22.4.2 Acute lymphoblastic leukaemia 5269 H. Josef

22.4.2 Acute lymphoblastic leukaemia 5269 H. Josef

Vormoor, Tobias F. Menne, and Anthony V. Moorman

22.4.2 Acute lymphoblastic leukaemia 5269 single cell with a rearranged antigen receptor locus. The pattern of gene rearrangement helps to characterize the lineage and stage of differentiation of the tumour. For example, pre-B-cell acute lympho- blastic leukaemia cells usually contain rearranged heavy-chain genes with germ-line light-chain genes, whereas B-CLL cells usually have a rearrangement of both heavy- and light-chain genes and ex- press surface immunoglobulin. Analysis as to whether the malig- nant lymphocytes have undergone somatic hypermutation also has prognostic significance in some diseases, such as CLL. The degree of genetic difference between the immunoglobulin heavy-chain gene in the malignant clone from germ-line sequence correlates with outcome in this disease, with an unmutated sequence being associ- ated with a poor prognosis. Furthermore, since clonal populations of lymphocytes all contain the same antigen receptor rearrange- ment, these cells possess a ‘molecular signature’ that is unique to the malignant clone. Consequently, antigen receptor rearrangements have become the target of DNA diagnostic techniques for diagnosing and following lymphoproliferative malignancies. Antigen receptor rearrange- ments can be detected largely by PCR-based techniques. For these studies, PCR is performed using oligonucleotide primers based on conserved sequences within the immunoglobulin heavy-chain locus; approximately 70 to 90% of rearrangements can be detected by this approach. To detect minimal residual disease with maximal sensitivity, such rearrangements are then subjected to sequence ana- lysis to determine the antigen-specific sequences unique to the tu- mour rearrangement. An allele-specific oligonucleotide can then be synthesized and used in a PCR analysis that can detect residual clonal populations representing as few as 1 in 105 cells. FURTHER READING Cooper MA, et al. (2006). Lymphocyte biology. In: Young

NS, Gerson SL, and High KA (eds) Clinical hematology, pp. 71–88. Elsevier, Philadelphia. Delves P, Roitt I (2000). Advances in immunology 1. N Engl J Med, 343, 37–49. Delves P, Roitt I (2000). Advances in immunology 2. N Engl J Med, 343, 108–17. Foon KA, Todd RF 3rd (1986). Immunologic classification of leukemia and lymphoma. Blood, 68, 1–31. Look A (1997). Oncogenic transcription factors in human acute leuke- mias. Science, 278, 1059–64. MacIntyre EA, Delabesse E (1999). Molecular approaches to the diag- nosis and evaluation of lymphoid malignancies. Semin Hematol, 36, 373–89. Rao DS (2017). Overview and compartmentalization of the immune system. In: Hoffman R, et al. (eds) Hematology: basic principles and practice, 7th edition, pp. 199–209. Elsevier, Philadelphia. Rose MG, Degar BA, Berliner N (2004). Molecular diagnostics of ma- lignant disorders. Clin Adv Hematol Oncol, 2, 650–60. Sell S (1996). Immunology, immunopathology, and immunity. Appleton & Lange, Stamford, CT. Strauchen J (1998). Diagnostic histopathology of the lymph node. Oxford University Press, New York. Wickremasinghe R, Hoftbrand A (1999). Biochemical and genetic control of apoptosis: relevance to normal hematopoiesis and hema- tological malignancies. Blood, 93, 3587–600. 22.4.2 Acute lymphoblastic leukaemia H. Josef Vormoor, Tobias F. Menne,
and Anthony V. Moorman ESSENTIALS Acute lymphoblastic leukaemia (ALL) is a malignant proliferation of lymphoid blasts, most commonly of B-lineage origin. The clin- ical symptoms and signs are either a consequence of bone marrow failure (infections, bruising, petechiae, pallor, and tiredness) or a consequence of the uncontrolled proliferation of the blasts (lymph- adenopathy, hepatosplenomegaly, and cranial nerve palsies). Its peak incidence is in young children but ALL occurs at all ages. More than 80% of all affected children are cured with modern chemotherapy, but unfortunately the outcome of adults is much worse despite some improvements led by the introduction of paediatric-inspired protocols and tyrosine kinase inhibitors in BCR-ABL1-positive ALL. Standard chemotherapy for ALL consists of several months of intensive multidrug induction, consolidation and intensification chemotherapy (including steroids, vincristine, asparaginase and anthracyclines), intrathecal methotrexate to target blasts in the central nervous system, and low-intensity maintenance therapy (with oral 6- mercaptopurine and methotrexate) for up to 3 years. Treatment is stratified according to the response and other prognostic biomarkers (including genetics). Allogeneic haematopoietic stem cell transplant- ation is used predominantly in the relapse setting for children but in frontline therapy for adult patients to consolidate chemotherapy. Novel targeted small molecules and, in particular, immunotherapy are promising to offer new treatment options for patients with high- risk or relapsed disease. Introduction The treatment of acute lymphoblastic leukaemia (ALL) in children constitutes one of the success stories of modern medicine. A le- thal disease in the 1960s, now over 80% of affected children are cured. Initially, single agents, such as methotrexate, pioneered by Sidney Farber, were used to achieve temporary remissions. The big breakthrough, however, came with the introduction of multidrug chemotherapy to prevent the evolution of chemotherapy-resistant subclones, combined with therapy targeting leukaemia cells in the brain (craniospinal irradiation). These approaches were pioneered and optimized by the first generation of physicians specializing in childhood leukaemia, including Donald Pinkel in the United States of America and Hansjörg Riehm in Europe. Both initially faced major resistance in the medical community, which widely believed that children with cancer should be palliated rather than exposed to experimental therapies. Paediatric haematology and oncology underwent a steep learning curve as the intense treatment caused toxic side effects, in particular life-threatening infections. Learning to manage these side effects and developing supportive care played

