Acute lymphoblastic leukaemia

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Acute lymphoblastic leukaemia develops in both children and adults, with a peak incidence between 1 year and 4 years. Most acute lymphoblastic leukaemia arises in healthy individuals, and predisposing factors such as inherited genetic susceptibility or environmental exposure have been identified in only a few patients. It is characterised by chromosomal abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells. Along with response to treatment, these abnormalities are important prognostic factors. Disease-risk stratification and the development of intensified chemotherapy protocols substantially improves the outcome of patients with acute lymphoblastic leukaemia, particularly in children (1–14 years), but also in adolescents and young adults (15–39 years). However, the outcome of older adults (≥40 years) and patients with relapsed or refractory acute lymphoblastic leukaemia remains poor. New immunotherapeutic strategies, such as monoclonal antibodies and chimeric antigen receptor (CAR) T cells, are being developed and over the next few years could change the options for acute lymphoblastic leukaemia treatment.

Introduction

Acute lymphoblastic leukaemia is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation that can invade bone marrow, blood, and extramedullary sites. In the USA, its incidence was estimated at 1·57 per 100 000 people in 2014, with approximately 5960 new cases diagnosed and 1470 deaths in 2018.[1,2] The male to female ratio is about 1·2:1,[2] and this disease is more frequently reported in children. Age-specific incidence is highest in children aged 1–4 years, then drops sharply through childhood (5–14 years), adolescence, and young adulthood (15–39 years), reaching the lowest point between 25 years and 45 years.[1] Only a small increase in the incidence of this disease is seen after this age range, with around 60% of acute lymphoblastic leukaemia diagnosed before the age of 20 years old.[1] Outcome has improved considerably over the past four decades, with an increase of 5-year overall survival from 31% in 1975 to nearly 70% in 2009. However, these results hide important disparities; although 5-year overall survival reached 90% in children with acute lymphoblastic leukaemia, only 25% of patients older than 50 years old were alive 5 years after diagnosis, highlighting the need for further improvements in treatment for older adult patients (≥40 years).[3–5] Furthermore, although overall survival improved from 1995 to 2009 across low, middle, and high-income countries, basic treatment for leukaemia has not been consistently available in some low and middle-income countries, and there remain important disparities between individual countries.[6] Over the past decade, major progress has been made in the understanding of acute lymphoblastic leukaemia pathophysiology with the advances in molecular biology, and treatment is also changing with the development of immunotherapy.

See Online for appendix

Search strategy and selection criteria

We searched PubMed, Embase, and the Cochrane Library for articles and reviews published in English between Jan 1, 2014, and May 1, 2019; although older references were also used when appropriate. We used the search term "acute lymphoblastic leukemia" and restricted the search to certain study designs: human, clinical studies, clinical trials (phases 2, 3, and 4), controlled clinical trials, guidelines, meta-analyses, observational studies, practice guidelines, pragmatic clinical trials, randomised controlled trials, and systematic reviews. We also searched the reference lists from articles and reviews identified by the search.

Predisposing factors

Although most acute lymphoblastic leukaemia arises in healthy individuals, inherited genetic susceptibility and environmental risk factors have been identified in some patients (panel; appendix pp 2–4).

Genetic susceptibility

In the paediatric population, several genetic syndromes have been identified that predispose individuals to acute lymphoblastic leukaemia, and common allelic variants have been associated with increasing disease susceptibility with an additive effect.[7] Therefore, the genetic basis appears to be polygenic. Genes identified in genome-wide association studies for this disease are directly involved in blood cell proliferation and differentiation, suggesting that the inherited genetic variant probably contributed directly to a genetic vulnerability of haemopoietic cells, leading to tumourogenesis initiation and promotion in utero and postnatally. Importantly, screening for genetic susceptibility is not recommended as most children with associated genetic variants will never develop acute lymphoblastic leukaemia.

Environmental factors

Epidemiological evidence has suggested that some paediatric leukaemias might be initiated in utero and, for identical twins with concordant leukaemia, this possibility has been strongly endorsed by molecular studies of clonality.[8,9] Therefore, the impact of exposure to some environmental factors during pregnancy and childhood on leukaemia has been investigated (panel).

Genetics of acute lymphoblastic leukaemia

B-cell acute lymphoblastic leukaemia

B-cell acute lymphoblastic leukaemia has many genetic subtypes characterised by major chromosomal alterations, including aneuploidy or chromosomal rearrangements that result in the deregulation of proteins through the formation of chimeric genes or the upregulation of genes by juxtaposition with a strong enhancer (table 1). These genes encode haemopoietic transcription factors, epigenetic modifiers, cytokine receptors, or tyrosine kinases. Identifying disease subtypes of acute lymphoblastic leukaemia on the basis of these chromosomal abnormalities is an important step for risk stratification. Secondary genomic events that contribute to leukaemogenesis include copy number alterations (involving lymphoid transcription factors) and sequence mutations.

Recurring chromosomal alterations

High hyperdiploidy (gain of at least five chromosomes) is present in 25% of childhood acute lymphoblastic leukaemia and in less than 3% of adolescents and young adults (AYAs) and adults, and is associated with a favourable outcome.[10] Patients with high-hyperdiploid acute lymphoblastic leukaemia have mutations on genes of histone modifiers (*CREBBP*, *WHSC1*, *SUV420H1*, *SETD2*, and *EZH2*) or the RTK-RAS signalling pathway (*FLT3*, *NRAS*, *KRAS*, and *PTPN11*), with frequent subclonal mutations (approximately 50%).[10,11] Intrachromosomal amplification of chromosome 21 is more frequently found in children with a median age of 9–10 years compared with other age groups; however, the prognostic power of this amplification remains a matter of debate. Although a retrospective comparison of two studies suggests patients with intrachromosomal amplification of chromosome 21 should be treated as high risk to improve their poor prognosis,[12] minimal residual disease status might be a stronger marker and should direct treatment strategies.[13]

Hypodiploid acute lymphoblastic leukaemia (<44 chromosomes) comprises two subtypes with distinct transcriptional profiles and genetic alterations.[14] Near-haploid acute lymphoblastic leukaemia (24–31 chromosomes) with RAS-activating and *IKZF3* mutations is rare both in children (approximately 2%) and in AYAs and adults (<1%). Low-hypodiploid acute lymphoblastic leukaemia (32–39 chromosomes) has alterations of *TP53* (which is frequently inherited), *IKZF2*, and *RB1*. Low-hypodiploid acute lymphoblastic leukaemia has a very poor outcome.[15,16] The frequency increases with age, from being extremely rare in children (<1%), to 5% in AYAs, and over 10% in adults.[14]

Regarding translocation, acute lymphoblastic leukaemia with rearrangements of the mixed lineage leukaemia (*KMT2A*, previously known as *MLL*) gene (11q23) has a biphasic distribution and is frequently diagnosed in infants of 0–1 years of age (up to 80%), at low numbers in children and in AYAs (5%), and increases in adults (approximately 15%). Infants with *MLL*-rearranged acute lymphoblastic leukaemia have very few additional mutations, suggesting that this genetic alteration alone is enough to induce leukaemic transformation.[17] *MLL* rearrangements are associated with a very poor prognosis.[18]

The fusion genes, *ETV6–RUNX1* (translocation [t(12;21)(q13;q22)]) and *TCF3–PBX1* (translocation [t(1;19)(q23;p13)]) are both associated with a favourable prognosis (table 1).[19,20] *ETV6–RUNX1* is frequent in childhood acute lymphoblastic leukaemia (approximately 30%) and rarer in AYAs and adults (<5%), whereas *TCF3–PBX1* is present in approximately 5% of children and adults with this disease. By contrast, the fusion gene *TCF3–HLF*, a variant of the t(1;19)(q23;p13) translocation, is associated with poor prognosis and is present in less than 1% of acute lymphoblastic leukaemia.[21]

The frequency of patients with *BCR–ABL (*Philadelphia chromosome [t(9;22)(q34;q11)])-positive acute lymphoblastic leukaemia increases with age: 2–5% in childhood, 6% in AYAs, and more than 25% in adults. This gene fusion event is associated with poor prognosis; however, outcome is considerably improved by treatment with tyrosine kinase inhibitors.[22–24] *IKZF1* mutations are a hallmark of *BCR–ABL1* and Philadelphia chromosome-like acute lymphoblastic leukaemia, and correlate with very poor prognosis.[25–27]

Other subgroups

Progress in genomic analysis and the development of next-generation sequencing has identified new subtypes of B-cell acute lymphoblastic leukaemia that were previously unclassified because of an absence of aneuploidy or single chromosomal rearrangements. These new groups often present cryptic cytogenetic alterations and have distinct gene expression profiles.

Philadelphia chromosome-like acute lymphoblastic leukaemia has a gene expression signature similar to

Panel: **Predisposing factors of acute lymphoblastic leukaemia**

Genetic susceptibility

- Congenital syndromes: Down's syndrome, Fanconi anaemia, Ataxia telangiectasia, Bloom syndrome, Nijmegen breakage syndrome
- Inherited gene variants: *ARID5B*, *IKZF1*, *CEBPE*, *CDKN2A* or *CDKN2B*, *PIP4K2A*, *ETV6*
- Constitutional Robertsonian translocation between chromosomes 15 and 21, rob(15;21)(q10;q10)
- Single nucleotide polymorphisms: rs12402181 in miR-3117 and rs62571442 in miR-3689d2

Environmental factors

- Pesticide exposure
- Ionising radiation
- Childhood infections

	Frequency	Mutations	Prognosis
High hyperdiploid (gain of ≥5 chromosomes)	25% children; 3% AYAs and adults	RTK-RAS signalling pathway, histone modifiers	Favourable
Near-haploid (24–31 chromosomes)	2% children; <1% AYAs and adults	RAS-activating, *IKZF3*	Poor
Low-hypodiploid (32–39 chromosomes)	<1% children; 5% AYAs; >10% adults	*TP53*, *IKZF2*, *RB1*	Very poor
MLL (*KMT2A*) rearrangements	>80% infants; <1% children; 4% AYAs; 15% adults	*MLL* (*KMT2A*) rearrangement, few additional mutations (PI3K-RAS signalling pathway)	Very poor
ETV6–RUNX1 translocation, t(12;21)(q13;q22)	30% children; <5% AYAs and adults	*ETV6–RUNX1*	Favourable
TCF3–PBX1 translocation, t(1;19)(q23;p13)	5% children, AYAs and adults	*TCF3–PBX1*	Favourable
TCF3–HLF variant of t(1;19)(q23;p13)	<1% acute lymphoblastic leukaemia	*TCF3–HLF*	Poor
BCR–ABL1 Philadelphia chromosome, t(9;22)(q34;q11)	2–5% children, 6% AYAs; >25% adults	*BCR–ABL1* fusion gene, common deletions of *IKZF1*, *CDKN2A*, *CDKN2B*, and *PAX5*	Poor (improved with tyrosine kinase inhibitors)
Philadelphia chomosome-like acute lymphoblastic leukaemia	10% children; 25–30% AYAs; 20% adults	Rearrangements of *CRLF2* (about 50%), *ABL*-class tyrosine kinase genes (12%) and *JAK2* (10%); mutations of *EPOR* (3–10%); mutations activating JAK-STAT (10%) and RAS (2–8%) signalling pathways	Poor
DUX4 and *ERG*-deregulated acute lymphoblastic leukaemia	5–10% acute lymphoblastic leukaemia	*DUX4* rearrangement and overexpression, *ERG* deletions	Favourable, including if coexistence of *IKZF1* mutations (about 40% of patients)
MEF2D-rearranged acute lymphoblastic leukaemia	4% children; 7% AYAs and adults	*MEF2D* is fused to *BCL9* (most frequent fusion event), *HNRNPUL1*, *SS18*, *FOXJ2*, *CSF1R*, or *DAZAP1*	Poor
ZNF384-rearranged acute lymphoblastic leukaemia	5% children; 10% AYAs and adults	*ZNF384* rearranged with a transcriptional regulator or chromatin modifier (*EP300*, *CREBBP*, *TAF15*, *SYNRG*, *EWSR1*, *TCF3*, *ARID1B*, *BMP2K*, or *SMARCA2*)	Intermediate

AYAs=adolescents and young adults.

