Chapter 5
Treatment of Adult B- and T-Cell Acute Lymphoblastic Leukemia: An Overview of Current Treatments and Novel Advances

Shimoli V. Barot and Anjali S. Advani

Clinical Case I

A 52-year-old woman presents with night sweats, fatigue, easy bruising, and dyspnea on exertion. Past medical history is notable for hypertension. Complete blood count (CBC) at presentation is as follows: white blood cell (WBC) count 11×10^9/L, hemoglobin 7.3 g/dL, and platelets 42×10^9/L. Bone marrow aspirate/biopsy demonstrates 90% blasts. Flow cytometry is positive for CD10, CD19, CD22, CD34, CD79a, HLA-DR, and TdT, diagnostic for pre-B-ALL. She is CD20- and has a normal karyotype. Tissue typing confirms a HLA-matched compatible sibling. Reverse transcriptase polymerase chain reaction (RT-PCR) for *BCR-ABL1* is negative. Testing for the Ph-like signature is negative for any ABL class fusions or JAK pathway alterations. Therefore, she does not have any high-risk features.

Risk Stratification

Accurate risk stratification is a key aspect in the management of ALL. It aids in determining optimal initial treatment and consideration of HSCT. Historically, the MRC UKALLXII/ECOG E2993 study [5] found that factors at diagnosis predictive of overall survival (OS) and disease-free survival (DFS) were age (P = 0.001), WBC count $<30 \times 10^9$/L for B-lineage or $< 100 \times 10^9$/L for T-lineage (P = 0.001), and immunophenotype, T-lineage vs. B-lineage (P = 0.001). With improved

S. V. Barot
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, USA
e-mail: barots@ccf.org

A. S. Advani (✉)
Department of Leukemia, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: advania@ccf.org

M. R. Litzow, E. A. Raetz (eds.), *Clinical Management of Acute Lymphoblastic Leukemia*, https://doi.org/10.1007/978-3-030-85147-7_5

understanding of the genetic landscape of ALL, recurrent cytogenetic and molecular abnormalities have been identified. These have now become more crucial in the prognosis and management of ALL [6–10]. One of these cytogenetic aberrations is the presence of the Ph chromosome (t[9;22][q34;q11]). It accounts for about 25% of adult ALL and 50% of cases in older adults. It has an aggressive clinical course with high risk of relapse [11]. However, the development of tyrosine kinase inhibitors (TKIs) has revolutionized the management of these patients and is discussed in a separate chapter. Some other adverse genetic abnormalities in ALL include complex karyotype (≥5 chromosomal abnormalities), intrachromosomal amplification of chromosome 21 (iAMP21), t(v;14)(v;q32)-*IGH*-r, low hypodiploidy/near triploidy, t(4;11)(q21;q23)-*KMT2A-AFF1*, and other *MLL* translocations. Conversely, t(12;21)(p13;q22)(ETV6–RUNX1), which is observed almost exclusively in children, and hyperdiploidy have significantly better outcomes (Fig. 5.1 and Table 5.1).