section 22 Haematological disorders 5270 a key role in facilitating the improvement in outcomes for children with ALL. More recently, stratifying therapy according to predictive biomarkers (genetics) and response to treatment has allowed further tailoring of management. This personalized or stratified approach has been the basis for further improvement in outcomes for slow re- sponders and a reduction of toxicity in low-risk patients. Treatment of ALL in adults has proven to be more challenging, partly as the leukaemias are more resistant to chemotherapy and partly as there is a reduced treatment tolerance particularly in eld- erly patients. However, the introduction of paediatric-inspired protocols for young adults, the introduction of tyrosine kinase in- hibitors in the treatment of BCR-ABL1-positive ALL, and improved supportive care have all led to significant improvements in the sur- vival and cure rate for adult patients. Novel targeted therapies and, in particular, the successful introduction of immunotherapy into the treatment of ALL promise to further improve the treatment of this condition. This spectacular progress in the treatment of ALL is underpinned by decades of research that have increased our understanding of the origin, key drivers, and genomic complexity of the different types of ALL. Epidemiology and pathogenesis ALL occurs at all ages but is more prevalent among children than adults and, importantly, accounts for a much higher proportion of cancers in that age group. In the United Kingdom, approximately 600 new patients are diagnosed each year with over 50% of cases occurring in patients less than 15 years old. The incidence of ALL among younger children aged between 1 and 4 years is at 6 to 7 per 100 000 per year, and this is often referred to as the ‘childhood peak’. The incidence in infants and older children is 2 to 3 per 100 000/year and drops to 1 to 2 per 100 000/year among adults. Although the precise aetiology of ALL remains unknown, it is now clear that several factors play a role in causation, including chance, exogenous exposures, endogenous exposures, and the individual’s genetic background. Epidemiological and laboratory-based studies indicate a two-stage process. The initial step is the development of a preleukaemic clone which arises when a normal cell acquires a genetic abnormality, often a chromosomal translocation, as the re- sult of a random error in DNA replication. The preleukaemic clone can lie dormant for several years but is susceptible to the acquisition of additional genetic or epigenetic abnormalities that promote de- velopment of the disease and the onset of symptoms. In childhood ALL, it has been demonstrated by elegant twin and back-tracking studies that this first stage occurs in utero in the majority of cases. A number of exogenous (e.g. infections, chemicals, and radiation) and endogenous (e.g. inflammation) factors have been postulated as potential triggers in the development of full-blown leukaemia. However, conclusive proof remains elusive because individuals har- bouring a silent preleukaemic clone will be more susceptible to these risk factors compared to other individuals. The role of infections has been explored extensively due to the existence of the childhood in- cidence peak and spatiotemporal leukaemia clusters. Two major hy- potheses exist in this area: Kinlen’s population mixing and Greaves’ delayed infection hypotheses. The key concept underlying these hypotheses is the unusual or abnormal response to an infection or infections not previously encountered by the individual due to mi- gration or the modern lifestyle. There is increasing evidence that an individual’s inherited genetic background plays a role in the development of ALL. Patients with Down syndrome are approximately 40 times more likely to develop ALL between the ages of 0 to 4 years compared to other children. More recently, genome-wide association studies (GWAS) have iden- tified several allelic variants that are significantly associated with an increased likelihood of developing ALL, including single nucleotide polymorphisms (SNP) in the IKZF1, ARID5B, CEPBE, CDKN2A/ B, and ETV6 genes. Of note most of these genes are also somatically altered in ALL. For example, 25% of children with ALL have ETV6-RUNX1 fusion (Table 22.4.2.1) while approximately 40% of cases harbour CDKN2A/B deletions.

A causative role for an individual's genetic make-up is further supported by observations that more than 50% of Down syndrome-ALL patients harbour CRLF2 deregulation which occurs in just 5 to 10% of non-Down syndrome ALL children; patients with a Robertsonian der(15;21)(q10;q10) translocation are over 2700 times more likely to develop intrachromosomal amplifi- cation of chromosome 21 (iAMP21) ALL and approximately 40% of individuals with low hypodiploidy have a germline mutation in the TP53 gene. The pathogenesis of ALL is directed by the accumulation of one or more driver mutations each of which enhances the tumour cap- ability of the preleukaemic clone until eventually the clone expands and develops into overt acute leukaemia. The vast majority of pa- tients will harbour a single primary genetic abnormality, which initiates the oncogenic process, coupled with one or more cooper- ating mutations. Primary chromosomal abnormalities are typically translocations or gross aneuploidy and frequently affect leukaemia-specific pathways such as B/T-cell development and differentiation. Table 22.4.2.1 describes the key primary genetic abnormalities that have been described in ALL. In childhood ALL, ETV6-RUNX1 and high hyperdiploidy together account for approximately 50% of cases whereas the most prevalent abnormality in adult ALL is BCR-ABL1 fusion accounting for approximately 25% (Fig. 22.4.2.1). These pri- mary genetic lesions are clonal (i.e. present in all leukaemic cells) and pathognomonic of ALL; hence their identification at diagnosis is key for effective treatment stratification (see later). Despite this key role, few of these abnormalities are sufficient to cause clinical disease and are usually accompanied by one or more additional abnormalities. The spectrum of additional aberrations is broad and over 30 genes have been implicated. In contrast to the pri- mary abnormality, secondary lesions are typically deletions, often microdeletions, or sequence mutations. The most prevalent sec- ondary aberrations are deletions of CDKN2A/B, IKZF1, and PAX5, and mutations of RAS pathway genes (e.g. KRAS and NRAS). There is a strong correlation between specific primary abnormalities and the spectrum of secondary lesions indicating epistatic interactions between the affected genes. Examples of cooperation between pri- mary and secondary lesions include (1) loss of the nontranslocated ETV6 allele in 60 to 70% of cases with ETV6-RUNX1 fusion; (2) acti- vating RAS pathway mutations in approximately 50% of cases with high hyperdiploidy; (3) deletion of IKZF1 in 80% of cases with BCR- ABL1 fusion; and (4) CDKN2A/B deletion in 80 to 90% of T-cell ALL (T-ALL) cases. Secondary genetic abnormalities are, by definition, subclonal and hence are present in less than 100% of leukaemic cells. Minor subclones accounting for 1% of leukaemic cells have been

