFINITION

Acute lymphoblastic leukemia (ALL) is a malignant disorder in which uncontrolled proliferation of lymphoblast occurs in the bone marrow and replaces the normal hematopoietic cells [1].

ALL is an aggressive type of leukemia and can spread to a lymph node, spleen, liver, central nervous system (CNS), and other organs. Without treatment ALL usually progresses quickly, thereby making it extremely dangerous [2].

EPIDEMIOLOGY

ALL represents 12 % of all leukemia cases, with a worldwide incidence projected to be 1–4.75 per 100000 people. Italy, United States (US), Switzerland, and Costa Rica are the countries with the highest incidence of ALL [3]. ALL has an annual incidence of up to 40 cases per million in Eastern European countries, but fewer than 20 per million in subs-Saharan Africa [4]. In Europe, ALL accounts for around 80 % of leukemia among children aged 0–14 years. Peak age of incidence occurs between the ages of 2–4 years, decreasing to become a much rarer disease of adulthood. A smaller peak occurs in people aged over 50 years.

In the year 2013, there were approximately 6020 new diagnoses of ALL in the USA resulting in 1440 death. In the year 2015, there were 6250 estimated new cases with 1450 estimated death. The number of deaths was 0.4 per 100000 men and women per year, these rates are age adjusted and based on 2008–2012 cases and deaths.

Approximately 0.1 % of men and women will be diagnosed with ALL at some point during their lifetime, based on 2010–2012 data. The prevalence of ALL in 2012 is estimated at 75176 people in the US [3–4].

The estimated overall incidence of ALL and lymphoblastic lymphoma in Europe is 1.28 per 100000 individuals annually, with significant age-related variations (0.53 at 45–54 years, ~1.0 at 55–74 years and 1.45 at 75–99 years) and that of Burkett leukemia/lymphoma is between 0.17 and 0.33 in the same age groups. These figures qualify ALL as a rare disease in adults, making assessment and care at qualified centers highly desirable. In Europe, 5-year overall survival (OS) improved from 29,8 % in the years 1997–1999 to 41,1 % in 2006–2008 ($P < 0.0001$), still as a function of age. Compared with the reference group (age 15–54 years: OS > 50 %), OS was <30% in the 55–64 years age group (hazard ratio 2.05) and <20 % in the ≥ 65 years age group (hazard ratios 2.71 and 3.75) [3–4].

RISK FACTORS

The risk factors can be divided into environmental, genetic and infectious [1, 5–7].

Environmental: ionizing radiation, paternal preconception exposure and close proximity to a nuclear facility (this implicates the link between childhood leukemia and paternal ionizing exposure in the workplace before conception or preconception); nonionizing radiation (e.g. electromagnetic fields); chemicals (hydrocarbons and pesticides); maternal alcohol, cigarette and illicit drug use.

Genetics: an identical twin is twice likely as the general population to develop ALL if his or her twin developed the illness before the age of 7 years.

Infections: a transmissible agent is potentially involved in the oncogenic process of childhood leukemia. A viral etiology has been shown for some human and animal cancers.

Other risk factors include: age, previous cancer treatment (children and adults who have had certain types of chemotherapy and radiation therapy for other kinds of cancer may have an increased risk of developing ALL), genetic disorders such as Down syndrome are associated with an increased risk.

PATHOGENESIS

Lymphoid cells are derived from pluripotent hematopoietic stem cells in the bone marrow, through stepwise maturation. ALL represents a group of B/T-precursor-stage lymphoid cell malignancies (arising from genetic insults) that blocks lymphoid differentiation and drives aberrant cell proliferation and survival.

ALL is characterized by gross numerical and structural chromosomal abnormalities including hyperdiploidy, hypodiploidy, translocations and rearrangements. However, several observations indicate that these lesions alone are insufficient to induce leukemia and cooperating lesions are required. It is suggested that the initial event confers self-renewal coupled with mutation, leading to developmental arrest and a secondary cooperative event in cell cycle regulation, tumor suppression and chromatin modification, eventually leading to establishment of the leukemic clone [8].