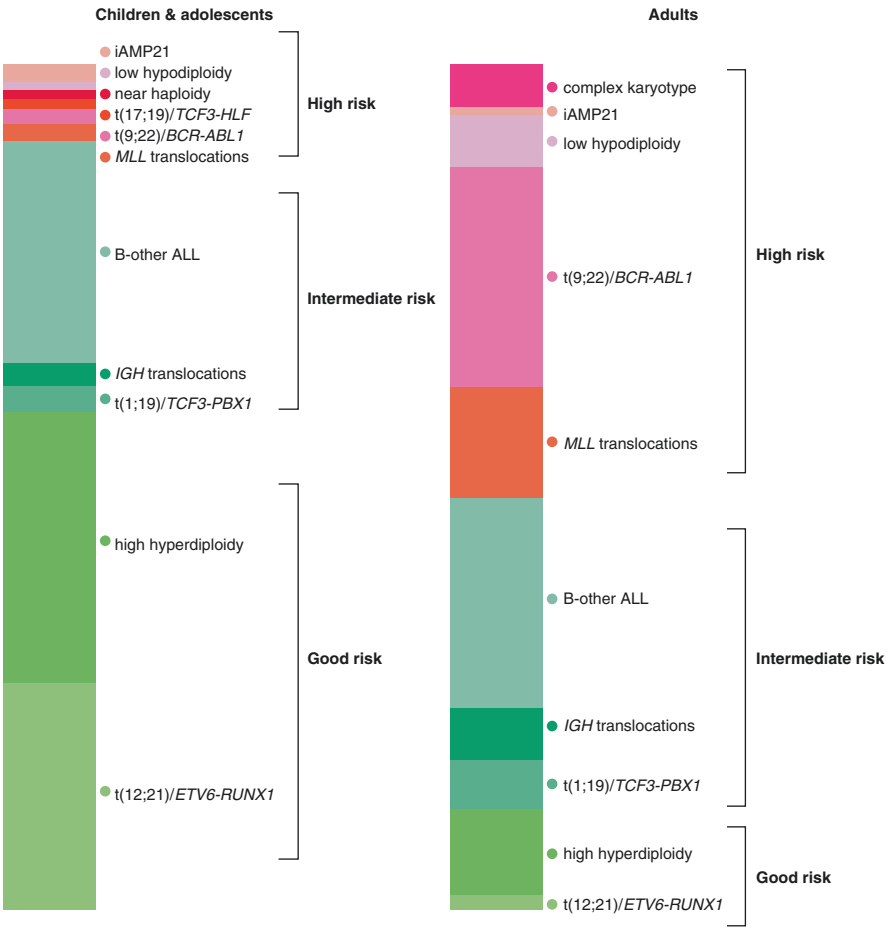

Fig. 5.1 Recurrent cytogenetic and molecular abnormalities in ALL. (Used with permission: Moorman [140])

Table 5.1 Common recurrent cytogenetic abnormalities in pediatric and adult B-ALL [130]

Risk groups	Cytogenetic abnormalities	Clinical significance	Frequency
Good risk	Hyperdiploidy (>50 chromosomes)	Favorable prognosis	25–30% in children; 7–8% in adults
	t(12;21)/*ETV-RUNX1*	Favorable prognosis in children, undetermined in adults	25% in children; 0–4% in adults
Intermediate risk	t(1;19)/*E2A-PBX1*	Intermediate to favorable prognosis	1–6% in children; 1–3% in adults
	t(5;14)/*IL3-IGH*	Intermediate	Rare
Poor risk	t(9;22)/*BCR-ABL1*	Poor prognosis	1–3% in children; 25–30% in adults
	t(v;11q23)/*KMT2A (MLL)* rearrangements	Poor prognosis	2/3 in infants; 1–2% in older children; 4–9% in adults
	Hypodiploidy (<44 chromosomes)	Poor prognosis	6% in children, 7–8% in adults

In 2009, a new subtype of ALL called Ph-like or *BCR/ABL1*-like ALL was identified which expresses a genomic signature reminiscent of *BCR/ABL1* in the absence of the *BCR/ABL1* fusion [12–14]. Ph-like ALL is detected in about 10% of children, 25% of AYAs, and 20–30% of adults. It is associated with poor chemotherapy response, high MRD, and significantly inferior outcomes [15–19]. Ninety-one percent of these patients harbor genetic alterations activating tyrosine kinase signaling. *CRLF2* rearrangements occur in up to 60% of adolescents and adults. ABL-class fusions are present in approximately 10–15% of children and adults. Other alterations include *JAK2* or *EPOR* rearrangements and mutations activating JAK-STAT or Ras signaling pathways [20]. Utilization of early HSCT, mAbs, and targeted therapies with kinase inhibitors is currently under investigation for Ph-like ALL and is discussed in a separate chapter.

Clinical Case I (Continued)

The patient is started on induction chemotherapy according to the CALGB 19802 protocol.

Treatment

The standard management approach in adult B-ALL consists of multi-agent chemotherapy administered over 2–3 years. Various protocols have been developed based on pediatric regimens. However, overall treatment consists of four integral components:

- Induction phase
- Consolidation phase

- Maintenance phase
- CNS prophylaxis and/or treatment

Induction Chemotherapy

The aim of the initial induction phase is to achieve CR which is defined as <5% blasts in the bone marrow and disease eradication at the molecular level (MRD negativity). Induction therapies are given over 4–6 weeks and typically involve either a four-drug regimen of vincristine, anthracycline, corticosteroid, and L-asparaginase or a five-drug regimen adding cyclophosphamide.