 detected with highly sensitive assays and ultra-deep next-generation sequencing may well identify even smaller subclones. The number of subclones present in each patient is difficult to determine accur- ately but all the available evidence indicates widespread genetic het- erogeneity with the majority of patients harbouring several (two to four) subclones and some with numerous subclones (more than five). Importantly, cell-based and sequencing studies have demon- strated that the same gene can be mutated/deleted independently in different subclones; further supporting the notion that secondary lesions actively cooperate with the primary abnormality to drive leukaemogenesis. Although the vast majority of patients with ALL (>90%) will achieve a complete remission, relapse does occur and is the leading cause of death. Therefore, identifying the genetic drivers of relapse is a key clinical and scientific challenge. Numerous genomic studies have attempted to determine the clonal origins of relapsed disease by comparing the genomic landscape relapse and initial presentation. Several key concepts have arisen from these studies: (1) the primary genetic abnormality is almost always retained at relapse; (2) the dominant leukaemic clone at relapse is usually present at diagnosis as

a major or minor subclone; and (3) the spectrum of abnormal- ities present at relapse is similar to that observed at initial diagnosis. Therefore, for the majority of relapsed patients it is likely that the relapse emerges via the natural selection of a pre-existing clone or clones under the evolutionary pressure of chemotherapy. The rare exceptions to this scenario are very late recurrences which are gen- etically unrelated to the presentation clone. These ‘relapses’ are likely to represent secondary ALL and have a strong germline compo- nent. Whether or not all genetic abnormalities observed at relapse are also present at initial diagnosis—as opposed to being induced by therapy—is a matter of debate. Currently our knowledge is limited by the sensitivity of the available assays. There are no truly relapse- specific mutations or abnormalities. However, mutations in TP53, CREBPB, NT5C2, and NR3C1 are more prevalent at relapse than ini- tial diagnosis. Moreover, they have been linked to resistance to spe- cific therapies: NT5C2 and nucleoside analogues, NR3C1/CREBPB, and glucocorticoids. There is a growing body of evidence suggesting a link between the presence of specific mutations at relapse and the Table 22.4.2.1 Immunophenotypic and genetic classification of acute lymphoblastic leukaemia Primary/class-defining abnormality Description Frequency Relative prognosis B-cell precursor ALL High hyperdiploidy 51–65 chromosomes 30% children, 10% adults Very good ETV6-RUNX1 t(12;21)(p13;q22) 25% children, 1% adults Very good TCF3-PBX1 t(1;19)(q23;p13) 3–6% Intermediate/good KMT2A (MLL) translocations Gene fusions involving different partner genes including AFF1 (AF4), MLLT1 (ENL), MLLT4 (AF6), MLLT3 (AF9), MLLT10 (AF10) 80% infants, 2% children, 10% adults Poor/very poor BCR-ABL1 t(9;22)(q34;q11.2) 2% children, 25% adults Very poor unless treated with tyrosine kinase inhibitors TCF3-HLF t(17;19)(q22;p13) <1% Extremely poor Near haploidy <30 chromosomes 1–2% children Extremely poor Low hypodiploidy/near triploidy 30–39/60–78 chromosomes 1–2% children, 5% adults Extremely poor iAMP21 Intrachromosomal amplification of chromosome 21q22.11–21q22.12 2–3% children Very poor unless treated as high risk Emerging subgroups of B-other ALL ERG deletions Expression of ERG isoforms 3–5% Very good IGH translocations Overexpression of various partner genes including members of the CEBP gene family and ID4 3–5% Intermediate/poor JAK–STAT pathway activation IGH-CRLF2, P2RY8-CRLF2, CRLF2 mutations, JAK2 mutations and translocations, IGH-EPOR 5–10% Intermediate/poor ABL-class fusions Rearrangements of ABL1, ABL2, PDGFRB and CSF1R with numerous partner genes, e.g. EBF1-PDGFRB 1–2% Poor T-cell ALL TAL/LMO Overexpression of TAL1, LM02 and related genes. Common rearrangements—SIL-TAL1, t(1;14)(p32;q11)/TRAD-TAL1 c.40% Good TLX3 Overexpression of TLX3. Common translocation—t(5;14) (q35;q32)/BCL111B-TLX3 c.25% Variable TLX1 Overexpression of TLX1, NKX2-1, and related genes. Common rearrangements: t(10;14)(q24;q11)/TCRAD-TLX1 c.15% Good HOXA Rearrangements resulting in HOXA deregulation e.g. KMT2A (MLL) translocation, CALM-AF10 fusion c.10% Variable Immature Rearrangements and mutations associated with an immature T-cell phenotype, e.g. MEF2C fusions c.10% Poor