Table 1: **Main genetic subtypes of B-cell acute lymphoblastic leukaemia**

the Philadelphia chromosome-positive subtype, but the *BCR–ABL1* fusion gene is absent.[28] Genomic alterations of Philadelphia chromosome-like leukaemia affect B-lymphoid transcription factors, cytokine receptors, and tyrosine kinase signalling. This change leads to a heterogeneous subtype of acute lymphoblastic leukaemia that can be identified according to the constitutively activated kinase or the deregulated signalling pathway. These classifications include rearrangement of *CRLF2* (*IGH-CRLF2* and *P2RY8-CRLF2;* 50% of patients), rearrangement of *ABL*-class tyrosine kinase genes (*ABL1, ABL2, CSF1R, PDGFRA,* and *PDGFRB;* approximately 12%), rearrangement of *JAK2* (5–10%), mutations of the *EPOR* (3–10%), activating mutations in the JAK-STAT (*JAK1, JAK2, TLT3, ILR7, SH2B3,* and *TSLP;* approximately 10%) and RAS (*NRAS, KRAS,* and *PTPN11;* 2–8%) signalling pathways, and other less common kinase alterations (*FLT3, NTRK3,* and *FGFR1*).[26,29] The incidence of Philadelphia chromosome-like acute lymphoblastic leukaemia increases with age, from 10% in childhood acute lymphoblastic leukaemia to 20% in adults, reaching a peak of 25–30% in AYAs.[26] The frequency of kinase subtypes varies with age: *ABL*-class rearrangements are more frequently found in children and adolescents than in other age groups, rearrangements of *CRLF2* and activating mutations in RAS signalling pathways are common in adolescents, *EPOR* mutations are more frequent in AYAs, and rearrangements of *JAK2* are more frequent in adults.[26,29] Philadelphia chromosome-like acute lymphoblastic leukaemia is associated with poor prognosis in both children and adults;[26,29,30] however, tyrosine kinase inhibitors targeting *ABL1* or *JAK2* might improve response rate.[30,31]

ETV6–RUNX1-like acute lymphoblastic leukaemia has a gene expression profile and immunophenotype (CD27 positive, CD44 low to negative) similar to the *ETV6–RUNX1* subgroup, but the *ETV6–RUNX1* fusion is absent.[32,33] Its genomic profile is enriched with *ETV6* and *IKZF1* lesions and *ARPP21* deletions. This subtype is predominantly diagnosed in children at a low frequency (approximately 3%), of which the affect on prognosis is unclear.

For *DUX4*-rearranged acute lymphoblastic leukaemia, this B-cell subtype is characterised by a distinct immunophenotype (CD2 positive) and a gene expression profile including deregulation of the double homeobox 4 (*DUX4*) gene and the ETS transcription factor ERG (*ERG*).[32,34–36] *DUX4* rearrangement is an early initiating event in leukaemogenesis, and ectopically expressed DUX4 binds to an intragenic region of *ERG*, resulting in a truncated C-terminal ERG protein that inhibits wild-type transcriptional activity of the *ERG* gene.[36] The *DUX4*-rearranged subtype accounts for about 5–10% of acute lymphoblastic leukaemia, with slightly higher frequencies seen in AYAs than in children and adults. Prognosis is good in patients

with this rearrangement, even when concomitant genomic alterations associated with a poor outcome are present, such as *IKZF1* deletions that coexist in approximately 40% of patients.[37,38]

Myocyte enhancer factor 2D (*MEF2D*)-rearranged B-cell acute lymphoblastic leukaemia is a genetic subtype associated with onset in older patients (approximately 4% of children versus 7% of AYAs and adults) and an aberrant immunophenotype (CD10 negative and CD38 positive).[39,40] The most frequent *MEF2D* fusion event is with *BCL9*, but this gene can also fuse with *HNRNPUL1, SS18, FOXJ2, CSF1R*, or *DAZAP1*. All these rearrangements are transforming and leukaemogenic, resulting in enhanced *MEF2D* transcriptional activity.[39,41] This subtype is associated with a poor outcome.[40]

The zinc finger 384 (*ZNF384*)-rearranged B-cell acute lymphoblastic leukaemia subtype is also associated with onset in older age (approximately 5% of children versus 10% of AYAs and adults). The rearrangement encompasses the entire *ZNF384* gene with a 5′ fusion partner, which is commonly a transcriptional regulator or chromatin modifier (*EP300, CREBBP, TAF15, SYNRG, EWSR1, TCF3, ARID1B, BMP2K,* or *SMARCA2*).[34,42] *ZNF384*-rearranged acute lymphoblastic leukaemia is often diagnosed as B-cell acute lymphoblastic leukaemia with aberrant expression of myeloid antigens such as CD13 and CD33, or as B/myeloid mixed-phenotype acute leukaemia.[43] Expression of both lymphoid and myeloid antigens on this disease subtype suggests that the *ZNF384* rearrangement might occur in an early haemopoietic progenitor cell with multilineage potential. In a small cohort of patients, the prognosis of *ZNF384*-rearranged acute lymphoblastic leukaemia was reported to be intermediate.[34,42]

Rearrangements of the *IGH* locus with different partners, including *CRLF2* and *EPOR* in Philadelphia chromosome-like acute lymphoblastic leukaemia, *CEBP* gene family members, and *ID4* are frequent in AYAs (approximately 10%) and confers a poor prognosis.[44]

PAX5 acts as a haploinsufficiency tumour suppressor with genetic alterations in 31% of B-cell acute lymphoblastic leukaemia.[45] *PAX5* translocations with different fusion partners are reported in 2–3% of this type of leukaemia.[46,47] In general, these rearrangements inhibit the transcriptional activity of *PAX5* and its loss accelerates the development of B-cell precursor leukaemia.[48]

IKZF1^{plus} is classified as *IKZF1* deletions that co-occur with deletions in *CDKN2A, CDKN2B, PAX5,* or *PAR1* when *ERG* deletions are absent.[49] This subgroup is found in about 6% of paediatric B-cell acute lymphoblastic leukaemia and is associated with a very poor prognosis, particularly in patients with positive minimal residual disease after induction.

Relapsed B-cell acute lymphoblastic leukaemia

Leukaemic evolution leading to relapse follows a complex branched pathway, with many abnormalities persisting from initial diagnosis and additional secondary genetic alterations or enriched lesions emerging in a clone that is minor at initial diagnosis (appendix p 13).[50–52] In particular, genetic alterations in epigenetic regulators and chromatin modifiers are common in patients with relapsed acute lymphoblastic leukaemia, possibly contributing to lower treatment response. Mutations in *CREBBP*, a transcriptional coactivator and acetyl transferase, are found in 20% of relapsed B-cell acute lymphoblastic leukaemia and impair response to glucocorticoids.[53] Similarly, gain-of-function mutations in the 5'-nucleotidase, cytosolic II (*NT5C2*) gene induce resistance to mercaptopurine and are selectively present in relapsed B-cell acute lymphoblastic leukaemia.[54,55] Other somatic mutations frequently enriched in relapsed B-cell acute lymphoblastic leukaemia target *WHSC1, TP53, USH2A, NRAS*, and *IKZF1* genes.[56] Finally, somatic mutations in DNA mismatch repair genes, *PMS2* and *MSH6*, are found in patients who have relapsed.[56]

T-cell acute lymphoblastic leukaemia

T-cell acute lymphoblastic leukaemia results from a multistep process where genetic mutations accumulate and alter the normal control of cell growth, differentiation, proliferation, and survival during thymopoiesis. The genetics of this disease is highly heterogeneous, with chromosomal abnormalities present in almost all patients.[57] Constitutive activation of NOTCH signalling through activating mutations in *NOTCH1*, or loss of function mutations in *FBXW7*, is the main oncogenic pathway found in about 80% of patients with T-cell acute lymphoblastic leukaemia.[57,58] Furthermore, loss of *p16*(*INK4A*) and *p14*(*ARF*) suppressor genes at the *CDKN2A* locus in more than 70% of individuals with this type of leukaemia suggests that constitutive activation of NOTCH signalling cooperates with deletions at the *CDKN2A* locus to promote oncogenesis.[59]

In approximately 50% of patients with T-cell acute lymphoblastic leukaemia, chromosomal translocations position transcription factor genes so that they are under the control of strong T-cell specific enhancers (T-cell receptor α, β, and δ). Overexpressed oncogenic transcription factors include TAL1, TAL2, LYL1, OLIG2, LMO1, LMO2, TLX1 (HOX11), TLX3 (HOX11L2), NKX2-1, NKX2-2, NKX2-5, HOXA genes, MYC, MYB, and TAN1.[60] Less frequently these translocations result in a loss of transcription factors important for tumour suppression, including genes encoding *WT1, LEF1, ETV6, BCL11B, RUNX1,* or *GATA3*.[60]

In almost 25% of T-cell acute lymphoblastic leukaemia, loss-of-function mutations and deletions of the *AZH2* and *SUZ12* genes, which encode two crucial components of the PRC2 complex involved in chromatin modification, have been reported.[61,62] Similarly, *PHF6*, a plant homeodomain-containing factor with a role in the epigenetic regulation of gene expression, is mutated or deleted in about 16% of paediatric patients and 38% of adults with T-cell acute lymphoblastic leukaemia.[63]

Genetic alterations in signal transduction pathways are observed in patients with T-cell acute lymphoblastic leukaemia, including mutational loss of *PTEN*, an essential regulator of the PI3K-AKT signalling pathway (5–10% of patients),[64] and rearrangements of *ABL1* to form gene fusions with *NUP214*, *EML1*, and *ETV6* (about 8% of patients).[65–67] Importantly, ABL1 fusion proteins are sensitive to tyrosine kinase inhibitors and integrating this treatment into chemotherapy regimens might improve response rate for patients with this disease subtype.[68]