Anthracyclines Cancer and Leukemia Group B (CALGB) 7612 [21] evaluated the addition of daunorubicin to an induction regimen of vincristine, prednisone, and L-asparaginase. CR was observed in 83% vs. 47% (P = 0.003) of patients, and it established the role of an anthracycline in induction therapy.

Corticosteroids Historically, prednisone was utilized in induction regimens. However, trials comparing dexamethasone vs. prednisone showed that dexamethasone was associated with a significantly improved event-free survival (EFS) and a lower risk of CNS relapse in children [22, 23]. This is because dexamethasone penetrates the blood-brain barrier (BBB) more effectively [24]. However, dexamethasone has been associated with a higher rate of infection-related deaths and avascular necrosis especially in AYAs and adults [25, 26].

L-Asparaginase Asparaginase is an enzyme that breaks down extracellular asparagine into aspartic acid and ammonia. Depletion of extracellular asparagine inhibits the growth of ALL cells. Four-agent induction with intensive asparaginase therapy improved EFS in childhood ALL [27]. Similarly, in adults, the CALGB 9511 [28] used PEG-asparaginase and determined that patients who achieved effective plasma asparagine depletion have improved median OS (31% vs. 13%). However, adverse effects associated with asparaginase include thrombosis, pancreatitis, hyperglycemia, hepatotoxicity, immunogenicity, and infusion reactions.

Cyclophosphamide The Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) 0288 [29] evaluated the addition of cyclophosphamide to a conventional four-drug induction of vincristine, prednisone, daunorubicin, and asparaginase. The addition of cyclophosphamide significantly influenced CR achievement in a multivariate analysis.

Some of the commonly used regimens combining these drugs are:

- *CALGB 8811 (Larson 1995) and 9111 (Larson 1998) regimen*
  Based on the success of pediatric regimens, the CALGB 8811 [30] utilized an intensive five-drug chemotherapy program of cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase for induction in 197 adults. A CR

was achieved in 85% of patients, the median survival was 36 months, and the median remission duration was 29 months. However, the CNS prophylaxis in this regimen incorporated cranial radiation which has largely fallen out of favor due to complications such as neurocognitive decline, endocrine abnormalities, and brain necrosis [31].

A major difficulty with these intensive chemotherapy regimens is prolonged myelosuppression. Hence, the CALGB 9111 [32] evaluated the benefit of recombinant human granulocyte colony-stimulating factor (G-CSF) support in shortening the neutrophil recovery time and allowing the use of dose-intensive regimens with acceptable toxicity. Patients in the G-CSF group had significantly shorter durations of neutropenia and thrombocytopenia and fewer days in the hospital. They also had a higher CR rate and fewer deaths during induction.

- *CALGB 19802 regimen*

  CALGB 19802 [33] tested dose intensification of daunorubicin and cytarabine (ara-c) as well as the use of high-dose intravenous, oral, and intrathecal MTX as a substitute to cranial radiation for CNS prophylaxis. The intensification of daunorubicin and ara-c failed to result in an overall improvement in DFS or OS compared with historical CALGB studies. However, intensive systemic, oral, and intrathecal MTX and ara-c dosing could effectively replace CNS radiation based on the results.

- *Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin [Adriamycin], and dexamethasone)*

  Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin [Adriamycin], and dexamethasone), a dose-intensive two-phase chemotherapy regimen, was developed at the MD Anderson Cancer Center. The dose-intensive phase consists of four cycles of hyper-CVAD alternating with four cycles of high-dose MTX and ara-c. It also includes a risk-stratified schedule of CNS prophylaxis with intrathecal MTX and intrathecal ara-c as well as supportive care with antibiotic prophylaxis and G-CSF therapy. Maintenance therapy consists of 6-mercaptopurine (6-MP, Purinethol), vincristine (Oncovin), MTX, and prednisone (POMP) for 2 years. The phase II trial of a hyper-CVAD-based regimen reported an excellent 91% CR rate and a 39% 5-year OS. A subsequent retrospective review from the same center with further follow-up reported an increased mortality during induction with advanced patient age (2% vs. 15% for <60 or ≥60 years, respectively) [34, 35]. The chief drawback of administering this regimen is the increased myelosuppression and the increased necessity for longer hospital admission.