 frontline treatment protocol indicating that some protocols may preferentially select or induce subclones carrying specific mutations. Clinical features/differential diagnosis The clinical features of ALL are mainly a consequence of the failure of normal haematopoiesis. In addition, local infiltration and expan- sion of the leukaemic blasts can cause pathology. Patients usually present with the symptoms and signs shown in Box 22.4.2.1. This clinical picture of bone marrow failure and the consequences of local leukaemic infiltration explain the differential diagnosis which consists of other types of leukaemia (including acute mye- loid leukaemia, chronic lymphoid leukaemia, and chronic mye- loid leukaemia); other causes of bone marrow failure (including myelodysplastic syndromes, drug-induced, aplastic anaemia, and

inherited bone marrow failure syndromes); rarely other ma- lignancies with widespread bone marrow infiltration (sarcomas, desmoplastic round cell tumours, and non-Hodgkin lymphoma or neuroblastoma,); other causes of bony pain (in particular, rheuma- toid arthritis and osteomyelitis); and idiopathic thrombocytopenic purpura. Clinical investigations If leukaemia is suspected, the investigations listed in Box 22.4.2.2 are routinely performed to establish or exclude the diagnosis and presence of leukaemia-related complications. If these investigations confirm or suggest a diagnosis of leukaemia is likely then a haematological opinion is required to discuss further investigations and initial management. Further leukaemia-specific investigations are listed in Box 22.4.2.3 and illustrated in Fig. 22.4.2.2. 100% 90% 80% 70% 60% 50% 40% 30% Estimated frequency 20% 10% 0% <1 1–9 10–14 15–19 Age at diagnosis (years) 20–24 25–39 40–59 60+ B-other IGH translocation TCF3-PBX1 BCR-ABL1 Low hypodiploidy/near haploidy iAMP21 KMT2A/MLL translocation High hyperdiploidy ETV6-RUNX1 Fig. 22.4.2.1 Age-specific frequency of key primary chromosomal abnormalities in B-cell precursor acute lymphoblastic leukaemia. Box 22.4.2.1 Symptoms and signs of acute lymphoblastic leukaemia • Weakness, lethargy, pallor—due to insufficient production of red cells (anaemia). • Petechiae, nose and gum bleeding—due to insufficient production of platelets (thrombocytopenia). • Febrile infections, sometimes with an unusual or prolonged course— due to insufficient production of immune cells, including granulocytes (neutropenia). • Lymphadenopathy (particularly cervical), hepatosplenomegaly—due to leukaemic expansion in lymphoid organs. • Bone pain—most likely as a consequence of osseous and periosteal leukaemic infiltration although the mechanism is poorly understood. • Painless testicular swelling—a consequence of leukaemic infiltration. • Superior vena cava syndrome with distension of the external jugular veins, facial and neck swelling, shortness of breath, cough—due to thymic enlargement (T-cell leukaemia). • Abdominal pain—due to hepatosplenomegaly (tension of the liver capsule) or abdominal lymph node enlargement. • Cerebral nerve palsies (including facial numbness), headache, meningism—due to CNS leukaemia (rare). • Other rare clinical presentations—hypoxia, confusion due to leucostasis (very high WCC >>100 × 109/litre); visual disturbances due to retinal infiltration or haemorrhage.

22.4.2 Acute lymphoblastic leukaemia 5273 Treatment Initial management The initial management steps should include transfer of the patient to the nearest specialist centre. Immediate treatment with broad- spectrum antibiotics should be considered (after taking appropriate samples for culture) in febrile patients or those with a suspected infection. Transfusion may be required, depending on symptoms and blood counts, but caution is advised in patients with espe- cially high white cell counts (WCCs) due to the risk of developing hyperviscosity syndrome. The presence of a large mediastinal mass is a clinical emergency as it can cause superior vena cava syndrome and/or tracheal obstruction very quickly. These patients should not be sedated or anaesthetized and—if possible—biopsy of the mass should be avoided: diagnostic samples can often be obtained from pleural or pericardial effusions, which are commonly present. Bone marrow examination may also confirm a diagnosis of T-lineage ALL. If the patient is very symp- tomatic, then it may be necessary to commence steroid therapy prior to establishing a diagnosis. The development of tumour lysis syndrome needs to be avoided; hence, it is important to monitor electrolytes and kidney function while giving appropriate hydration and allopurinol. In patients with a high WCC or with a large mediastinal mass, the administration of rasburicase, a recombinant urate oxidase, should be considered. All patients with ALL who undergo intensive chemotherapy will require central venous line access, mostly port catheters in children and Hickman lines or peripherally inserted central catheters in adults. Current multidrug chemotherapy Multidrug combination chemotherapy