Finally, *DNMT3A* mutations are usually found in myeloid malignancies, but have also been detected in lymphoid malignancies of T-cell lineage, including in around 10% of patients with T-cell acute lymphoblastic leukaemia, and is associated with a poor prognosis.[69] The incidence of these mutations increases with age (median age of 44 years for *DNMT3A* mutated *vs* 29 years for wild-type, p<0·001), and detection of *DNMT3A* alterations in non-leukaemic bone marrow suggests that some T-cell leukaemias might arise from *DNMT3A*-mutated clonal haemopoiesis.[69]

Diagnosis

The diagnosis of acute lymphoblastic leukaemia is based on 2016 WHO classification guidelines[70] that integrate the characterisation of cell morphology, immunophenotypes, genetics, and cytogenetics (appendix p 5). Morphological identification of lymphoblasts by microscopy can assess peripheral blood and bone marrow infiltration, whereas immunophenotyping is the gold standard for lineage assessment, classification, and detection of features that are important for the assessment of minimal residual disease.[71] For chromosomal analysis, conventional cytogenetics should be done in every patient and complemented with fluorescence in-situ hybridisation or RT-PCR for the detection of selected genomic abnormalities; in particular, cryptic translocations that cannot be detected by conventional cytogenetics. Flow cytometry is also a useful method to identify aneuploidy.[72] Recent advances in next-generation sequencing have made possible whole genome sequencing and diagnostic techniques might be replaced once this approach becomes routinely available and affordable.

Prognostic factors

Accurate identification of prognostic factors and risk stratification is required for the selection of appropriate treatment regimens and assessing eligibility for allogeneic haemopoietic cell transplantation (table 2).

Clinical and biological factors

Classical prognostic factors include age, blood count at diagnosis, CNS involvement, race and ethnicity, gender, and cell lineage (table 2). However, some of these parameters have been identified, at least in part, as surrogate markers for other abnormalities, in particular, genetic alterations.

AYAs and adults have a higher prevalence of acute lymphoblastic leukaemia with high-risk molecular abnormalities (*BCR–ABL1* rearrangement, Philadelphia chromosome-like) and fewer low-risk subtypes (hyperdiploidy, *ETV6–RUNX1*), and have less intensive chemotherapy given their lower tolerance to treatment than children.[73] Over the past decade, more intensive therapeutic strategies adapted from paediatric regimens and targeted therapy (eg, tyrosine kinase inhibitors in the *BCR–ABL1* and Philadelphia chromosome-like disease variants) have partly overcome the poor prognosis observed in AYAs and adult patients.[23,74–77] Similarly, *MLL* rearrangement is associated with hyperleukocytosis

	Favourable factor	Adverse factor
Demographic and clinical features		
Age	1 year to <10 years	<1 year or ≥10 years
Sex	Female	Male
Race and ethnicity	White, Asian	Black, Hispanic
Clinical, biological, or genetic features of leukaemia		
CNS involvement	No	Yes
Blood count at diagnosis	Low blood count; $<50 \times 10^9$ cells per L for B-cell acute lymphoblastic leukaemia and $<100 \times 10^9$ cells per L for T-cell acute lymphoblastic leukaemia	High blood count; $\geq 50 \times 10^9$ per L for B-cell acute lymphoblastic leukaemia and $\geq 100 \times 10^9$ cells per L for T-cell acute lymphoblastic leukaemia
Immunophenotype	B-cell lineage	T-cell lineage
Cytogenetic features	Hyperdiploidy, *ETV6–RUNX*, *TCF3–PBX1*, and trisomy of chromosomes 4, 10, or 17	Hypodiploidy, *BCR–ABL1* Philadelphia chromosome-positive, *MLL* rearrangements, *TCF3–HLF*, and complex karyotype (≥5 chromosomal abnormalities)
Genomic features	*DUX4*-rearrangement (*ERG* deletion)	*IKZF1* deletions or mutations, Philadelphia chromosome-like, *MEF2D*-rearrangement
Response to treatment		
Minimal residual disease at specified time points	Low minimal residual disease $<10^{-3}$ nucleated cells or undectectable	Persistence of minimal residual disease $\geq 10^{-3}$ nucleated cells, the higher this value the worse the prognosis

Table 2: **Prognostic factors for acute lymphoblastic leukaemia**

and very poor prognosis, contributing to the poor outcome in infants with acute lymphoblastic leukaemia (up to 80% of infants have the *MLL* rearrangement subtype).[17,18]

Cytogenetic risk groups are defined as good risk (hyperdiploidy [51–65 chromosomes or DNA index >1·16], cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favourable outcome; t(12;21) (p13;q22): *ETV6–RUNX1*) or poor risk (hypodiploidy [<44 chromosomes or DNA index <0·81]; t(v;11q23): *MLL* rearranged; t(9;22)(q34;q11·2): *BCR–ABL* [defined as high risk in the era before tyrosine kinase inhibitors]; or complex karyotype [five or more chromosomal abnormalities]; table 2).

The adverse prognostic factors associated with race (black) and ethnicity (Hispanic) have been linked to socioeconomic factors and differences in genomic variations.[78–80] For example, somatic *CRLF2* rearrangements associated with poor prognosis is over-represented in Hispanic children.[78]

After adjustment for other prognostic factors, the presence of blasts in the cerebrospinal fluid at diagnosis remains associated with an inferior outcome, even in patients with low levels of CNS leukaemia.[81]

Response to treatment

Response to treatment has long been recognised as a prognostic factor in acute lymphoblastic leukaemia. Minimal residual disease, which is the presence of disease in patients in complete remission by conventional analysis, has become the standard measure for evaluating prognostic impact of response to treatment regimens. Multiparametric flow cytometry and molecular methods can be used to measure minimal residual disease, with a high correlation in results between molecular and immunophenotypic studies.[82–85] Molecular methods rely on the detection of leukaemia-specific rearrangement of immunoglobulin and T-cell receptor genes and leukaemia-specific transcripts (eg, *BCR–ABL1*) by real-time quantitative PCR and next-generation sequencing. The sensitivity of molecular methods routinely reaches one acute lymphoblastic leukaemia cell in 10^4 to 10^5 cells, whereas detection of minimal residual disease with multiparametric flow cytometry is about 1 log lower.[86] Therefore, molecular methods will probably replace classic flow cytometry techniques to evaluate the depth of the response in patients with this disease.

Minimal residual disease should be evaluated at the end of each treatment stage (ie, postinduction and postconsolidation) to monitor changes in this measurement over time. It is the most powerful prognostic factor in all age groups, including in patients at low risk.[87–95] In paediatric B-cell and T-cell acute lymphoblastic leukaemia, better outcomes were reported in patients with low minimal residual disease after induction; however, patients converting from positive to negative minimal residual disease by the end of consolidation also had a more favourable outcome. This highlights the importance of evaluating minimal residual disease at different time-points for accurate disease-risk stratification.[96,97] By contrast, adult patients with positive minimal residual disease after induction chemotherapy and negative for this measurement after consolidation do not seem to overcome their initial poor prognosis.[98] Importantly, some paediatric studies have shown that genetic subtypes might influence minimal residual disease kinetics, affect the optimal cutoff for minimal residual disease assessment, and the predictive impact of response to treatment.[49,99] Finally, continuous monitoring after a negative minimal residual disease result could be useful to detect early preclinical relapse and adaptation of the therapeutic strategy.

Current treatment

The first-line treatment for acute lymphoblastic leukaemia typically includes four phases over 2–3 years: induction, consolidation, intensification, and long-term maintenance (figure 1). In addition, directed treatment is given to prevent CNS relapse. Allogeneic haemopoietic cell transplantation is reserved for patients with high-risk disease or persistent minimal residual disease. This intensive therapeutic approach has led to an estimated 5-year overall survival of 90% in childhood acute lymphoblastic leukaemia.[3,74] In adults, the outcome is more disappointing than the results seen in children, with 5-year overall survival at less than 45%.[100] The development of paediatric-inspired regimens in older patients, first in AYAs,[75,77,101] and later in patients up to 50–60 years of age,[102–104] has increased 5-year overall survival to 50% or more, and up to 70–80% in disease subsets that are associated with a favourable prognosis. In older patients (>60 years old), however, the results remain poor, with 5-year overall survival at less than 20%.[105]

Induction

Induction chemotherapy aims to eradicate disease burden and restore normal haemopoiesis to achieve complete remission. Induction is based on a combination of chemotherapy, usually including a glucocorticoid, vincristine, L-asparaginase and an anthracycline (figure 1).

Prednisone has been the standard steroid of choice for the treatment of acute lymphoblastic leukaemia,

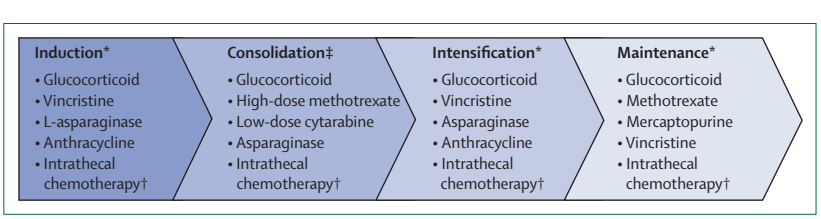

Figure 1: **Front-line treatment of acute lymphoblastic leukaemia**
*Tyrosine kinase inhibitors are given during each phase of treatment in Philadelphia chromosome-positive acute lymphoblastic leukaemia. †Intrathecal chemotherapy consists of methotrexate alone or combined with cytarabine and hydrocortisone. ‡Allogeneic haemopoietic cell transplantation is optional after consolidation.

before being gradually replaced by dexamethasone in children. At a prednisone-to-dexamethasone dose ratio of 7 or less, prospective randomised trials have established the superiority of dexamethasone over prednisone in terms of managing leukaemia in the CNS and event-free survival.[106–109] However, this outcome did not translate into improved overall survival in most children; although dexamethasone was associated with an improved overall survival in a subgroup of children with T-cell acute lymphoblastic leukaemia and a good response to the prednisone prephase.[108] Furthermore, no differences were seen in disease-free survival between the two steroids when using higher doses of prednisone (dose ratio >7).[110,111] Steroids are associated with numerous short-term and long-term side-effects: infections, psychological and behavioural disturbances, osteoporosis, osteonecrosis, myopathy, endocrine and metabolic dysfunction, cardiovascular events, and cataracts. The risk of side-effects increases when patients are given a high dose of steroids, and these side-effects are generally worse and seen more frequently when using dexamethasone compared with prednisone. Overall, given the absence of a benefit to overall survival and increased toxicity with high-dose dexamethasone, this treatment is not recommended by the research community for AYAs with B-cell acute lymphoblastic leukaemia.