CLASSIFICATION

ALL can be classified as ALL B-cells or T-cells based on their stage of maturity. B-cell ALL can be divided into early pre-B, common ALL, pre-B ALL, mature B-cell ALL (also called Burkett Leukemia). T-cell ALL includes: pre-T ALL, mature T-cell ALL [1].

According to WHO, ALL is classified based on precursor lymphoid neoplasms [9]:

- B lymphoblastic leukemia/lymphoma;
- B lymphoblastic leukemia/lymphoma, NOS;

- B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities;
- B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2), BCR-ABL1;
- 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) TCF3-PBX1;
- T lymphoblastic leukemia/lymphoma:

FAB classification of acute lymphoblastic leukemia includes:

- ALL-L1: Small cells with homogeneous nuclear chromatin, a regular nuclear shape, small or no nucleoli, scanty cytoplasm, and mild to moderate basophilia;
- ALL-L2: Large, heterogeneous cells with variable nuclear chromatin, an irregular nuclear shape, 1 or more nucleoli, a variable amount of cytoplasm, and variable basophilia;
- ALL-L3: Large, homogeneous cells with fine, stippled chromatin; regular nuclei; prominent nucleoli; and abundant, deeply basophilic cytoplasm. The most distinguishing feature is prominent cytoplasmic vacuolation.

SYMPTOMS

ALL usually begins abruptly and intensely, but in some cases symptoms may develop slowly. Symptoms develop when there are not enough healthy mature WBCs (leukocytes) to mount a defense against infection; there are not enough healthy blood-clotting cells (platelets) to prevent bleeding; the depleted oxygen-bearing RBCs cannot provide enough oxygen to organs [9–11].

Symptoms observed include bone and joint pain, easy bruising and bleeding (such as bleeding gums, skin bleeding, nosebleeds, abnormal periods), fatigue, fever, loss of appetite and weight loss, paleness, pain or feeling of fullness below the ribs, pinpoint red spots on the skin (petechiae), pitting edema (swelling) in the lower limbs and/or abdomen, lymphadenopathy in the neck, under arms and groin, night sweats.

DIAGNOSIS (Table)

Full blood count (FBC): anemia is usual and hemoglobin may be below 5 g/L; thrombocytopenia is also usual, to varying degrees; white blood cell count may be high, normal or low but there is usually neutropenia. Leukemia is unlikely in the presence of a normal FBC but the FBC will not always be abnormal in all cases of ALL, as some patients may not yet have marrow suppression [11]. If the blood count is abnormal, a blood film is essential to help decide whether leukocytosis is likely to be caused by malignancy or inflammation. Blood film is likely to show blast cells but can be normal if blast cells are confined to the bone marrow.

Clotting: DIC (Disseminated intravascular coagulation) may occur and this produces an elevated prothrombin time, reduced fibrinogen level and the presence of fibrin and degradation products.

Biochemistry analysis: lactic dehydrogenase levels are usually raised and rapid cell turnover may raise uric acid. Liver and renal function must be checked before initiating chemotherapy.

Bone marrow aspiration and biopsy: WHO (World Health Organization) classification requires 20 % or greater amount of blasts in bone marrow and/or peripheral blood for the diagnosis of ALL.

Immunophenotyping helps to reveal the subtypes. Positive confirmation of lymphoid rather than myeloid origin should be sought by flow cytometric demonstration of lymphoid antigens. To determine the subtype of ALL by comparing the cancer cells to normal cells in the immune system (may reveal terminal deoxynucleotidyl transferase (TdT -a specialized DNA polymerase expressed in immature, pre-B, pre-T lymphoid cells, and ALL/lymphoma cells or common acute lymphoblastic leukemia antigen (CALLA). Therapeutically, it is important to differentiate between T-cell, mature B-cell and B-cell precursor phenotypes.