including steroids, vincris- tine, asparaginase, daunorubicin or doxorubicin, cytarabine, cyclo- phosphamide, methotrexate, 6-mercaptopurine, and etoposide is the backbone of any successful therapy for patients with ALL. ALL treatment protocols take 2 to 3 years and are some of the most com- plex chemotherapy regimens in haemato-oncology. Most modern treatment protocols are risk stratified, based on WCC at presenta- tion, genetics, age, and response to therapy assessed by morpho- logical bone marrow appearance and minimal residual disease (MRD) status. Modern treatment protocols will utilize these risk factors to assign patients to risk groups each of which will receive different treatment. The precise definitions of risk groups vary from one protocol to the next. The key elements of modern ALL therapy can be divided into sev- eral discrete phases and most ALL patients will be treated following standardized national treatment protocols (Fig. 22.4.2.3). Induction phase The main aim of this 4- to 6-week long chemotherapy block is to achieve morphological and molecular remission. This treatment cycle includes steroids, vincristine, and asparaginase, which are the three most useful induction agents for ALL. Based on recent evi- dence, dexamethasone appears to be more effective in inducing apoptosis of B-cell blasts compared to prednisolone and has a higher penetrance into brain tissue. While dexamethasone is still given continuously for 28 days in most childhood ALL protocols, in adult ALL protocols pulsed courses of dexamethasone are becoming the standard of care to reduce steroid toxicity. Asparaginase significantly reduces intracellular and circulating asparagine levels in ALL blasts leading to apoptosis of the ALL blasts. At the end of the induction block, nearly all children will achieve complete remission whereas in adults the rate is around 80 to 90%. Importantly, this is not a cure and the disease will nearly always relapse if no further therapy is given. Consolidation phase/intensification phase To prevent relapse in the central nervous system (CNS) and to consoli- date remission, patients undergo several more intensive combination chemotherapy phases lasting in total 6 to 8 months. In each of the blocks the chemotherapy varies and new drugs are introduced aiming to pre- vent development of chemoresistance in the remaining leukaemic blasts. Maintenance therapy After patients have completed the intensive chemotherapy phases, treatment is commenced with low-dose maintenance therapy con- sisting of daily oral mercaptopurine and weekly oral methotrexate for 18 to 30 months. Patients might also receive periodic intravenous vincristine and short courses of oral glucocorticoids. The aim of this phase is to suppress and kill any persisting leukaemic blasts. Significant shortening of maintenance length or reduced compliance with daily administration of 6-mercaptopurine leads to higher relapse rates. Box 22.4.2.2 Routine investigations in patients with possible leukaemia • Careful history and clinical examination, including testicular examination • FBC and blood film—to check for presence of circulating leukaemia blasts • Clotting screen • Liver function tests, lactate dehydrogenase, and C-reactive protein • Urea, creatinine, K, Ca^{2+}, PO_4^{3-}, uric acid—to check for evidence of tumour lysis syndrome • Chest radiography—to exclude presence of mediastinal mass Box 22.4.2.3 Specific investigation of patients with leukaemia • Bone marrow aspirate and biopsy—for cytology and histology. • Genetic analysis including G-banding cytogenetics and fluorescence in situ hybridization (FISH) on bone marrow aspirate or peripheral blood sample analysis—to identify low- and high-risk patients (Table 22.4.2.1). • Flow cytometric immunophenotyping of the leukaemia—to determine lineage and maturation stage (e.g. B-cell precursor ALL, T-ALL, mature leukaemia). • Leukaemia-specific immunoglobulin or T-cell receptor gene re- arrangements may be identified by a PCR-based method or the leukaemia-associated immunophenotype is identified using multi- colour flow cytometry—for future minimal/measurable residual disease (MRD) monitoring of disease response. • Lumbar puncture—to exclude central nervous system (CNS) involvement. • Magnetic resonance imaging of the head and/or spine—if the patient has

neurological symptoms at presentation. • If mediastinal mass is present—staging computed tomography (CT) or positron emission tomography (PET)/CT scan of neck, chest, ab- domen and pelvis is indicated.

section 22 Haematological disorders 5274 Fig. 22.4.2.2 Patient with infant B-cell ALL presenting with a high WCC. (a) Blood film showed presence of lymphoid blasts with high nucleocytoplasmic ratio. (b) Immunophenotyping plots shows presence of CD19+, CD79a+, terminal deoxyribonucleotidyl transferase (TdT)+,
CD15+ and CD117– cells in keeping with B-ALL. (c) Cytogenetic analysis depicts a t(4:11) translocation with the long arm of chromosome 4 being translocated to chromosome 11 leading to the generation of MLL-AF4 fusion protein. (d) Fluorescence in situ hybridization confirms rearrangement of MLL (red arrows cells with rearranged MLL; yellow arrow cells with wildtype MLL). Break Apart Rearrangement Probe used to check for MLL rearrangement (see inset). ALL protocol for children and young adults ALL protocol for adults Standard-risk patients Intermediate-risk patients High-risk patients High-risk patients 0 5 10 15 20 25 30 35 weeks Standard-risk patients Fig. 22.4.2.3 Outline of ALL treatment protocols for clinical risk group as per current UKALL2011 trial for children and young adults and UKALL14 trial for adults.

22.4.2 Acute lymphoblastic leukaemia 5275 Central nervous system-directed prophylaxis/therapy In the 1950s and 1960s, relapses in the CNS after completion of ALL therapy were common and were explained by the fact that the blood– brain barrier prevented chemotherapy reaching adequate concentration levels in cerebrospinal fluids. Therefore, cranial or craniospinal irradi- ation was introduced and was administered to all patients with ALL. This step dramatically improved overall survival in the 1960s and 1970s, but unfortunately came at a cost of significant long-term toxicity including cognitive impairment, decreased growth, endocrinopathies, and sec- ondary brain tumours. Over the last two decades, most ALL protocols have gradually eliminated cranial irradiation and have replaced it suc- cessfully with more intensive CNS prophylaxis including frequent ad- ministration of intrathecal methotrexate. As methotrexate crosses the blood–brain barrier effectively, many ALL protocols will include several high-dose methotrexate infusions followed by folinic acid ‘rescue’ to avoid increased methotrexate-related toxicity to normal tissue. Treatment of BCR-ABL-positive ALL and BCR-ABL-like ALL The management of BCR-ABL-positive ALL was very challenging prior to the discovery of BCR-ABL1 tyrosine kinase inhibitors (TKIs) such as imatinib and related agents. Since the introduction of TKIs, complete remission rates post induction close to 100% have been reported in adults and children even with reduced cytotoxic therapy, and the overall survival has doubled. Consequently, in children, the need for allogeneic haematopoietic stem cell transplantation in first remission has dimin- ished. This is in contrast to adult patients where allogeneic haemato- poietic stem cell transplantation is still advocated in first remission. Many patients with BCR-ABL-positive ALL will relapse and frequently acquire point mutations in the BCR-ABL1 oncoprotein especially the T315I mutation within the ABL kinase domain. These mutations confer resistance to first- and second-generation TKIs. Currently, ponatinib, a third-generation TKI, which has significant activity against wild-type and most mutant forms of BCR-ABL1 tyrosine kinase has been ap- proved for patients who have failed second generation TKI or who have acquired a T315I mutation. BCR-ABL-like ALL has a gene expression profile very similar to BCR-ABL-positive ALL and is also associated with a poor prognosis. This entity is present in approximately 10 to 15% of children and adults. In these cases, the leukaemic blasts harbour gen- etic alterations, which activate kinase and JAK–STAT signalling (Table 22.4.2.1).