Clinically available L-asparaginase is derived from two sources, namely *Escherichia coli* and *Erwinia chrysanthemi*. The native enzyme and an enzyme modified by the addition of monomethoxypolyethylene glycol (pegylated) are derived from *E coli*. The half-life varies between different forms, with the PEG-asparaginase conjugates having the longest half-life and the *E chrysanthemi*-derived protein the shortest, and should be accounted for when designing protocols to maintain asparagine depletion.[112] Given the non-human origin of asparaginase, patients can produce antibodies that substantially reduce asparaginase activity and negatively affect outcome.[113,114] Importantly, although development of neutralising antibodies is generally associated with symptoms of clinical hypersensitivity, some patients develop antibodies and reduced asparaginase activity without any sign of allergy (silent inactivation). Therefore, asparaginase activity should be measured after L-asparaginase administration to assess therapeutic efficacy in accordance with expert recommendations.[115] The incidence of developing anti-asparaginase antibodies is higher when the native protein is expressed in *E coli* (up to 60% of patients receiving *E coli*-derived L-asparaginase) than for the pegylated form (2–18%), and the use of an alternative bacterium for protein production (*Erwinia caratovora*) can also reduce incidence (8–33%).[112,113] Antibodies frequently crossreact between the native and pegylated versions of asparagine but do not bind to the *E caratovora*-derived protein, suggesting that patients with allergic reactions or silent inactivation should switch to using this alternatively produced form.[112] Furthermore, asparaginase toxicities also include hepatotoxicity, pancreatitis, and coagulation disorder. Asparagine treatment for adults with the Philadelphia chromosome-positive subtype is associated with increased mortality and severe adverse events, in particular hepatotoxicity, possibly owing to overlapping hepatotoxicity with imatinib. Because of associated side-effects and possible risk of death, use of an asparaginase-based regimen at the induction phase in older adults should be carefully considered.[116]

Patients with the *BCR–ABL1* translocation have a poor prognosis, but tyrosine kinase inhibitors can improve the outcome. Initial results found that addition of imatinib to standard chemotherapy was associated with a high complete remission rate (over 90%); however, treatment failure because of CNS relapse was observed when imatinib had reduced penetration.[117,118,119] A second-generation tyrosine kinase inhibitor, dasatinib, is better at penetrating the CNS than imatinib,[120] and treatment with this drug in combination with chemotherapy can achieve similar complete remission rates (more than 90% of patients).[121] However, in children and AYAs with Philadelphia chromosome-positive acute lymphoblastic leukaemia, long-term outcome after dasatinib-based treatment is better than with imatinib, with 5-year overall survival of 86% for patients receiving dasatinib and 70–72% for those receiving imatinib. Nevertheless, no study prospectively compares both drugs.[22,23,24] The most common cause of relapse in adult acute lymphoblastic leukaemia is from the Thr315Ile mutation in the *ABL* kinase domain.[122] A third-generation tyrosine kinase inhibitor, ponatinib, is effective at treating individuals with this mutation, with 47% of patients who had no response to dasatinib or nilotinib showing major cytogenetic responses with ponatinib.[123] Furthermore, comparison of two non-randomised studies showed higher event-free survival and overall survival with front-line ponatinib than with dasatinib, suggesting a role for ponatinib in that setting, provided these data are confirmed prospectively.[124]

Consolidation

Consolidation is the second step of the treatment regimen and consists of several short sequential courses of chemotherapy every 2 weeks, usually with cytarabine, high-dose methotrexate (>500 mg/m²), vincristine, asparaginase, mercaptopurine, and glucocorticoids, over a 12-week period. This sequence is followed by a late intensification phase (reinduction therapy) that includes a similar combination of drugs used during the induction therapy.

Folic acid rescue after high-dose methotrexate is necessary, but should be used cautiously, as high doses have been associated with an increased risk of relapse.[125] Pharmacogenomic studies have found that somatically acquired lesions significantly increase or decrease (depending on the lesion) the accumulation of methotrexate polyglutamate in leukaemia cells, which is the

active metabolite of methotrexate, and that this correlates with antileukaemic activity (appendix p 6).

Intensification

Consolidation is followed by a late intensification (reinduction therapy), which includes drugs similar to those used in treatment during induction therapy.

Maintenance

Maintenance therapy consists of daily mercaptopurine and weekly methotrexate, with or without vincristine, and glucocorticoid pulses every 1–3 months. Maintenance is administered for 2–3 years following induction, beyond which no benefit has been shown.[126] As with mercaptopurine, tioguanine inhibits de novo purine synthesis, but with a higher lymphoblast cytotoxicity in vitro. However, there was no clinical benefit in randomised studies comparing both drugs, and long-term doses of tioguanine at 40 mg/m² per day were associated with death and significant side-effects (sinusoidal obstruction syndrome, thrombocytopenia, and portal hypertension).[127–129] Therefore, mercaptopurine remains the standard treatment for maintenance therapy. Pharmacogenomics is also important in the monitoring of mercaptopurine and tioguanine (appendix p 6).

CNS prophylaxis and treatment

Routine CNS prophylaxis is recommended in conjunction with systemic chemotherapy. Fractionated prophylactic cranial irradiation (12–24 Gy) has long been the standard but it is associated with late neurocognitive deficits, endocrinopathy, secondary cancers, and excess late mortality. Therefore, efforts have been made to avoid prophylaxis cranial irradiation, initially in children, and then in adult patients.[130,131] Therapeutic strategies now include serial intensive intrathecal chemotherapy with methotrexate alone, or methotrexate, cytarabine, and hydrocortisone in conjunction with high-dose intravenous methotrexate and cytarabine.[131] One meta-analysis did not show a benefit of prophylactic cranial irradiation, including in patients at high risk of CNS relapse (slow early response, high initial leucocyte count, *MLL*-rearrangement or T-cell acute lymphoblastic leukaemia), suggesting that cranial irradiation should be reserved for patients with CNS involvement at the time of diagnosis.[132]

Allogeneic haemopoietic cell transplantation

Allogeneic haemopoietic cell transplantation remains the standard consolidation treatment in patients at high risk who are fit and have an available donor. Progress in supportive care, infection prophylaxis and treatments, and the development of reduced toxicity conditioning regimens significantly decreases non-relapse mortality after transplantation.[133] Furthermore, in a large prospective paediatric trial, standardisation of donor selection (stem cell source), the conditioning regimen, and graft-versus-host disease prophylaxis substantially improved the outcome, in particular non-relapse mortality, of patients after transplantation.[134]

Allogeneic haemopoietic cell transplantation is recommended as first-line consolidation for the Philadelphia chromosome-positive subtype, and might also be a suitable treatment option for adult patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia and persistent minimal residual disease after induction or consolidation.[135] The use of transplantation indication based on minimal residual disease was validated for patients older than 18 years who had paediatric-inspired intensive chemotherapy.[135] However, for patients receiving less intensive chemotherapy, the relevance of minimal residual disease is weaker, and transplantations should probably be recommended on the basis of conventional parameters of poor prognosis. In fit patients with relapsed or refractory acute lymphoblastic leukaemia who achieved second complete remission, allogeneic haemopoietic cell transplantation is usually recommended, especially for adults, due to their very poor prognosis. Efforts should be made to achieve the best disease response before transplantation, as a positive minimal residual disease status is associated with relapse after this treatment.[136,137] In regards to the donor choice, a matched sibling is always preferable, but a matched unrelated donor, a haploidentical donor, and umbilical cord blood could also be used.[135]

New agents

Over the past decade, several new targeted therapies have been developed for acute lymphoblastic leukaemia treatment (figure 2; table 3).[138–143]

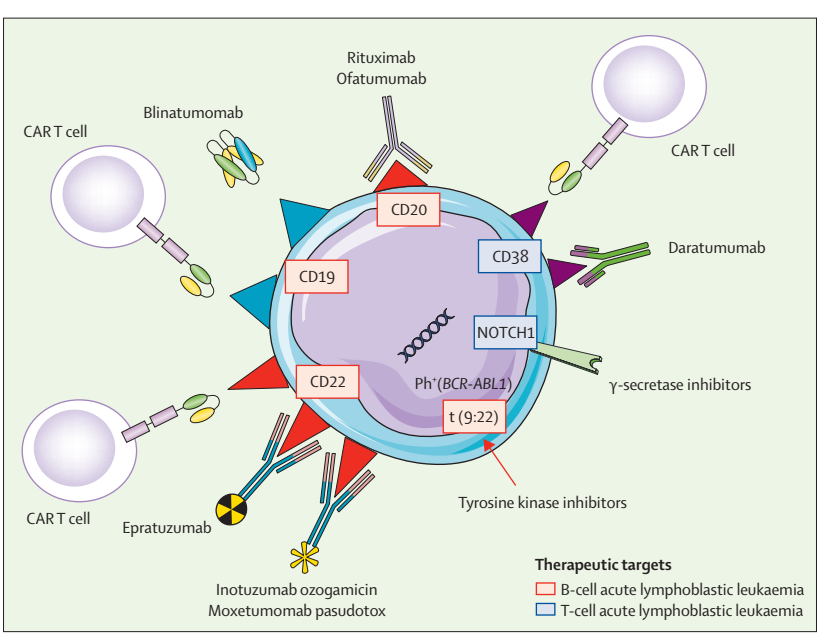

Figure 2: **New targeted therapy for acute lymphoblastic leukaemia**
Ph⁺=Philadelphia chromosome-positive.