- *MRC UKALL XII/ECOG 2993 regimen*

  In one of the largest multicenter prospective trials conducted to date, 1521 adolescent and adult patients received induction therapy consisting of vincristine, daunorubicin, prednisone, and L-asparaginase for 4 weeks (phase I) followed by cyclophosphamide, ara-c, oral 6-MP, and intrathecal MTX for 4 weeks (phase II). With a CR rate of 91% and OS of 45% for patients who achieved CR, this induction regimen is highly efficacious [5].

- Regimens commonly used in older adults include the GRAALL-SA1 regimen [36], GMALL regimen [37], PETHEMA-based regimen [38], Modified DFCI 91-01 protocol [39], and others (Table 5.2). The treatment of elderly patients with ALL is discussed in a separate chapter.

Central Nervous System Prophylaxis and/or Treatment

Prior to the use of CNS prophylaxis, about 75% of recurrences in children involved the CNS [40]. In adults, CNS involvement at the time of presentation is uncommon (5–7%) [41, 42]. However, CNS relapse occurs in about 30% of patients who have achieved a CR [43]. CNS prophylaxis is thus imperative, and the method used should be congruent with the studies investigating the particular regimen. The modalities include CNS radiation, intrathecal chemotherapy, and systemic high-dose therapy with MTX and/or ara-c [44].

Radiation is an effective form of CNS-directed therapy but is frequently associated with long-term adverse effects, such as secondary neoplasms, endocrinopathy, neurocognitive dysfunction, and neurotoxicity [31]. In a CNS prophylaxis study of adults who received intrathecal and systemic therapy, the frequency of CNS recurrence was similar to that observed in protocols that included cranial radiation [45]. Similarly, Pui et al. concluded that a combination of early intensive systemic and intrathecal chemotherapy allows omission of cranial radiation [24]. Systemic chemotherapy alone is limited for CNS prophylaxis given the poor penetration of drugs in the BBB. The ability of ara-c and MTX to penetrate the BBB makes them useful agents [46]. However, maintaining prolonged therapeutic concentrations in the CSF requires high doses which frequently lead to toxicity. Hence, intrathecal chemotherapy is now used widely, because it allows direct intra-CSF treatment and a

Table 5.2 Commonly used regimens in adult ALL

Number	Trial	Number of patients	Rate of CR (%)	Reference
1	CALGB 8811	197	85	[30]
2	CALGB 9111	198	85	[32]
3	CALGB 19802	161	80	[33]
4	EORTC ALL-3	340	74	[131]
5	GIMEMA 0288	767	82	[29]
6	GIMEMA 0496	450	80	[9]
7	GMALL 05	1163	83	[132]
8	JALSG ALL 93	263	78	[133]
9	LALA 87	572	76	[134]
10	LALA 94	922	84	[62]
11	MDACC	288	92	[34]
12	MRC UKALL XII/ECOG E2993	1521	91	[5]
13	PETHEMA ALL 93	222	82	[103]
14	UCSF	109	88	[135]

sustained therapeutic drug concentration in the CSF. The various regimens used are MTX in mono- or triple-therapy with ara-c and steroids, and their effectiveness has been established in various studies [47–49]. This is further elaborated in a separate chapter.

Addition of Monoclonal Antibodies for CD20+ ALL

The CD20 antigen is present on 30–50% of B-ALL blasts and was previously associated with an adverse prognosis [50]. Currently, the addition of rituximab, a mAb against CD20, to chemotherapy has improved OS in adult patients <60 years of age with CD20+ ALL [51, 52]. In contrast, older adults (≥60 years) did not appear to benefit from the addition of rituximab. In a recent study, 209 patients (18–59 years) with newly diagnosed CD20+ B-ALL were randomly assigned to receive chemotherapy ±16–18 infusions of rituximab spanning induction through maintenance. EFS was longer in the rituximab group than in the control (P = 0.04), and the 2-year EFS rates were 65% vs. 52%, respectively [50]. Given this data, incorporation of rituximab with chemotherapy has become standard of care for newly diagnosed CD20+ B-ALL in patients <60 years of age.

Ofatumumab, a type I human antibody that targets a different CD20 epitope compared to rituximab, induces more potent antibody-dependent and complement-mediated cell death and is being evaluated in clinical trials [53, 54]. Similarly, obinutuzumab, a novel type II glycoengineered humanized anti-CD20 mAb, working primarily by inducing direct cell death and antibody-dependent cell-mediated cytotoxicity is being investigated as well [55].