Bone marrow samples should undergo cytogenetic. Hyperploid is common. A number of balanced translocations have been identified in ALL. A negative myeloperoxidase stain helps to diagnose ALL, although acute monocyte leukemia also gives negative stain with myeloperoxidase.

Testing for BCR-ABL (oncoprotein) by polymerase chain reaction or cytogenetics may help identify those patients in whom ALL arose as the lymphoblastic phase of chronic myeloid leukemia (CML).

Table 1

Diagnostic work-up in adult ALL [1]

Diagnostic step	Results/ALL subsets	Recommendations
Morphology		
Bone marrow and peripheral blood and/or cerebra-spinal fluid	Lymphoid/undifferentiated blasts (≥ 20 % bone marrow involvement); FAB L3 morphology in Burkett leukemia; CNS involvement	Mandatory Recommended Mandatory
Immunophenotype		
MPO (differential diagnosis versus AML) B-lineage markers: CD19, CD79a, cCD22 (at least 2); others: TdT, CD10, CD20, CD24, cIgM, sIg (kappa or lambda) T-lineage markers: cCD3; others: TdT, CD1a, CD2, CD5, CD7 CD4, CD8, TCR α/β or γ/δ Stem/myeloid cell markers (variable): CD34, CD13, CD33, CD117	MPO negative; B/T markers > 20 % (CD3, CD79a > 10 %) B-lineage ALL: Pro-B/B-I (CD19/CD79a/cCD22+) Common/B-II (CD10+/cIgM−) Pre-B/B-III (cIgM+/sIg−) Mature-B/B-IV (sIg+) T-lineage ALL: Pro-T/T-I (cCD3/CD7+) Pre-T/T-II (CD2/CD5) Cortical-T/T-III (CD1a+) Mature-T/T-IV (CD3+/CD1a−)	Mandatory Mandatory Mandatory
Cytogenetics/genetics		
Cytogenetics/FISH/RT-PCR CGH/SNP/GEP/NGS	ALL with adverse clinic-biological features: Ph+ ALL (rapid detection, to TKI therapy) t(4;11)+ ALL t(1;19)+ ALL other high-risk cytogenetics ALL with adverse clinic-biological features: Ph-like ALL ETP ALL NOTCH1/FBW7-unmutated/RAS/ PTEN-altered T-ALL IKZF1, CLRF2, MLL, TP53, CREBBP, RAS alterations	Mandatory Recommended for new clinical trials
MRD study		
MRD marker(s): LAIP (immunophenotype)/molecular probe (PCR)	MRD-based risk classification	Mandatory
Storage of diagnostic material		
Cell banking/storage of DNA/RNA/protein lysates	Additional/future studies	Highly recommended
HLA typing		
Patient/siblings	Early application of SCT if required	Recommended

Note: *ALL, acute lymphoblastic leukemia; CNS, central nervous system; MPO, myeloperoxidase; AML, acute myelogenous leukemia; c, cytoplasmic; IgM, immunoglobulin M; s, surface; Ig, immunoglobulin; FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase polymerase chain reaction; Ph+, Philadelphia-positive; TKI, tyrosine kinase inhibitor; CGH, comparative genomic hybridization; SNP, single nucleotide polymorphism; GEP, gene expression profiling; NGS, next-generation sequencing; Ph, Philadelphia; ETP, early T-cell precursor; T-ALL, T-cell ALL; MRD, minimal residual disease; LAIP, leukemia-associated immunophenotype; PCR, polymerase chain reaction; HLA, human leucocyte antigen; SCT, stem-cell transplantation.*

DIFFERENTIAL DIAGNOSIS

Acute myeloid leukemia (AML): In many cases, the leukemic cells of AML or biphenotypic ALL are poorly differentiated with minimal amount of cytoplasm. These cells are difficult to differentiate. In such case, bone marrow biopsy, peripheral blood smear, cytochemistry, and immunological marker may be helpful in establishing the diagnosis [1].