CD20

CD20 is expressed in 30–50% of patients with B-cell acute lymphoblastic leukaemia and is associated with a poor prognosis in adults.[144,145] The anti-CD20 monoclonal antibody, rituximab, showed promising results for adults with relapsed or refractory disease,[146] prompting its evaluation in first-line treatment in combination with chemotherapy. A combination of rituximab with

	Study type	Number of patients	Disease	Treatment schedule	Response	Allogeneic haemopoietic cell transplantation	Median follow-up (months)	Overall survival (months)	Toxicity
Inotuzumab ozogamycin									
DeAngelo et al (2017)[138]	Phase 1/2	72 adults	Relapse or refractory B-cell acute lymphoblastic leukaemia, 22% of patients were positive for the Philadelphia chromosome	Inotuzumab ozogamicin treatment of 1·2–1·8 mg/m² per cycle given on days 1, 8, and 15 for 4-week cycles (1·8 mg/m² per cycle for the phase 2 trial)	Objective response (CR or CRi) achieved in 49 (68%) patients; CR achieved in 23 (32%) patients; 41 (84%) of 49 patients were minimal residual disease negative	24 (33%) patients	23·7	Median of 7·4; 30% of patients at 12 months	4 (6%) patients had sinusoidal obstruction syndrome (2 patients after allogeneic haemopoietic cell transplantation)
Kantarjian et al (2016);[139] Kantarjian et al (2019)[140]	Phase 3	326 adults	Relapse or refractory B-cell acute lymphoblastic leukaemia, 22 (13%) patients in the treatment group *vs* 27 (17%) patients in the standard chemotherapy group were positive for the Philadelphia chromosome	Inotuzumab ozogamicin treatment group (n=164), 1·8 mg/m² per cycle given on days 1, 8, and 15 for 4-week cycles (1·5 mg/m² when in CR); conventional chemotherapy group (n=162), standard of care	Objective response (CR or CRi) achieved in 121 (74%) of 164 patients in the treatment group *vs* 50 (31%) of 162 patients on conventional chemotherapy; 69 (78%) of 88 *vs* 9 (28%) of 32 patients were minimal residual disease negative	79 (48%) of 164 *vs* 36 (22%) of 162 patients	29·4	Median of 7·7 *vs* 6·2; 23% *vs* 10% at 24 months	23 (14%) *vs* 3 (2%) patients had sinusoidal obstruction syndrome
Blinatumomab									
Topp et al (2015)[141]	Phase 2	189 adults	Relapse or refractory B-cell acute lymphoblastic leukaemia	Blinatumomab intravenous-continuous infusion for 4 weeks and 2 weeks without (2 cycles, followed by 3 additional cycles or an allogeneic haemopoietic cell transplantation for patients in CR or CRh after the first 2 cycles)	Objective response (CR or CRh) achieved in 81 (43%) patients; CR achieved in 63 (33%) patients; 60 (82%) of 73 evaluable patients with an objective response were minimal residual disease negative	32 (17%) of 189 patients	9·8	Median of 6·1	3 (2%) patients had severe cytokine release syndrome; 24 (13%) patients had severe neurotoxicity
Kantarjian et al (2017)[142]	Phase 3	405 adults	Relapse or refractory B-cell acute lymphoblastic leukaemia, Philadelphia chromosome-negative	Blinatumomab treatment group (n=271), intravenous-continuous infusion for 4 weeks and 2 weeks without (2 week cycles, followed by 3 additional cycles and maintenance for 12 months for patients in CR or CRh after the first 2 cycles); chemotherapy group (n=134),* standard of care; allogeneic haemopoietic cell transplantation possible after cycle 1 in both groups	Objective response (CR, CRh, or CRi) achieved in 119 (44%) patients in the treatment group vs 33 (25%) on chemotherapy; CR in 91 (34%) *vs* 21 (16%) patients; 76% *vs* 48% of patients with an objective response were minimal residual disease negative	65 (24%) of 271 *vs* 32 (24%) of 134 patients	11·7 *vs* 11·8	Median of 7·7 *vs* 4·0	38 (14%) *vs* 0% of patients had cytokine release syndrome (13 [5%] *vs* 0% severe); 25 (9%) *vs* 9 (8%) patients had severe neurotoxicity

(Table 3 continues on next page)

	Study type	Number of patients	Disease	Treatment schedule	Response	Allogeneic haemopoietic cell transplantation	Median follow-up (months)	Overall survival (months)	Toxicity
(Continued from previous page)									
Tisagenlecleucel									
Maude et al (2018)[143]	Phase 2, multicentre	75 children and AYAs (age range, 3–21 years)	Relapse or refractory B-cell acute lymphoblastic leukaemia	CTL019 (tisagenlecleucel [4-1BB]; Novartis, Switzerland) single infusion	Objective response (CR or CRi) achieved in 61 (81%) patients; 100% of patients with an objective response were minimal residual disease negative	8 (11%) patients	13·1	Median of 19.1; 76% at 12 months	58 (77%) patients had cytokine release syndrome (35 [47%] severe); 30 (40%) patients had neurotoxicity (10 [13%] severe)

CR=complete response. CRi=complete response with incomplete haematological recovery. CRh=complete response with partial haematological recovery. AYAs=adolecents and young adults. *Investigator's choice of one of four regimens: fludarabine, high-dose cytosine arabinoside, and granulocyte colony-stimulating factor with or without anthracycline; a high-dose cytosine arabinoside-based regimen; a high-dose methotrexate-based regimen; or a clofarabine-based regimen.

Table 3: **Studies supporting the approval of inotuzumab ozogamycin, blinatumomab, and tisagenlecleucel in B-cell acute lymphoblastic leukaemia**

hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) or paediatric-inspired regimens was consistently associated with lower rates of relapse and improved event-free survival and overall survival than the same treatment without rituximab.[147,148] Similar results have also been reported with ofatumumab.[149] An anti-CD20 monoclonal antibody might therefore be included in first-line treatment for adult patients with CD20-positive B-cell leukaemias.

CD22

CD22 is expressed in around 90% of B-cell acute lymphoblastic leukaemia, and its rapid internalisation upon binding with an antibody makes it an ideal target for immunoconjugate treatment. Inotuzumab ozogamicin is an anti-CD22 monoclonal antibody conjugated to a calicheamicin. Based on promising results in phase 1/2 studies,[138,150] weekly administration of inotuzumab ozogamicin was compared with standard chemotherapy in a phase 3 trial for adult patients with relapsed or refractory acute lymphoblastic leukaemia.[139,140] Complete remission was higher at 81% in the inotuzumab ozogamicin treatment group versus 29% for standard chemotherapy (p<0·001). This result was translated into a significantly higher median progression-free survival (5 months *vs* 1·8 months) and median overall survival (7·7 months *vs* 6·2 months) for patients in the inotuzumab ozogamicin treatment group. Longer follow-up confirmed these results, with a 2-year overall survival of 22·8% in the inotuzumab ozogamicin group compared with 10% in the standard chemotherapy group (p=0·001).[140] These results led to fast-track approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for single-agent inotuzumab ozogamicin treatment in adult patients with relapsed or refractory acute lymphoblastic leukaemia. Although we must highlight that inotuzumab ozogamicin was associated with a higher incidence of hepatic toxicity (51% of patients in the treatment group *vs* 34% of patients on standard chemotherapy alone), including sinusoidal obstruction syndrome (13% *vs* <1%).[151]

As part of a compassionate-use programme in paediatric patients (age range of 2-21 years), 67% of individuals with relapsed or refractory acute lymphoblastic leukaemia were in complete remission when treated with inotuzumab ozogamicin.[152] As of February, 2020, inotuzumab ozogamicin is not yet approved for children younger than 18 years of age with relapsed or refractory acute lymphoblastic leukaemia, and prospective studies are ongoing (NCT02981628, NCT03094611).

Additional anti-CD22 targeted therapies include epratuzumab, moxetumomab pasudotox, and combotox (appendix p 7).

CD19

As with CD22, CD19 is expressed in around 90% of individuals with B-cell acute lymphoblastic leukaemia and is rapidly internalised upon binding with an antibody, making this antigen another suitable therapeutic target.

Blinatumomab is a bispecific anti-T-cell receptor and anti-CD19 antibody that engages T cells to activate a B-cell specific inflammatory and cytolytic response. A phase 2 trial showed that 43% of 189 adult patients with the Philadelphia chromosome-negative subtype had an objective response after treatment with blinatumomab.[141] Of note, 82% of patients in complete remission were minimal residual disease negative. A phase 3 trial also reported an objective response in 44% of patients treated with blinatumomab compared with 25% on standard chemotherapy.[142] In patients who achieved complete remission, 76% were minimal residual disease negative in the blinatumomab treatment group versus 48% in the chemotherapy group.[142] A phase 1/2 trial evaluated blinatumomab in 93 paediatric patients with relapsed or refractory acute lymphoblastic leukaemia. In the 70 patients that received the recommended dose of blinatumomab, 39% achieved complete remission within the first two cycles, of which 14 (52%) of 27 were minimal residual disease negative.[153]

The FDA and EMA have approved blinatumomab for treatment of adults with Philadelphia chromosome-negative, CD19-positive, acute lymphoblastic leukaemia with relapsed or refractory disease, or in first or second complete remission with persistent minimal residual disease. For paediatric patients aged 1 year or older, blinatumomab is approved for patients with Philadelphia chromosome-negative and CD19 positive acute lymphoblastic leukaemia that is refractory or in relapse after at least two previous therapies, or in relapse after having an allogeneic haemopoietic cell transplantation.

Blinatumomab has an acceptable toxicity profile compared with other treatments for B-cell acute lymphoblastic leukaemia, with fever, chills, neutropenia, anaemia, and hypo-γ-globulinemia being the most frequent side-effects. Nevertheless, cytokine release syndrome (grade≥3: 0–6% of patients) and neurological toxicity (grade≥3: 7–14% of patients) are severe events that have also been seen with blinatumomab.[154]

Other anti-CD19 monoclonal antibodies are still being established (NCT01786096, NCT01685021, NCT01440179). For example, denintuzumab mafodotin, an anti-CD19 antibody coupled to the microtubule-disrupting agent monomethyl auristatin, was tested in a phase 1 study to treat patients with refractory or relapsed B-cell acute lymphoblastic leukaemia, resulting in an objective response of 35%.[155]

Chimeric antigen receptor (CAR) T cells

Cellular immunotherapy with CD19-directed CAR T cells is a promising approach for the treatment of B-cell acute lymphoblastic leukaemia. CAR T cells are genetically engineered T cells that express the antigen-binding domain of an immunoglobulin linked to a costimulatory molecule (most commonly 4-1BB [TNFRSF9] or CD28) and the intracellular T-cell receptor signalling domain. CAR T cells can recognise unprocessed antigens and be activated in a major histocompatibility complex-independent manner. Autologous CAR T-cell treatment involves collection of patients' T cells, the delivery of the CAR construct, and the autologous administration of the modified CAR T cells to the patient.

Because of its expression on nearly all B-cell acute lymphoblastic leukaemia, CD19 was considered an ideal target for the development of anti-CD19 CAR T cells (tisagenlecleucel; table 3). In the phase 1/2 pilot study, CAR T cells were given after T-cell depleting chemotherapy in 30 children and adults with relapsed or refractory B-cell leukaemia. Complete remission was achieved in 90% of participants, and minimal residual disease was negative in 88% of patients with complete remission.[156] A larger study was subsequently done, which showed complete remission in 61 (81%) of 75 children and AYAs, all of whom were minimal residual disease negative (age range, 3–21 years).[143] At 1 year, 50% of patients achieved event-free survival and 76% overall survival. An initial publication showed complete remission in 14 (88%) of 16 adult patients with relapsed or refractory acute lymphoblastic leukaemia using an alternative anti-CD19 CAR T-cell construct.[157] This study was updated in February, 2018, to include 53 patients and a longer follow-up. The proportion of patients who achieved complete remission was 83% (with 73% of these patients minimal residual disease negative), and the median time period for follow-up (29 months), event-free survival (6·1 months), and overall survival (12·9 months) was also reported.[158] CAR T cells (tisagenlecleucel) have been approved by the EMA and FDA for treating children or AYAs of 25 years or younger with refractory or relapsed disease after two lines of alternative treatment or after haematopoietic cell transplantation.