Importantly, ongoing studies, in vitro data, and anecdotal re- ports suggest that patients with ABL-class fusions and JAK–STAT ab- normalities can be targeted by TKIs and JAK2 inhibitors. Treatment of relapsed/refractory ALL Until recently the outlook for relapsed ALL in adult patients was poor with standard fludarabine based salvage chemotherapy. However, in the last few years, significant inroads have been made and several novel compounds have been approved in the USA and Europe for the treat- ment of relapsed/refractory ALL. These include antibodies targeting B-lymphoid-specific antigens such as CD19 or CD22, and modified T cell therapies. Two antibodies have been shown to be superior to standard salvage chemotherapy in large phase 3 studies. Inotuzumab ozogamicin, an antibody–drug conjugate targeting CD22, delivers the potent cytotoxic agent calicheamicin to CD22 expressing cells indu- cing DNA damage and apoptosis. The bispecific T-engager (BiTE) blinatumomab binds to CD3 and CD19 simultaneously, bringing CD3 expressing T cells in close proximity to CD19 expressing B-ALL cells leading to activation of T cells with subsequent cytotoxic activity on the target cells. Both of these compounds achieve good responses and measurable residual disease negativity. Furthermore, blinatumomab is used to treat patients with B-ALL, who have achieved complete remis- sion but still have presence of measurable/minimal residual disease. In contrast, children who have a late first relapse have a high re- mission rate after salvage therapy and an overall survival of 60%. Patients who relapse early have a 50 to 70% chance of regaining re- mission and have an overall survival of 20 to 30%. Most patients in second complete remission will undergo myeloablative allogeneic haematopoietic stem cell transplantation to consolidate their remis- sion. MRD monitoring can be used to help with the decision process. In 2017, tisagenlecleucel a chimeric antigen receptor CAR-T cell therapy targeting CD19-positive cells was approved by the FDA for patients up to 25 years of age with B-ALL that is refractory or in second or later relapse. Autologous T cells from the patient are gen- etically modified to kill leukaemic blasts and then reinfused into the patient. CAR T cell therapies have significant toxicities (causing cytokine release syndrome and neurotoxicity). The initial response rates are very good and durability of remissions are very promising but relapses with novel immunological relapse mechanisms have been observed (e.g. loss of the epitope in the CD19 protein that is recognized by both the currently used antibodies and chimeric T-cell receptors). Relapses post CAR-T cell infusions are more diffi- cult to manage and survival figures become poor. Role of allogeneic haematopoietic stem cell transplantation In children, allogeneic haematopoietic stem cell transplantation is usu- ally not recommended in first remission but is of significant benefit in patients who attain a second complete remission after relapse. The role of allogeneic haematopoietic stem cell transplantation in patients with high-risk disease (e.g. BCR-ABL-positive ALL and infant ALL with KMT2A rearrangements) in first remission remains controversial. In adults, the poor outcome after relapse has changed the strategy over the last few years and patients regarded to be at high risk for re- lapse (e.g. patients with high-risk genetics such as BCR-ABL positive ALL and those with complex cytogenetics, or MRD positivity after the first or second block of chemotherapy) will typically undergo an allogeneic haematopoietic stem cell transplant in first remis- sion. This improves overall survival by 10 to 20%. Reduced-intensity conditioning is used in adults older than 40 years, whereas a myeloablative allogeneic haematopoietic stem cell transplantation is preferred in children and younger adults. The antileukaemic benefit of allogeneic haematopoietic stem cell transplantation is attributed to two factors: high-dose chemotherapy with or without total-body irradiation conditioning regimens and the graft-versus-leukaemia effect of donor cells against recipient malignant cells. Management of ALL in elderly patients The treatment of elderly patients is difficult and very little progress has been made over the last decades. The expected 5-year overall survival is between 5 and 10%. This poor outcome reflects the pro- portion

of elderly patients with ALL who have either BCR-ABL1 positivity or other high-risk genetics, but also highlights the diffi- culty elderly patients have in tolerating intensive ALL chemotherapy protocols, Hence, the focus over the last years has become more se- lective. Elderly patients who are fit enough will be considered for a