Reactive lymphocytosis («Leukaemoid reaction»): CMV infection and Bordetella pertussis infection may present with significant lymphocytosis. It could be differentiated by bone marrow aspiration and biopsy in which will be normal hematopoiesis. Immuno-phenotyping may show increased numbers of hematogones (normal reactive B-cell progenitors).

Small-cell lung cancer: It can be differentiated by chest X-ray (pulmonary mass), and biopsy.

Merkel-cell tumor: it can be differentiated also by biopsy. The Merkel cell exhibits immunocytochemical properties of both epithelial and neuroendocrine cells.

Rhabdomyosarcoma: It can be differentiated by immunohistochemically staining (IHC) or electron microscopy may provide evidence supporting myogenic differentiation. IHC can detect muscle-specific proteins.

Aplastic anemia: It can be differentiated by absence of blast cells in peripheral blood or leucoerythroblastic features [11]. Bone marrow aspiration and peripheral blood smear are helpful in differentiating diagnosis.

Idiopathic thrombocytopenic purpura (ITP): Childhood ITP may resemble the aleukaemic pancytopenic subtype of ALL. It can be differentiated by absence of blast cells in peripheral blood or leucoerythroblastic features. Bone marrow aspiration and peripheral blood smear are also helpful in differentiating diagnosis.

TREATMENT OF NEWLY DIAGNOSED ALL

Pre-phase therapy and supportive measures [1]**.** When the diagnosis is established, treatment should start immediately, preferably in a specialized hospital; that is, physicians with experience in the treatment of acute leukemia, a well-trained nursing staff, sufficient supportive care (e.g. platelet substitution) and access to an intensive care unit. A pre-phase therapy with corticosteroids (usually prednisone 20–60 mg/day or dexamethasone 6–16 mg/day, either IV or per os) alone, or in combination with another drug (e.g. vincristine, cyclophosphamide), is often given together with allopurinol and hydration for ~5–7 days. The first intra-thecal therapy for central nervous system (CNS) prophylaxis is administered in this period in some studies. The pre-phase therapy allows a safe tumor reduction, avoiding in most cases a tumor lysis syndrome (TLS). In some cases, rasburicase may be given to prevent TLS. In cases with a very high WBC count (e.g. >100000/µl), either measure is sufficient, and a leukapheresis is needed only in very rare cases. The time needed for pre-phase therapy will also allow obtaining the results of the diagnostic work-up, e.g. cytogenetics, molecular genetics. The response to pre-phase therapy defines the chemosensitivity of the disease, and is included in some studies for risk assessment, since good responders to prednisone may have a better outcome [7, 12].

Supportive therapy should be initiated whenever necessary early on, e.g. to treat infections or to substitute platelets/erythrocytes. Severe neutropenia (< 500/µl) is often seen at diagnosis and is most frequent (>80 %) during induction therapy, causing infections and infection-related death. A joint analysis of five randomized trials revealed a shorter duration of neutropenia, and reduction in the rate of febrile neutropenia in some but not all cases, and based on that, prophylactic granulocyte colony-stimulating factor should be considered during induction therapy.

Remission induction therapy and *consolidation [9, 13–18].* The goal of induction therapy is the achievement of a CR, or even better, a molCR/good molecular response, usually evaluated within 6–16 weeks from start of chemotherapy, after which time the achievement of molCR is rather uncommon. Most regimens are centered on vincristine, corticosteroids, and anthracycline (daunorubicin, doxorubicin, rubidazone, idarubicin), with or without cyclophosphamide or cytarabine. L-Asparaginase is the only ALL-specific drug that depletes the asparagine levels and has been particularly explored in pediatric trials. It is now more intensively used in adults. Pegylated asparaginase (PEG-Asp) has the advantage of a significantly longer period of