Nevertheless, CAR T cells directed against CD19 are associated with severe side-effects, including cytokine release syndrome and neurotoxicity, which can be life-threatening. The American Society for Blood and Marrow Transplantation published consensus guidelines in 2018 for cytokine release syndrome and neurotoxicity management.[159] Tocilizumab, an anti-IL6 receptor monoclonal antibody, is well tolerated and rapidly effective for the management of cytokine release syndrome.[160] For neurotoxicity, steroids are effective,[161] but must be used with caution as they might reduce the antitumour effects of CAR T cells. Finally, B-cell aplasia is systematic after admistration of CAR T cells directed against CD19, and substitutive polyvalent immunoglobulin could be used to treat this complication.

Next challenges for treatment of relapse

These new therapies have considerably improved outcomes in patients with relapsed or refractory B-cell acute lymphoblastic leukaemia and several phase 3 clinical trials are continuing to evaluate their use in relapse and front-line settings (appendix p 8). However, monoclonal antibodies and CAR T cells are dependent on the expression of their target antigen and loss of these targets is a major mechanism by which tumour cells can escape immunotherapy. Multiple mechanisms of antigen loss have been identified, including genetic mutations of the target gene, epitope masking, or a cell lineage change with loss of the target epitope.[162] To overcome tumour escape mechanisms mediated by antigen loss, a dual CAR T-cell therapy that targets multiple molecules (eg, CD19 and CD22) has been established with promising results.[163–167]

For relapsed or refractory T-cell acute lymphoblastic leukaemia, therapeutic options at relapse are much more restricted. Nelarabine (a purine nucleoside analogue) is the only drug approved in the last 20 years for relapsed or refractory T-cell acute lymphoblastic leukaemia in both children and adults. In children and AYAs, the overall response rate in patients treated with nelarabine monotherapy was 55% for the first relapse and 27% for the second.[168] In adult patients with relapsed or refractory

T-cell leukaemia, single agent nelarabine achieved an overall response of 41–46%.[169,170]

Several targeted therapeutic approaches are being investigated for acute lymphoblastic leukaemia of T-cell lineage,[171] with NOTCH1 signalling an attractive target because of the high frequency of mutations in this oncogenic pathway.[57,58] The development of γ-secretase inhibitors that target the NOTCH1 pathway have been hampered by severe gastrointestinal toxicity; although the generation of more selective inhibitors against γ-secretase might overcome this problem.[172] So far, CAR T-cell therapies for T-cell acute lymphoblastic leukaemia are in the early stage of clinical development.[173] Development of CAR T cells for T-cell acute lymphoblastic leukaemia was slowed down by the difficulty to identify a suitable surface antigen, as expression of most targetable surface antigens is shared between normal and malignant T-cells, resulting in CAR T-cell death (fratricide mechanism) or profound immunodeficiency. Nevertheless, several clinical studies of CAR T cells targeting CD5 or CD7 for treatment of T-cell acute lymphoblastic leukaemia are ongoing (NCT04033302, NCT03690011, NCT03081910, NCT04004637). Furthermore, strong aberrant expression of CD38 by T-cell leukaemia cells suggests that CAR T-cell therapies against CD38 warrant further investigation.[174] Daratumumab, a monoclonal antibody targeting CD38, has also been successfully used for eradication of minimal residual disease in relapsed T-cell acute lymphoblastic leukaemia.[175]

Conclusion

Development of dose-intensive chemotherapy is a major success in paediatric oncology, as a large proportion of patients can achieve sustainable complete remission. By contrast, the results in AYAs and adults have been disappointing. The benefits of intensive paediatric-inspired protocols were initially shown in AYAs and then in adults. However, the accurate identification of adult patients who will benefit from such treatment is necessary given the toxicity and treatment-related mortality. More frequent use of allogeneic haemopoietic cell transplantation in this age group is also responsible for increased treatment-related mortality. Treatment regimen design remains challenging for patients older than 60 years of age and patients with relapsed or refractory disease (all age groups) as conventional therapy shows a low frequency of complete remission and short overall survival. Monoclonal antibodies will probably be implemented as first-line treatment within the next few years, contributing to improved disease control. CAR T-cell therapies will also change treatment regimens, as can already be seen for relapsed or refractory disease, and in the future might also be incorporated into first-line treatment strategies, provided severe toxicity can be successfully prevented and managed.

Disease-risk classifications are also substantially improved through development of next-generation sequencing, which allows identification of novel subsets of acute lymphoblastic leukaemia with a more accurate definition of subset prognosis, and the development of minimal residual disease monitoring. These advances translate into better risk-adapted treatment, particularly regarding allogeneic haemopoietic cell transplantation. Conversely, reduced treatment intensity in children with low-risk disease should be investigated to minimise side-effects. In addition, molecular biology methods have aided disease classification, enabling the identification of signalling pathways that can be targeted by specific treatments, such as tyrosine kinase inhibitors in Philadelphia chromosome-positive and Philadelphia chromosome-like acute lymphoblastic leukaemia. We hope that the implementation of these new therapeutic strategies will improve patient outcome, and that in the next few years, treatment of adult patients will follow the success of that of paediatric patients.

Contributors

FM searched the literature and wrote the first version of the manuscript. MM designed the Seminar, provided scientific expertise, guidance, and support in the manuscript writing, reviewed all the data, and had editorial overview of the entire manuscript.

Declaration of interests

MM reports grants and lecture honoraria from Janssen, Sanofi, and Jazz Pharmaceuticals; lecture honoraria from Celgene, Amgen, Bristol-Myers Squibb, Takeda, and Pfizer; and grants from Roche, all outside the submitted work. FM declares no competing interests.

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References

1 Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975–2014. Bethesda, MD: National Cancer Institute; April, 2017. https://seer.cancer.gov/csr/1975_2014/ (accessed Feb 7, 2020).
2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68:** 7–30.
3 Pulte D, Gondos A, Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. *Blood* 2009; **113:** 1408–11.
4 Pulte D, Jansen L, Gondos A, et al. Survival of adults with acute lymphoblastic leukemia in Germany and the United States. *PLoS One* 2014; **9:** e85554.
5 Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. *J Clin Oncol* 2012; **30:** 1663–69.
6 Bonaventure A, Harewood R, Stiller CA, et al. Worldwide comparison of survival from childhood leukaemia for 1995–2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries. *Lancet Haematol* 2017; **4:** e202–17.
7 Xu H, Yang W, Perez-Andreu V, et al. Novel susceptibility variants at 10p12.31–12.2 for childhood acute lymphoblastic leukemia in ethnically diverse populations. *J Natl Cancer Inst* 2013; **105:** 733–42.
8 Gale KB, Ford AM, Repp R, et al. Backtracking leukemia to birth: identification of clonotypic gene fusion sequences in neonatal blood spots. *Proc Natl Acad Sci USA* 1997; **94:** 13950–54.
9 Greaves MF, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: lessons in natural history. *Blood* 2003; **102:** 2321–33.
10 Paulsson K, Lilljebjörn H, Biloglav A, et al. The genomic landscape of high hyperdiploid childhood acute lymphoblastic leukemia. *Nat Genet* 2015; **47:** 672–76.

11 Jerchel IS, Hoogkamer AQ, Ariës IM, et al. RAS pathway mutations as a predictive biomarker for treatment adaptation in pediatric B-cell precursor acute lymphoblastic leukemia. *Leukemia* 2018; **32:** 931–40.

12 Moorman AV, Robinson H, Schwab C, et al. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. *J Clin Oncol* 2013; **31:** 3389–96.

13 Attarbaschi A, Panzer-Grümayer R, Mann G, et al. Minimal residual disease-based treatment is adequate for relapse-prone childhood acute lymphoblastic leukemia with an intrachromosomal amplification of chromosome 21: the experience of the ALL-BFM 2000 trial. *Klin Padiatr* 2014; **226:** 338–43.

14 Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet* 2013; **45:** 242–52.

15 Pui CH, Rebora P, Schrappe M, et al. Outcome of children with hypodiploid acute lymphoblastic leukemia: a retrospective multinational study. *J Clin Oncol* 2019; **37:** 770–79.

16 McNeer JL, Devidas M, Dai Y, et al. Hematopoietic stem-cell transplantation does not improve the poor outcome of children with hypodiploid acute lymphoblastic leukemia: a report from Children's Oncology Group. *J Clin Oncol* 2019; **37:** 780–89.

17 Andersson AK, Ma J, Wang J, et al. The landscape of somatic mutations in infant MLL-rearranged acute lymphoblastic leukemias. *Nat Genet* 2015; **47:** 330–37.

18 Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet* 2007; **370:** 240–50.

19 Barber KE, Harrison CJ, Broadfield ZJ, et al. Molecular cytogenetic characterization of TCF3 (E2A)/19p13.3 rearrangements in B-cell precursor acute lymphoblastic leukemia. *Genes Chromosomes Cancer* 2007; **46:** 478–86.

20 Burmeister T, Gökbuget N, Schwartz S, et al. Clinical features and prognostic implications of TCF3-PBX1 and ETV6-RUNX1 in adult acute lymphoblastic leukemia. *Haematologica* 2010; **95:** 241–46.

21 Hunger SP. Chromosomal translocations involving the E2A gene in acute lymphoblastic leukemia: clinical features and molecular pathogenesis. *Blood* 1996; **87:** 1211–24.

22 Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia* 2014; **28:** 1467–71.

23 Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: results of Children's Oncology Group trial AALL0622. *J Clin Oncol* 2018; **36:** 2306–14.

24 Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol* 2012; **13:** 936–45.

25 Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature* 2008; **453:** 110–14.

26 Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014; **371:** 1005–15.

27 Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med* 2009; **360:** 470–80.

28 Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol* 2009; **10:** 125–34.

29 Roberts KG, Gu Z, Payne-Turner D, et al. High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. *J Clin Oncol* 2017; **35:** 394–401.

30 Tasian SK, Loh ML, Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. *Blood* 2017; **130:** 2064–72.

31 Roberts KG, Yang YL, Payne-Turner D, et al. Oncogenic role and therapeutic targeting of ABL-class and JAK-STAT activating kinase alterations in Ph-like ALL. *Blood Adv* 2017; **1:** 1657–71.

32 Lilljebjörn H, Henningsson R, Hyrenius-Wittsten A, et al. Identification of ETV6-RUNX1-like and DUX4-rearranged subtypes in paediatric B-cell precursor acute lymphoblastic leukaemia. *Nat Commun* 2016; **7:** 11790.

33 Zaliova M, Kotrova M, Bresolin S, et al. ETV6/RUNX1-like acute lymphoblastic leukemia: a novel B-cell precursor leukemia subtype associated with the CD27/CD44 immunophenotype. *Genes Chromosomes Cancer* 2017; **56:** 608–16.

34 Liu YF, Wang BY, Zhang WN, et al. Genomic profiling of adult and pediatric B-cell acute lymphoblastic leukemia. *EBioMedicine* 2016; **8:** 173–83.