Clinical Case I (Continued)

The patient completes induction chemotherapy according to the CALGB 19802 protocol without significant complications. Bone marrow biopsy on day 28 demonstrates a CR with no detectable MRD by multicolor flow cytometry (MFC). At this stage, a decision is made not to proceed to HSCT given her MRD negative status and lack of high-risk features. She continues consolidation/maintenance chemotherapy per protocol.

Minimal Residual Disease

With any of the above induction regimens, about 85–90% of newly diagnosed adults will achieve CR. However, patients in initial clinical and morphologic CR can have persistent leukemia cells below the detection limits of conventional cytomorphologic testing. This is defined as minimal residual disease. A study on molecular MRD

analysis carried out by the German Multicenter Study Group for Adult ALL (GMALL) on 580 patients demonstrated that the molecular response to standard induction and consolidation treatment was the only significant prognostic factor for remission duration and survival in both standard-risk and high-risk groups [56]. These data have been confirmed by other groups, regardless of the cutoff values, MRD technique, timing of MRD analysis, and target patient population [57, 58]. The three most widely used techniques are RT-PCR, MFC, and next-generation sequencing (NGS). EuroFlow-based next-generation flow cytometry and high-throughput sequencing of Ig/TCR are also used [59]. The clonoSEQ assay is an in vitro diagnostic that uses multiplex PCR and NGS to identify and quantify certain gene sequences in DNA extracted from the bone marrow of ALL patients. It is capable of detecting MRD at levels below 1 in one million cells and received FDA approval in September 2018 [60]. Although the timing of MRD assessment in adult ALL varies in different studies, it is commonly accepted that the initial measurement should be performed upon completion of induction therapy. Thereafter, ongoing MRD monitoring is extremely important since the presence of MRD $>10^{-4}$ is consistently predictive of subsequent hematologic relapse at every stage of the disease as seen in the GMALL studies [61]. MRD is now widely accepted and is regarded today as the most important prognostic factor in the management of childhood and adult ALL. It is further discussed in a separate chapter.

Consolidation/Intensification Chemotherapy

The primary aim of post-remission therapy is therefore to eradicate MRD. The three main approaches are chemotherapy, autologous HSCT, and allogeneic HSCT.

The French LALA-87 [62] investigated the use of allogeneic HSCT, autologous HSCT, or consolidation chemotherapy in 436 patients in first remission. Fifteen to forty-year-old patients with an HLA-identical sibling underwent a matched sibling HSCT. Those 40–50-year-old patients without an HLA-identical sibling were randomly assigned treatment with either autologous HSCT or chemotherapy. All patients >50 years were treated with chemotherapy alone. This trial demonstrated a significant superiority of allogeneic HSCT in high-risk ALL patients (defined as CNS-positive ALL; presence of Ph chromosome, t(4;11), t(1;19), or other abnormalities involving 11q23 rearrangements; a WBC count $>30 \times 10^9$/L; and patients who did not achieve CR after one course of chemotherapy). Similarly, there was a trend in favor of autologous HSCT over chemotherapy in high-risk patients. Conversely, allogeneic HSCT was not superior to autologous HSCT or chemotherapy in standard-risk ALL.

The International MRC UKALLXII/ECOG E2993 was the largest prospective study of 1484 patients to evaluate the role of allogeneic HSCT in first remission [63]. All patients aged 15–55 years with an HLA-matched sibling donor were assigned to receive an allogeneic HSCT in first CR, whereas those without a compatible sibling donor were randomized to receive either autologous HSCT or prolonged chemotherapy. Five-year OS for patients with and without a donor was

53% vs. 45% (P = 0.02) indicating the superiority of allogeneic HSCT overall. For the high-risk patients (defined as patients >35 years; those with a high WBC count at presentation of $\geq 30 \times 10^9$/L for B-lineage and $\geq 100 \times 10^9$/L for T-lineage; and Ph chromosome positive), relapse rate was significantly reduced (63% vs. 37%; P ≤ 0.001). However, unexpectedly, the 5-year OS was not significantly superior (41% vs. 35%; P = 0.2) secondary to HSCT-associated toxicities. In contrast, for the standard-risk patients, having a donor was associated with significantly superior OS (62% vs. 52%; P = 0.02) and reduced relapse rate (49% vs. 24%; P ≤ 0.001). Additionally, an autologous transplantation was found to be less effective than conventional consolidation/maintenance chemotherapy in all patients.