asparagine depletion. Dexamethasone is often preferred to prednisone, since it penetrates the blood–brain barrier and also acts on resting leukemic blast cells (LBCs). There are no randomized trials comparing different induction regimens; however, there is asubstantial number of large (> 100 patients) prospective nonrandomized trials. In 6617 patients from 14 studies, the weighted mean for the CR rate was 83 % (62–92 %). Using current approaches, the CR rate had increased to 80–90 %, higher for SR patients at ≥ 90 %, and less in HR patients at ~ 75%. There is only one randomized study for induction therapy; this compares prednisone to dexamethasone, demonstrating equal outcome.

There are two chemotherapy regimens; one is a widespread schema patterned after the pediatric BFM (Berlin–Frankfurt–Munster) protocols with Induction I, Induction II, Consolidation cycles, sometimes an intermittent re-induction cycle, and is mostly used in European adult ALL trials.

Another approach is to repeat two different alternating intensive chemotherapy cycles, identical for Induction and Consolidation, accounting for a total of eight cycles, such as the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) protocol, preferentially used in the United States, but also in other parts of the world.

The rationale to use systemic high-dose (HD) therapy is particularly to reach sufficient drug levels in sanctuary sites, such as the CNS. Most protocols employ 6–8 courses which contain either HD methotrexate or HD cytarabine ± asparaginase. HD cytarabine is usually administered for 4–12 doses at 1–3 g/m^2 and methotrexate at 1–1.5 g/m^2 and up to 3 g/m^2.

Maintenance therapy [9, 13–18]. Maintenance therapy usually consists of daily 6-ercaptopurine and weekly methotrexate. In some treatment regimens, repeated cycles of vincristine, dexamethasone or other drugs in monthly or longer intervals are given. In one randomized study, the maintenance arm with reinforcement cycles was not superior to conventional maintenance therapy (37 % versus 38 % at 8 years). Treatment duration of 2,5–3 years is optimal and is usually recommended.

Omission of maintenance worsens outcome significantly in BCP-ALL, but less so in T-ALL, and not in B-ALL.

CNS prophylaxis [19]. Effective prophylaxis to prevent CNS relapse is an essential part of ALL therapy. Treatment modalities of CNS prophylaxis are CNS irradiation, intra-thecal (i.th.) methotrexate, mono- or i.th. triple (usually methotrexate, steroids, cytarabine) and systemic HD therapy with either methotrexate and/or cytarabine. With a combination of these CNS prophylactic measures, the CNS relapse rate in recent adult ALL trials could be reduced from 10 % to < 5 %. CNS irradiation is also effective to eradicate residual LBCs in the CNS; however, in most studies, it is either omitted or restricted to HR patients. Furthermore, it is given only as an irradiation of the skull (mostly 24 Gy), and no longer of the whole neuroaxis, since this aggravates cytopaenias. Patients with CNS involvement (mostly of the leptomeninges) at diagnosis are treated with the standard chemotherapy regimen, and additional i.th. applications until blast clearance in the spinal fluid. Their OS is identical to the CNS-negative cohort of patients or slightly inferior.

AGE-ADAPTED PROTOCOLS

The outcome of ALL is strictly related to the age of a patient, with cure rates from 80 % to 90 % in childhood ALL, decreasing to < 10 % in elderly/frail ALL patients. Therefore, age-adapted protocols have emerged, where the age limits are mainly directed by the hematological and non-hematological toxicities. Although there is no uniform consensus, the following age groups are separated [9–10, 13–18]:

- Adolescents and young adults (AYA), differently defined from 15 to 40 years,
- Adult ALL, age range from 40 up to 60 years,
- Elderly ALL protocols for patients above the age of 60 years, and
- Frail patients not suitable for any intensive therapy, usually considered above the age of 75 years.