35 Yasuda T, Tsuzuki S, Kawazu M, et al. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. *Nat Genet* 2016; **48:** 569–74.

36 Zhang J, McCastlain K, Yoshihara H, et al. Deregulation of DUX4 and ERG in acute lymphoblastic leukemia. *Nat Genet* 2016; **48:** 1481–89.

37 Harvey RC, Mullighan CG, Wang X, et al. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-wide DNA copy number alterations, clinical characteristics, and outcome. *Blood* 2010; **116:** 4874–84.

38 Clappier E, Auclerc MF, Rapion J, et al. An intragenic ERG deletion is a marker of an oncogenic subtype of B-cell precursor acute lymphoblastic leukemia with a favorable outcome despite frequent IKZF1 deletions. *Leukemia* 2014; **28:** 70–77.

39 Gu Z, Churchman M, Roberts K, et al. Genomic analyses identify recurrent MEF2D fusions in acute lymphoblastic leukaemia. *Nat Commun* 2016; **7:** 13331.

40 Suzuki K, Okuno Y, Kawashima N, et al. MEF2D-BCL9 fusion gene is associated with high-risk acute B-cell precursor lymphoblastic leukemia in adolescents. *J Clin Oncol* 2016; **34:** 3451–59.

41 Prima V, Hunger SP. Cooperative transformation by MEF2D/DAZAP1 and DAZAP1/MEF2D fusion proteins generated by the variant t(1;19) in acute lymphoblastic leukemia. *Leukemia* 2007; **21:** 2470–75.

42 Shago M, Abla O, Hitzler J, Weitzman S, Abdelhaleem M. Frequency and outcome of pediatric acute lymphoblastic leukemia with ZNF384 gene rearrangements including a novel translocation resulting in an ARID1B/ZNF384 gene fusion. *Pediatr Blood Cancer* 2016; **63:** 1915–21.

43 Alexander TB, Gu Z, Iacobucci I, et al. The genetic basis and cell of origin of mixed phenotype acute leukaemia. *Nature* 2018; **562:** 373–79.

44 Russell LJ, Enshaei A, Jones L, et al. IGH@ translocations are prevalent in teenagers and young adults with acute lymphoblastic leukemia and are associated with a poor outcome. *J Clin Oncol* 2014; **32:** 1453–62.

45 Mullighan CG, Goorha S, Radtke I, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. *Nature* 2007; **446:** 758–64.

46 Coyaud E, Struski S, Prade N, et al. Wide diversity of PAX5 alterations in B-ALL: a Groupe Francophone de Cytogenetique Hematologique study. *Blood* 2010; **115:** 3089–97.

47 Nebral K, Denk D, Attarbaschi A, et al. Incidence and diversity of PAX5 fusion genes in childhood acute lymphoblastic leukemia. *Leukemia* 2009; **23:** 134–43.

48 Dang J, Wei L, de Ridder J, et al. PAX5 is a tumor suppressor in mouse mutagenesis models of acute lymphoblastic leukemia. *Blood* 2015; **125:** 3609–17.

49 Stanulla M, Dagdan E, Zaliova M, et al. IKZF1^{plus} defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. *J Clin Oncol* 2018; **36:** 1240–49.

50 Yang JJ, Bhojwani D, Yang W, et al. Genome-wide copy number profiling reveals molecular evolution from diagnosis to relapse in childhood acute lymphoblastic leukemia. *Blood* 2008; **112:** 4178–83.

51 Kawamata N, Ogawa S, Seeger K, et al. Molecular allelokaryotyping of relapsed pediatric acute lymphoblastic leukemia. *Int J Oncol* 2009; **34:** 1603–12.

52 Mullighan CG, Phillips LA, Su X, et al. Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. *Science* 2008; **322:** 1377–80.

53 Mullighan CG, Zhang J, Kasper LH, et al. CREBBP mutations in relapsed acute lymphoblastic leukaemia. *Nature* 2011; **471:** 235–39.

54 Tzoneva G, Dieck CL, Oshima K, et al. Clonal evolution mechanisms in NT5C2 mutant-relapsed acute lymphoblastic leukaemia. *Nature* 2018; **553:** 511–14.

55 Meyer JA, Wang J, Hogan LE, et al. Relapse-specific mutations in NT5C2 in childhood acute lymphoblastic leukemia. *Nat Genet* 2013; **45:** 290–94.

56 Ma X, Edmonson M, Yergeau D, et al. Rise and fall of subclones from diagnosis to relapse in pediatric B-acute lymphoblastic leukaemia. *Nat Commun* 2015; **6:** 6604.

57 Jang W, Park J, Kwon A, et al. CDKN2B downregulation and other genetic characteristics in T-acute lymphoblastic leukemia. *Exp Mol Med* 2019; **51:** 4.

58 Weng AP, Ferrando AA, Lee W, et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science* 2004; **306:** 269–71.

59 Ferrando AA, Neuberg DS, Staunton J, et al. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. *Cancer Cell* 2002; **1:** 75–87.

60 Van Vlierberghe P, Ferrando A. The molecular basis of T cell acute lymphoblastic leukemia. *J Clin Invest* 2012; **122:** 3398–406.

61 Ntziachristos P, Tsirigos A, Van Vlierberghe P, et al. Genetic inactivation of the polycomb repressive complex 2 in T cell acute lymphoblastic leukemia. *Nat Med* 2012; **18:** 298–301.

62 Zhang J, Ding L, Holmfeldt L, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature* 2012; **481:** 157–63.

63 Van Vlierberghe P, Palomero T, Khiabanian H, et al. PHF6 mutations in T-cell acute lymphoblastic leukemia. *Nat Genet* 2010; **42:** 338–42.

64 Palomero T, Sulis ML, Cortina M, et al. Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. *Nat Med* 2007; **13:** 1203–10.

65 Hagemeijer A, Graux C. ABL1 rearrangements in T-cell acute lymphoblastic leukemia. *Genes Chromosomes Cancer* 2010; **49:** 299–308.

66 De Keersmaecker K, Graux C, Odero MD, et al. Fusion of EML1 to ABL1 in T-cell acute lymphoblastic leukemia with cryptic t(9;14) (q34;q32). *Blood* 2005; **105:** 4849–52.

67 Van Limbergen H, Beverloo HB, van Drunen E, et al. Molecular cytogenetic and clinical findings in ETV6/ABL1-positive leukemia. *Genes Chromosomes Cancer* 2001; **30:** 274–82.

68 Quintás-Cardama A, Tong W, Manshouri T, et al. Activity of tyrosine kinase inhibitors against human NUP214-ABL1-positive T cell malignancies. *Leukemia* 2008; **22:** 1117–24.

69 Bond J, Touzart A, Leprêtre S, et al. *DNMT3A* mutation is associated with increased age and adverse outcome in adult T-cell acute lymphoblastic leukemia. *Haematologica* 2019; **104:** 1617–25.

70 Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; **127:** 2391–405.

71 Béné MC, Nebe T, Bettelheim P, et al. Immunophenotyping of acute leukemia and lymphoproliferative disorders: a consensus proposal of the European LeukemiaNet Work Package 10. *Leukemia* 2011; **25:** 567–74.

72 Tembhare P, Badrinath Y, Ghogale S, et al. A novel and easy FxCycle™ violet based flow cytometric method for simultaneous assessment of DNA ploidy and six-color immunophenotyping. *Cytometry A* 2016; **89:** 281–91.

73 Schafer ES, Hunger SP. Optimal therapy for acute lymphoblastic leukemia in adolescents and young adults. *Nat Rev Clin Oncol* 2011; **8:** 417–24.

74 Pui CH, Pei D, Campana D, et al. Improved prognosis for older adolescents with acute lymphoblastic leukemia. *J Clin Oncol* 2011; **29:** 386–91.

75 Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. *Blood* 2008; **112:** 1646–54.

76 de Bont JM, Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld P, Pieters R. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. *Leukemia* 2004; **18:** 2032–35.

77 Boissel N, Auclerc MF, Lhéritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *J Clin Oncol* 2003; **21:** 774–80.

78 Harvey RC, Mullighan CG, Chen IM, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. *Blood* 2010; **115:** 5312–21.

79 Yang JJ, Cheng C, Devidas M, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. *Nat Genet* 2011; **43:** 237–41.

80 Xu H, Cheng C, Devidas M, et al. ARID5B genetic polymorphisms contribute to racial disparities in the incidence and treatment outcome of childhood acute lymphoblastic leukemia. *J Clin Oncol* 2012; **30:** 751–57.

81 Winick N, Devidas M, Chen S, et al. Impact of initial CSF findings on outcome among patients with National Cancer Institute standard- and high-risk B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. *J Clin Oncol* 2017; **35:** 2527–34.

82 Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. *Haematologica* 2012; **97:** 1582–93.

83 Irving J, Jesson J, Virgo P, et al. Establishment and validation of a standard protocol for the detection of minimal residual disease in B lineage childhood acute lymphoblastic leukemia by flow cytometry in a multi-center setting. *Haematologica* 2009; **94:** 870–74.

84 Malec M, van der Velden VH, Björklund E, et al. Analysis of minimal residual disease in childhood acute lymphoblastic leukemia: comparison between RQ-PCR analysis of Ig/TcR gene rearrangements and multicolor flow cytometric immunophenotyping. *Leukemia* 2004; **18:** 1630–36.

85 Ryan J, Quinn F, Meunier A, et al. Minimal residual disease detection in childhood acute lymphoblastic leukaemia patients at multiple time-points reveals high levels of concordance between molecular and immunophenotypic approaches. *Br J Haematol* 2009; **144:** 107–15.

86 Brüggemann M, Kotrova M. Minimal residual disease in adult ALL: technical aspects and implications for correct clinical interpretation. *Hematology Am Soc Hematol Educ Program* 2017; **2017:** 13–21.

87 Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol* 2017; **3:** e170580.

88 Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood* 2008; **111:** 5477–85.

89 Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. *Lancet Oncol* 2013; **14:** 199–209.

90 Brüggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood* 2006; **107:** 1116–23.

91 Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood* 2009; **113:** 4153–62.

92 Patel B, Rai L, Buck G, et al. Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993. *Br J Haematol* 2010; **148:** 80–89.

93 Cavé H, van der Werff ten Bosch J, Suciu S, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European Organization for Research and Treatment of Cancer–Childhood Leukemia Cooperative Group. *N Engl J Med* 1998; **339:** 591–98.

94 Coustan-Smith E, Behm FG, Sanchez J, et al. Immunological detection of minimal residual disease in children with acute lymphoblastic leukaemia. *Lancet* 1998; **351:** 550–54.

95 van Dongen JJM, Seriu T, Panzer-Grümayer ER, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. *Lancet* 1998; **352:** 1731–38.

96 Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* 2015; **126:** 964–71.

97 Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. *Blood* 2011; **118:** 2077–84.