section 22 Haematological disorders 5276 more intensive approach including allogeneic haematopoietic stem cell transplantation. However, the majority of elderly patients will receive specifically designed less intense chemotherapy protocols, which have a chance of cure but at the same time are not too toxic; thus, the treatment can be administered in outpatient settings with reduced hospitalization in order to provide improved quality of life. Prognosis/outcome Without treatment, ALL is fatal and its treatment is one of the success stories of modern medicine (Fig. 22.4.2.4). There are five key risk factors predicting treatment response: age, sex, immuno- genetic subtype, initial disease burden, and response to therapy. Age is one of the main risk factors and, with the exception of infants (<1 year), risk increases with age. Traditionally, males have had a greater risk of relapse compared to females, largely due to the risk of testicular relapse. However, modern protocols which sometimes prolong the length of maintenance therapy for boys now rarely re- port major differences in outcome by sex. Initial disease burden is also an indicator of relapse risk and overall survival. High levels of burden are indicated by a high WCC, the presence of CNS dis- ease, and the infiltration of the lymph nodes, spleen, and liver. Age and disease burden form the basis for the widely used paediatric National Cancer Institute (NCI) risk score (NCI risk: age <1 year (infant leukaemia), age ≥10 years, and a high WCC ≥50 × 109/litre). Immunophenotype and acquired genetic abnormalities, which are tightly related, are key predictors of outcome (Table 22.4.2.1). In childhood B-cell precursor (BCP) ALL, there are two well-established good-risk abnormalities—ETV6-RUNX1 and high hyperdiploidy— along with six high-risk abnormalities—KMT2A translocations, BCR- ABL1, TCF3-HLF, near haploidy, low hypodiploidy, and iAMP21 (Fig. 22.4.2.1). The age-specific frequency of these abnormalities likely explains some of the risk associated with age (Figs. 22.4.2.5 and 22.4.2.6). Among children, T-ALL is associated with a poorer outcome whereas in adults it is associated with a lower risk of relapse. The underlying genetics of T-ALL is less age related than in BCP-ALL and this is likely to explain the difference in relative risk. In adult ALL, although the distribution of genetic abnormalities is different, there are also strong prognostic genetic markers. The most important risk factor is the response to initial treat- ment. Traditionally, this has been measured by morphological examination of early bone marrow samples to assess the propor- tion of blasts remaining after treatment has been initiated or by clearance of blasts in the peripheral blood after 1 week of steroid treatment. However, this is a crude measurement and has now been superseded by MRD monitoring, which utilizes polymerase chain reaction (PCR) or flow cytometry assays to quantify the size of the leukaemic clone at predefined time points after therapy. PCR can be used to track clone-specific physiological rearrangements of the Ig or TCR gene loci or leukaemia-specific gene fusions (e.g. BCR-ABL1). Alternatively, flow cytometry can be used to track the presence and abundance of a leukaemia-associated aberrant immunophenotypic profile. These assays are able to detect very low- level leukaemic clones (up to 1 leukaemic cell out of 10 000–100 000 bone marrow cells). The greater the rate of disease clearance at key 100% 90% 80% 70% 60% 50% 40% 30% 20% 10% 0% UKALLVIII (1980–85) UKALLX (1985–90) UKALLXI (1990–97) UKALLXII (1993–2006) UKALLXA (1985–1992) ALL97/99 (1997–2002) ALL2003 (2003–10) EFS OS Fig. 22.4.2.4 Improvement in event-free (EFS) and overall survival (OS) for patients with acute lymphoblastic leukaemia treated on successive United Kingdom clinical trials.

120 100 80 60 40 20 0 00 to 01 01 to 04 05 to 09 10 to 14 15 to 19 20 to 24 25 to 29 30 to 34 35 to 39 40 to 44 45 to 49 Age at diagnosis Rate per 100 000 Average number of cases per year 50 to 54 55 to 59 60 to 64 65 to 69 70 to 74 75 to 79 80 to 84 85 to 89 90+ 0 1 2 3 4 5 6 Male Cases Female Cases Male Rates Female Rates Fig. 22.4.2.5 United Kingdom incidence of ALL in 2010 to 2012: average number of new cases per year and age-specific incidence rates
per 100 000 population. The main incidence peak is between years 2 to 4. Data from Cancer Research UK, 'Acute lymphoblastic leukaemia (ALL) incidence statistics', available from: http://www.cancerresearchuk.org/health-professional/ cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-One (accessed December 2015). 1.00 0.75 0.50 Event-free survival 0.25 0.00 0 1 2 3 Years from diagnosis 4 5 BCP-ALL Cytogenetic Good Risk BCP-ALL Cytogenetic Intermediate Risk BCP-ALL Cytogenetic High Risk T-ALL Fig. 22.4.2.6 Event-free survival of children and young adults (1–24 years) treated on UKALL2003 stratified by immuno-genetic subgroup. Data courtesy of Dr Nick Goulden and Professor Ajay Vora, UKALL2003 trial coordinators.

1.00 End of induction MRD level 0% <0.01% <0.1% <1% <10%

> 10% 0.75 0.50 0.25 0.00 0 1 2 3 Years from diagnosis Relapse rate 4 5
> Fig. 22.4.2.7 Relapse rate of children and young adults (1–24 years) treated on UKALL2003 stratified by the end of induction minimal residual disease (MRD) level. Data courtesy of Dr Nick Goulden and Professor Ajay Vora, UKALL2003 trial coordinators. 1.00 0.75 0.50 0.25 0.00 0 2 4 6 Years Overall survival 8 10 Good risk Intermediate risk I Intermediate risk II High risk t(9;22)/BCR-AB/1 Fig. 22.4.2.8 Outcome heterogeneity among adult patients (25–59 years) with ALL by genetic subtype. Definition of risk groups: Good risk, high hyperdiploidy; intermediate risk I, B-other, iAMP21; intermediate risk II, IGH translocations, CRLF2 rearrangements, IKZF1 deletions, TCF3- PBX1; high risk, BCR-ABL1, KMT2A-AFF1, low hypodiploidy, complex karyotype. Data courtesy of Professors Adele Fielding, Tony Goldstone and Jacob Rowe, UKALLXII trial coordinator.