Pediatric-inspired therapy provides increased drug intensity at several treatment steps, including larger cumulative doses of drugs such as corticosteroids, vincristine, L-asparaginase and consequent CNS-directed therapy, which should be strictly adhered to, with a reduced role of SCT. In a systemic review and meta-analysis in 2012, in 11 trials including 2489 AYA patients, pediatric-inspired regimens were superior to conventional adult chemotherapy. None of the trials were a

randomized comparison. In recent studies for AYAs, survival rates at 5 years were 67–78 %, compared with 34–41 % with the former protocols.

The treatment results for adult ALL patients have also improved. In the above-mentioned 14 studies, the weighted mean for DFS was 34 % (25 % at 5 years, 48 % at 3 years) and the OS 38 % (27 % at 9 years, 54 % at 5 years). Currently, the OS rates for SR adult ALL patients is 50–70 % with chemotherapy alone. The outcome for HR patients has also improved, from 20–30 % to ~50 % when they receive an allogeneic SCT in CR1. Prospective adult studies applying the same drugs and time–dose intensity, using or not using the term 'pediatric-inspired', or some using the term 'pediatric-derived', achieved identical results compared with AYAs, with survival rates of 60–70 % or more.

The incidence of ALL is increasing after the age of 50 years. Different approaches have been applied in this patient cohort. Older patients (55–91 years) with a palliative treatment had a CR rate of 43 % (34–53 %), an early death rate of 24 % (18–42 %) and an OS of only 7 months (3–10 months). In contrast, those with an intensive chemotherapy designed for adult ALL had a CR rate of 56 % (40–81 %), but still an early death rate of 23 % (6–42 %), and an OS of 14 months (3–29 months). In recent decades, several elderly specific ALL protocols have been initiated. Their principle is a less intensive therapy, based on corticosteroids, vincristine and asparaginase, and largely avoiding anthracyclines and alkylating agents, to reduce early treatment-related death. In nine prospective studies for older ALL patients (55–81 years), with this less intensive protocol, the CR rate was 71 % (43–90 %), early death decreased to 15 % (0–36 %) and OS was significant at 33 months (16–71 months). Thus, all patients, irrespective of age, should be offered a treatment.

TREATMENT OF RELAPSED OR REFRACTORY ALL

Relapsed ALL in adults is still a major clinical challenge. There is no universally accepted treatment protocol and a lack of evidence based on randomized, controlled trials [1, 6, 13, 15, 20]. However, there is consensus on the general approach to managing these patients.

Therapy-related AML should be excluded. Enumeration of CD19, CD20 and CD22 expression on blast cells is important as it may have therapeutic relevance. Cytogenetic evaluation should take into account fusion proteins that may indicate a BCR-ABL like phenotype. If allogeneic SCT is a possible therapeutic option, and if this was not done at diagnosis, the HLA profiling of the patient and siblings should be carried out urgently, and an unrelated donor search should be initiated if a sibling match is not available. In the case of Ph+ ALL, BCR-ABL1 tyrosine kinase domain mutations should be evaluated.

Overall evaluation of the clinical situation should take into account the disease-specific factors (BCP-ALL or T-ALL, BCRABL1 status), patient factors (age, performance status, organ function and presence of extramedullary disease, in particular CNS), previous therapy (with particular reference to prior allograft, anthracycline dose) and specific toxicities of prior treatment which might guide therapeutic selection (e.g. osteonecrosis, vinca alkaloid neuropathy and specific infectious complications such as fungal infections).

Treatment with a curative aim involves achievement of CR followed by allogeneic SCT. In four large trials, the outcome was very similar. The rate of second CR achieved was 44–45 %, the median OS 4,5–8,4 months (24 % at 3 years in one study). Long duration of first CR (> 2 years), then re-induction with a standard induction regimen - such as that used for original treatment - may be used. Short first CR or primary refractory disease is a very high-risk situation, and consideration should immediately be given to the availability of trials of novel agents that may be non-cross-resistant with chemotherapy. For BCP-ALL, such agents are now more widely available. Both blinatumomab and inotuzumab have shown promising results in phase II studies and are being evaluated in randomized, controlled trials where the comparator arm is 'standard of care' chemotherapy. A clinical trial involving immunotherapy with CD19 CAR T-cell therapy is also a possibility.