98 Beldjord K, Chevret S, Asnafi V, et al. Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia. *Blood* 2014; **123:** 3739–49.

99 O'Connor D, Enshaei A, Bartram J, et al. Genotype-specific minimal residual disease interpretation improves stratification in pediatric acute lymphoblastic leukemia. *J Clin Oncol* 2018; **36:** 34–43.

100 Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. *J Clin Oncol* 2011; **29:** 532–43.

101 Ribera JM, Oriol A, Sanz MA, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Español de Tratamiento en Hematología pediatric-based protocol ALL-96. *J Clin Oncol* 2008; **26:** 1843–49.

102 Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol* 2009; **27:** 911–18.

103 DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia* 2015; **29:** 526–34.

104 Storring JM, Minden MD, Kao S, et al. Treatment of adults with BCR-ABL negative acute lymphoblastic leukaemia with a modified paediatric regimen. *Br J Haematol* 2009; **146:** 76–85.

105 Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood* 2012; **119:** 34–43.

106 Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TO. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol* 2005; **129:** 734–45.

107 Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood* 2003; **101:** 3809–17.

108 Möricke A, Zimmermann M, Valsecchi MG, et al. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. *Blood* 2016; **127:** 2101–12.

109 Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from Children's Oncology Group study AALL0232. *J Clin Oncol* 2016; **34:** 2380–88.

110 Igarashi S, Manabe A, Ohara A, et al. No advantage of dexamethasone over prednisolone for the outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in the Tokyo Children's Cancer Study Group L95-14 protocol. *J Clin Oncol* 2005; **23:** 6489–98.

111 De Moerloose B, Suciu S, Bertrand Y, et al. Improved outcome with pulses of vincristine and corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL) and lymphoblastic non-Hodgkin lymphoma (NHL): report of the EORTC randomized phase 3 trial 58951. *Blood* 2010; **116:** 36–44.

112 Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. *Leuk Lymphoma* 2015; **56:** 2273–80.

113 Panosyan EH, Seibel NL, Martin-Aragon S, et al. Asparaginase antibody and asparaginase activity in children with higher-risk acute lymphoblastic leukemia: Children's Cancer Group study CCG-1961. *J Pediatr Hematol Oncol* 2004; **26:** 217–26.

114 Woo MH, Hak LJ, Storm MC, et al. Anti-asparaginase antibodies following E. coli asparaginase therapy in pediatric acute lymphoblastic leukemia. *Leukemia* 1998; **12:** 1527–33.

115 van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica* 2016; **101:** 279–85.

116 Patel B, Kirkwood AA, Dey A, et al. Pegylated-asparaginase during induction therapy for adult acute lymphoblastic leukaemia: toxicity data from the UKALL14 trial. *Leukemia* 2017; **31:** 58–64.

117 Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica* 2015; **100:** 653–661.

118 Jones D, Thomas D, Yin CC, et al. Kinase domain point mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia emerge after therapy with BCR-ABL kinase inhibitors. *Cancer* 2008; **113:** 985–94.

119 de Labarthe A, Rousselot P, Huguet-Rigal F, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. *Blood* 2007; **109:** 1408–13.

120 Porkka K, Koskenvesa P, Lundán T, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood* 2008; **112:** 1005–12.

121 Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer* 2015; **121:** 4158–64.

122 Foà R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2011; **118:** 6521–28.

123 Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013; **369:** 1783–96.

124 Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. *Cancer* 2016; **122:** 3650–56.

125 Skärby TV, Anderson H, Heldrup J, Kanerva JA, Seidel H, Schmiegelow K. High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. *Leukemia* 2006; **20:** 1955–62.

126 Childhood ALL Collaborative Group. Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. *Lancet* 1996; **347:** 1783–88.

127 Harms DO, Göbel U, Spaar HJ, et al. Thioguanine offers no advantage over mercaptopurine in maintenance treatment of childhood ALL: results of the randomized trial COALL-92. *Blood* 2003; **102:** 2736–40.

128 Stork LC, Matloub Y, Broxson E, et al. Oral 6-mercaptopurine versus oral 6-thioguanine and veno-occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the Children's Oncology Group CCG-1952 clinical trial. *Blood* 2010; **115:** 2740–48.

129 Vora A, Mitchell CD, Lennard L, et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006; **368:** 1339–48.

130 Pui C-H, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. *Lancet Oncol* 2008; **9:** 257–68.

131 Richards S, Pui CH, Gayon P. Systematic review and meta-analysis of randomized trials of central nervous system directed therapy for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2013; **60:** 185–95.

132 Vora A, Andreano A, Pui CH, et al. Influence of cranial radiotherapy on outcome in children with acute lymphoblastic leukemia treated with contemporary therapy. *J Clin Oncol* 2016; **34:** 919–26.

133 Malard F, Chevallier P, Guillaume T, et al. Continuous reduced nonrelapse mortality after allogeneic hematopoietic stem cell transplantation: a single-institution's three decade experience. *Biol Blood Marrow Transplant* 2014; **20:** 1217–23.

134 Peters C, Schrappe M, von Stackelberg A, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors-the ALL-SCT-BFM-2003 trial. *J Clin Oncol* 2015; **33:** 1265–74.

135 Giebel S, Marks DI, Boissel N, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 2019; **54:** 798–809.

136 Leung W, Pui CH, Coustan-Smith E, et al. Detectable minimal residual disease before hematopoietic cell transplantation is prognostic but does not preclude cure for children with very-high-risk leukemia. *Blood* 2012; **120:** 468–72.

137 Bader P, Kreyenberg H, Henze GH, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. *J Clin Oncol* 2009; **27:** 377–84.

138 DeAngelo DJ, Stock W, Stein AS, et al. Inotuzumab ozogamicin in adults with relapsed or refractory CD22-positive acute lymphoblastic leukemia: a phase 1/2 study. *Blood Adv* 2017; **1:** 1167–80.

139 Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016; **375:** 740–53.

140 Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. *Cancer* 2019; **125:** 2474–87.

141 Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2015; **16:** 57–66.

142 Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017; **376:** 836–47.

143 Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* 2018; **378:** 439–48.

144 Maury S, Huguet F, Leguay T, et al. Adverse prognostic significance of CD20 expression in adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. *Haematologica* 2010; **95:** 324–28.

145 Thomas DA, O'Brien S, Jorgensen JL, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. *Blood* 2009; **113:** 6330–37.

146 Chevallier P, Pigneux A, Robillard N, et al. Rituximab for the treatment of adult relapsed/refractory CD20 positive B-ALL patients: a pilot series. *Leuk Res* 2012; **36:** 311–15.

147 Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol* 2010; **28:** 3880–89.

148 Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med* 2016; **375:** 1044–53.

149 Maiti A, Kantarjian HM, Ravandi F, et al. Hyper-CVAD plus ofatumumab as frontline therapy in CD20+ acute lymphoblastic leukemia: updated results of a phase II trial. *Blood* 2017; **130:** 3876.

150 Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody in refractory and relapsed acute lymphocytic leukemia. *Cancer* 2013; **119:** 2728–36.

151 Kantarjian HM, DeAngelo DJ, Advani AS, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. *Lancet Haematol* 2017; **4:** e387–98.

152 Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Leukemia* 2019; **33:** 884–92.

153 von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol* 2016; **34:** 4381–89.

154 Jain T, Litzow MR. Management of toxicities associated with novel immunotherapy agents in acute lymphoblastic leukemia. *Ther Adv Hematol* 2020; published online January 20. DOI:10.1177/2040620719899897.

155 Fathi AT, Borate U, DeAngelo DJ, et al. A phase 1 study of denintuzumab mafodotin (SGN-CD19A) in adults with relapsed or refractory B-lineage acute leukemia (B-ALL) and highly aggressive lymphoma. *Blood* 2015; **126:** 1328.

156 Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 2014; **371:** 1507–17.

157 Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med* 2014; **6:** 224ra25.

158 Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med* 2018; **378:** 449–59.

159 Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019; **25:** 625–38.

160 Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018; **23:** 943–47.

161 Karschnia P, Jordan JT, Forst DA, et al. Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells. *Blood* 2019; **133:** 2212–21.

162 Shah NN, Maatman T, Hari P, Johnson B. Multi targeted CAR-T cell therapies for B-cell malignancies. *Front Oncol* 2019; **9:** 146.

163 Schultz LM, Davis KL, Baggott C, et al. Phase 1 study of CD19/CD22 bispecific chimeric antigen receptor (CAR) therapy in children and young adults with B cell acute lymphoblastic leukemia (ALL). *Blood* 2018; **132** (suppl 1)**:** 898.

164 Liu S, Deng B, Lin Y, et al. Sequential CD19- and CD22-CART cell therapies for relapsed B-Cell acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation. *Blood* 2018; **132** (suppl 1)**:** 2126.

165 Amrolia PJ, Wynn R, Hough R, et al. Simultaneous targeting of CD19 and CD22: phase I study of AUTO3, a bicistronic chimeric antigen receptor (CAR) T-cell therapy, in pediatric patients with relapsed/refractory B-cell acute lymphoblastic leukemia (r/r B-ALL): amelia study. *Blood* 2018; **132** (suppl 1)**:** 279.

166 Yang J, Li J, Zhang X, et al. A Feasibility and safety study of CD19 and CD22 chimeric antigen receptors-modified T cell cocktail for therapy of B cell acute lymphoblastic leukemia. *Blood* 2018; **132** (suppl 1)**:** 277.

167 Gardner R, Annesley C, Finney O, et al. Early clinical experience of CD19 x CD22 dual specific CAR T cells for enhanced anti-leukemic targeting of acute lymphoblastic leukemia. *Blood* 2018; **132** (suppl 1)**:** 278.

168 Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol* 2005; **23:** 3376–82.

169 Gökbuget N, Basara N, Baurmann H, et al. High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. *Blood* 2011; **118:** 3504–11.

170 DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood* 2007; **109:** 5136–42.

171 Durinck K, Goossens S, Peirs S, et al. Novel biological insights in T-cell acute lymphoblastic leukemia. *Exp Hematol* 2015; **43:** 625–39.

172 Habets RA, de Bock CE, Serneels L, et al. Safe targeting of T cell acute lymphoblastic leukemia by pathology-specific NOTCH inhibition. *Sci Transl Med* 2019; **11:** 11.

173 Hill LC, Rouce RH, Smith TS, et al. Safety and anti-tumor activity of CD5 CAR T-cells in patients with relapsed/refractory T-cell malignancies. *Blood* 2019; **134:** 199.

174 Bride KL, Vincent TL, Im SY, et al. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. *Blood* 2018; **131:** 995–99.

175 Ofran Y, Ringelstein-Harlev S, Slouzkey I, et al. Daratumumab for eradication of minimal residual disease in high-risk advanced relapse of T-cell/CD19/CD22-negative acute lymphoblastic leukemia. *Leukemia* 2020; **34:** 293–95.