time points (usually end of induction), the lower the likelihood of relapse (Fig. 22.4.2.7). Children with standard or low-risk ALL are usually defined as those less than 10 years old, with low WCCs (<50 × 109/litre), low levels of postinduction MRD, and good-risk cytogenetics. These children will have an excellent chance of a cure and many protocols have reported overall survival rates of greater than 90% for this sub- group. In contrast, children with high-risk cytogenetics, high levels of postinduction MRD and high WCCs (>100 × 109/litre) will have relapse rates up to 50% and will typically be treated with more inten- sive protocols and possibly stem cell transplantation. Overall survival rates for adults aged 25 to 59 years range from 25 to 60% depending on the genetic subtype (Fig. 22.4.2.8) but average approximately 40% and are even lower (<15%) for patients over 60 years. Complications/long-term follow-up
Approximately 2 to 4% of children and 5 to 10% of adults will die from direct toxic effects of treatment, mostly due to intractable bacterial or fungal infections. Infants, patients with Down syn-

drome, and elderly patients have a higher risk of dying from toxic complications. Short-term toxic effects The commonest of these is febrile neutropenia due to bacterial and fungal infections, which can be life-threatening as patients have sig- nificant treatment-induced immunosuppression. Broad-spectrum antibiotics should be commenced immediately as per hospital policy. In most adult ALL protocols, patients will receive antifungal prophylaxis. Pneumocystis (carinii) jirovecii pneumonia is now a rela- tively rare complication as it can be prevented by antipneumocystis prophylaxis (standard of care while on chemotherapy for ALL). Varicella zoster infections can be severe. Common noninfective short-term toxic effects include nausea and vomiting, hair loss (intermittent), and transfusion reactions. Specific side effects of particular drugs are listed in Box 22.4.2.4. Long-term toxic effects Anthracycline-induced cardiomyopathy is rare, but if it occurs it can cause severe cardiac failure, often decades after the original treatment. As with all chemotherapy regimens, the risk of secondary malignan- cies is increased and is in low single figures. A few patients will become infertile; this occurrence is significantly higher if patients undergo allogeneic haematopoietic stem cell transplantation and reaches nearly 100% if patients receive total-body irradiation as part of the conditioning protocol. There is also an increased risk of premature ovarian failure in women who received chemotherapy in childhood. A significant number of long-term survivors of childhood ALL appear to have an increase in neurocognitive impairment during later life. Future developments Until recently, no new curative drug agents had become available for the management of ALL since the early 1970s. However, in the last few years, significant inroads have been made and sev- eral novel compounds have been approved in relapsed/refractory B-ALL. Currently the main focus of clinical ALL research is how to combine blinatumomab or inotuzumab with frontline B-ALL chemotherapy and use of CAR-T cells or similar immune effector cells in the treatment of relapsed/refractory adult B-ALL patients. In adult patients with de novo ALL, rituximab, an antibody against CD20, was shown to improve overall survival by nearly 10% when added to standard therapy in a large French randomized trial. With the advent of immunotherapy and a pipeline of novel tar- geted drugs, treatment of ALL will continue to improve and become more effective, particularly for high-risk and relapsed patients, as well as being less toxic for the many patients who are cured on cur- rent treatment protocols. FURTHER READING Eswaran J, et al. (2015). The pre-B-cell receptor checkpoint in acute lymphoblastic leukaemia. Leukemia, 29, 1623–31. Fielding AK (2015). Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia in adults: a broader range of options, improved outcomes, and more therapeutic dilemmas. Am Soc Clin Oncol Educ Book, 2015, e352–9. Guerra VA, et al. (2019). Novel monoclonal antibody-based treatment strategies in adults with acute lymphoblastic leukemia. Ther Adv Hematol, doi: 10.1177/2040620719849496. Hunger SP, Mullighan CG (2015). Acute lymphoblastic leukemia in children. N Engl J Med, 373, 1541–52. Hunger SP, Mullighan CG (2015). Redefining ALL classification:
toward detecting high-risk ALL and implementing precision medi- cine. Blood, 125, 3977–87. Inaba H, Greaves M, Mullighan CG (2013). Acute lymphoblastic leu- kaemia. Lancet, 381, 1943–55. Jabbour E, et al. (2015). Monoclonal antibodies in acute lymphoblastic leukemia. Blood, 125, 4010–16. Maude SL, et al. (2015). CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood, 125, 4017–23. Box 22.4.2.4 Side effects of drugs used to treat ALL Steroids • Mood and behavioural changes (emotional instability, aggressiveness, depression)—can be severe and very stressful for the families • Cushing syndrome and obesity • Diabetes mellitus • Osteonecrosis (avascular necrosis) affecting major joints—can occur in 5 to 10% of children, sometimes requiring surgical procedures including joint replacement Vincristine • Neuropathy (neuropathic pain, jaw pain, loss of deep tendon reflexes, ‘foot drop’, constipation) Asparaginase • Allergic reactions—more common after intravenous as opposed to intramuscular administration •

Coagulopathy • Sinus venous thrombosis and other thromboembolic complications • Pancreatitis
Methotrexate • Seizures (following intrathecal and high-dose methotrexate) • Encephalopathy •
Mucositis

Revision #1
Created 2026-01-22 16:42:33 UTC by Omar Ayman
Updated 2026-01-22 16:42:33 UTC by Omar Ayman