The most commonly used regimens in Europe are fludarabine- and anthracycline-containing regimens, for example, FLAG-Ida (fludarabine, high-dose ara-C, granulocyte colony-stimulating factor and idarubicin). Despite its common use and inclusion as 'standard of care' arm in current randomized,

controlled trials of relapsed ALL, there is remarkably little published on FLAG-Ida in relapsed ALL. Clofarabinebased regimens including cytarabine, cyclophosphamide or etoposide are also commonly used based mostly on data in childhood ALL. Liposomal vincristine is licensed for the treatment of relapsed ALL. These standard chemotherapy approaches are applicable in BCP-ALL as well as in T-ALL.

Additionally, nelarabine is licensed for this indication, and a response rate of about 50 % is noted. Myelotoxicity is mild to moderate, but the neurotoxicity can be severe and irreversible. Co-administration with agents used to treat CNS disease can increase the risk.

Patients with relapsed Ph+ ALL should be offered the new generations of TKIs, according to the results of mutational analysis of their BCR-ABL1 transcripts. Patients who have lost response to imatinib may respond to nilotinib or dasatinib and there is even an option, ponatinib, for patients with the T315I mutation. Although TKIs are not without adverse events (ponatinib, in particular, carries a risk of cardiovascular events), they are nonetheless a vastly superior option compared with repetitive treatment with myelosuppressive chemotherapy, as they preserve performance status and are better tolerated by elderly

There is no evidence of long-term survival induced by TKIs post-relapse and the majority of patients will have to receive allogeneic SCT. Second allografts are being reported, and there are case reports of good outcomes, although of uncertain long-term benefit.

Even in a palliative setting BCR-ABL1, kinase domain mutational analysis should be carried out and used to guide therapy with TKIs and to monitor treatment response and impending relapse.

COMPLICATIONS

Patients with ALL are usually immuno-compromised. There are 2 reasons for this: the lack of healthy WBCs and many of the medicines used to treat ALL can weaken the immune system.

Other commonly observed complications include pancytopenia, febrile neutropenia, tumor lysis syndrome, chemotherapy related GI toxicity, treatment-related alopecia, leukostasis, ocular involvement, chemotherapy-related CNS toxicity, avascular necrosis, anthracycline-related cardiotoxicity, vincristine-related neuropathy, bleeding (intracranial, pulmonary, GI hemorrhage), infertility [2, 6–7, 12, 19].

PROGNOSIS

Acute lymphoblastic leukemia is a curable disease, and the chance of cure for a specific patient depends on a number of prognostic factors (females tend to fare better than males; Caucasians are more likely to develop acute leukemia than African-Americans, Asians, or Hispanics; children 1–10 years of age are most likely to develop ALL and to be cured of it; cases in older patients are more likely to result from chromosomal abnormalities, etc.

Outcome is heavily age dependent in adult ALL. For the age groups under 30 years, 30–60 years, and over 60 years, complete remission rates are 90 %, 81 % and 52 % and overall survival at 3 years is 58 %, 38 %, and 12 % respectively [2, 6].

The 5-year survival rate has improved from zero six decades ago, to 85 % currently, largely because of clinical trials on new chemotherapeutic agents and improvements in SCT technology.

An individual's risk depends on a variety of clinical and biological factors. Negative prognostic features include older age, elevated WBC at presentation above 100×10^9/L, failure to achieve complete remission within 4 weeks of treatment, adverse cytogenetic and immunophenotype abnormalities. Younger patients with WBC less than 30×10^9/L and who respond to treatment within 4 weeks have the best prognosis [7].