These data have been further validated in a meta-analysis of 13 trials with 2648 patients which concluded that allogeneic HSCT was superior to autologous HSCT or chemotherapy for patients with ALL in first remission and the survival advantage was of greater statistical significance for patients with standard-risk than with high-risk ALL [64]. Similarly, Gupta et al. analyzed data from 13 studies including 2962 patients and found no benefit of autologous HSCT in comparison to chemotherapy for adults in first remission but found that allogeneic HSCT improved survival for patients <35 years of age [65]. It is important to note that the younger patients in these original studies were not treated with pediatric regimens and currently AYA patients achieve better outcomes on pediatric regimens than conventional adult regimens.

In conclusion, for patients with high-risk features and persistent MRD and patients with relapsed/refractory disease, allogeneic HSCT offers the best chance for a durable response. However, it is important to take into account the risk/benefit ratio with higher morbidity and mortality associated with allogeneic HSCT. Patients at standard risk who achieve and maintain molecular remission can be treated with consolidation/maintenance chemotherapy including the AYA population given the improved outcomes with the current pediatric regimens.

Maintenance Chemotherapy

Maintenance therapy is a standard component of ALL management and is given for 2–3 years after consolidation beyond which it has not been shown to have benefit [66]. The most commonly used drugs are 6-MP, MTX, vincristine, and prednisone. CNS prophylaxis is continued during this time in some regimens, particularly pediatric protocols.

Clinical Case I (Continued)

She relapses 2.5 years from diagnosis and after receiving maintenance therapy. CBC is as follows: WBC 12 × 10^9/L, hemoglobin 6.6 g/dL, and platelets 15 × 10^9/L. Her bone marrow is completely replaced with lymphoblasts with the

original immunophenotype. She is treated with blinatumomab and achieves a second remission. Thereafter, she undergoes HSCT from her sibling donor.

Relapsed/Refractory Disease

While 85–90% of patients achieve remission after induction therapy, there is a subset that is refractory to induction therapy. Additionally, despite a high frequency of CR, relapses are common and overall long-term survival is poor in adults [3]. Once patients relapse, the only hope of curative therapy is successful re-induction followed by allogeneic HSCT. Thus, attaining a CR to bridge patients to HSCT is currently the goal of salvage therapies. Re-induction regimens include standard or novel chemotherapeutic agents or immunotherapies (Fig. 5.2).

Liposomal Vincristine

Vincristine sulfate liposome injection (VSLI) encapsulates vincristine in a sphingomyelin/cholesterol envelope for targeted delivery, increased efficacy, and lower neurotoxicity. In August 2012, VSLI received FDA approval for relapsed/refractory

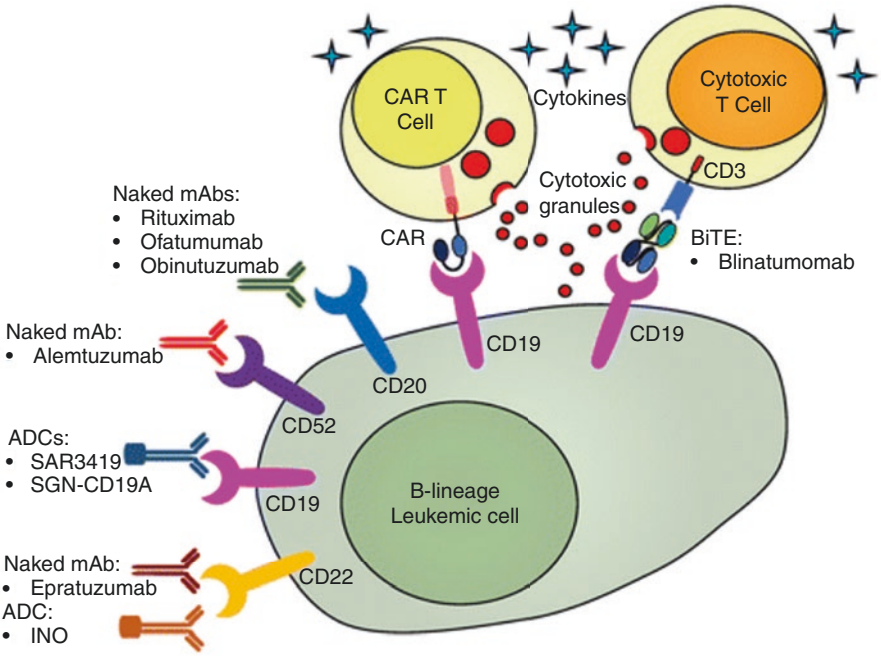

Fig. 5.2 Novel immunotherapies in ALL. mAb monoclonal antibody, ADC antibody-drug conjugate, INO inotuzumab ozogamicin, BiTE bispecific T-cell engager, CAR chimeric antigen receptor. (Used with permission: Wei et al. [141])