FOLLOW-UP AND LONG-TERM IMPLICATIONS

The follow-up of asymptomatic patients should include blood cell counts and routine chemistry during maintenance therapy; usually every 2 weeks during the first 2 years to adjust treatment accordingly. Thereafter, follow-up should be 3-monthly in years 1, 2 and 3, since the majority of relapses occur within the first 2,5 years after initiation of treatment; then half-yearly in the 4^{th} and 5^{th} year. For evaluation of MRD, which is now the most important prognostic parameter, bone marrow aspiration is required 3-monthly. It is also desirable in Ph+ MRD to search for MRD (BCR-ABL) and, if possible, for mutations to switch to another TKI inhibitor.

In adults, adverse long-term effects are fewer compared with children with ALL, and most adult ALL patients are in good clinical conditions. Relevant late toxicities are: endocrinological disorders (thyroid, gonadal), osteonecrosis/osteoporosis, skin and mucosal disorders, cataract, cardiovascular disorders, infection, graft versus host disease/sicca syndrome, fatigue and cognitive disorders. Second malignancies can also occur but with a low frequency (< 3 %) after chemotherapy as well as SCT. Long-term observation including quality-of-life assessment of cured ALL patients is an essential part of treatment optimization studies [1].

CONCLUSIONS [1]

Diagnostic work-up of ALL:

- Morphology, immunophenotype and cytogenetics to confirm the diagnosis and ALL subsets are mandatory.
- New genetics and molecular genetics are recommended to detect rare subtypes, such as Ph-like ALL, ETP ALL.
- Targets for therapy with TKIs or antibodies have to be identified.
- Minimal residual disease by immunophenotype or molecular probe at diagnosis, for MRD-based risk classification and treatment algorithm, mandatory.

Risk assessment and prognostic factors:

- It is essential to stratify patients as standard-risk or high-risk patients.
- Risk stratification is currently determined by a combination of prognostic factors at diagnosis and treatment-related parameters, preferentially MRD.
- MRD during therapy is now the most relevant prognostic parameter for treatment decisions.

Treatment:

- Chemotherapy includes induction therapy 1–2 months, consolidation cycles (alternating) 6–8 months and maintenance therapy 2–2,5 years.
- Ongoing chemotherapy protocols for AYAs use pediatric-type regimens.
- Prophylactic treatment to prevent CNS relapse is mandatory.
- Anti-CD20 rituximab in combination with chemotherapy is strongly recommended for Burkett leukemia/lymphoma.
- Anti-CD22 immunoconjugates directed against CD22 currently under investigation.
- Anti-CD19; activation of patients' own T cells directed against CD19.
- Bispecific (CD3/CD19) blinatumomab under investigation.
- Chimaeric antigen receptor-modified T cells directed against CD19 in early phase.
- A TKI should be combined with chemotherapy in front-line therapy.
- The TKI imatinib (400–800 mg/day) should be administered continuously, also post-SCT.
- Prolonged monitoring of BCR-ABL-1 MRD is recommended, as well as resistance mutation screening. In case of persisting MRD, increasing MRD level, or resistance mutation, switch to a second- or third-generation TKI.
- AlloSCT in CR1 significantly improves OS and EFS in high-risk patients/MRD+ patients and is the best post-remission option for Ph+ ALL and MLL-rearranged ALL.
- Conditioning regimens are age-adapted with full allo versus RIC for elderly patients or patients unfit for full conditioning.
- The role of autoSCT should be investigated for MRD-negative patients, in the setting of clinical trials.
- All patients in CR ≥ 2 are candidates for alloSCT.

Approach for relapsed/ refractory ALL:

- Full diagnostic work-up necessary to exclude/reveal clonal aberrations, and to provide bases for targeted therapies.
- Different treatment for patients with short versus long first remission duration (> 18/24 months) where re-induction is considered.
- Treatment; there is no standard re-induction therapy established, most often used new drugs.

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