ALL based on a phase II trial in which overall response rate (ORR) with VSLI monotherapy was 35% and 20% of the patients achieved a CR/complete response with incomplete hematologic recovery (CRi). Nineteen percent of the complete responders were successfully bridged to HSCT [67].

Clofarabine

Clofarabine is a deoxyadenosine analog approved by the FDA for the treatment of younger patients (1–21 years) with relapsed/refractory ALL [68]. In adults, phase I/II trials demonstrated an ORR of 17% [69]. A similar 17% rate of CR/CRi was observed among patients treated with clofarabine combined with ara-c [70]. In a study from GRAALL, adult patients with relapsed/refractory ALL were treated with clofarabine in combination with conventional chemotherapy (ENDEVOL cohort) or a more intensive regimen (VANDEVOL cohort) yielding a CR rate of 50% vs. 41% and median OS of 6.5 months [71].

Blinatumomab

Blinatumomab is a bi-specific T-cell engager (BiTE) mAb construct that binds simultaneously to CD3+ cytotoxic T cells and to CD19+ ALL blasts. This facilitates the patient's T cells to recognize and eliminate CD19+ ALL blasts.

In a phase II clinical trial with blinatumomab for relapsed/refractory B-ALL, the CR/CRi rate was 69% after the first two cycles and 88% of responders achieved a molecular remission [72]. A separate multicenter phase II study demonstrated that 43% patients achieved a CR/CRi after only 2 cycles of treatment with blinatumomab with a median OS of 6.1 months [73]. Based on these results, blinatumomab was approved by the FDA in December 2014 for patients with relapsed/refractory pre-B-ALL. Thereafter, the phase III TOWER trial of 405 adults with heavily pretreated pre-B-ALL found that treatment with blinatumomab resulted in significantly improved CR rates and longer OS than standard chemotherapy. 6-month EFS rates were 31% vs. 12% and median remission duration was 7.3 vs. 4.6 months for blinatumomab vs. chemotherapy respectively [74].

Blinatumomab is also currently approved for pre-B-ALL in first or second remission with MRD $\geq$0.1% based on the multicenter BLAST trial [75] in which 78% of patients achieved a complete MRD response. The relapse-free survival was 54% at 18 months and the median OS was 36.5 months. Importantly, MRD responders had longer relapse-free survival (23.6 vs. 5.7 months; P = 0.002) and OS (38.9 vs. 12.5 months; P = 0.002) compared with MRD non-responders. At present, blinatumomab is also being investigated for use in frontline therapy of newly diagnosed B-ALL and in combination with other therapies [76–81].

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (InO) is an antibody-drug conjugate composed of a humanized anti-CD22 mAb conjugated to the cytotoxic agent calicheamicin. It binds with high affinity to CD22, a cell-surface antigen expressed by >90% of B-cell blasts in nearly all patients with B-ALL. The antibody-drug conjugate is then rapidly internalized, and subsequent intracellular release of unconjugated calicheamicin leads to apoptosis via its binding to and cleavage of double-stranded DNA [82].

The phase III INO-VATE trial compared InO with one of three standard chemotherapy regimens, FLAG (fludarabine, ara-c, and G-CSF), ara-c+mitoxantrone, and single-agent ara-c, and found that the risk of progression or death was reduced by 55% with InO vs. standard chemotherapy. 80.7% vs. 29.4% of patients achieved CR/CRi, and 78.4% vs. 28.1% of responders attained MRD negativity with InO vs. chemotherapy. The CR/CRi rates for first and second salvage therapy were 87.7% and 66.7%, respectively (vs. 28.8% and 30.6% in the chemotherapy arm) [83, 84]. Based on these results, InO was FDA approved for relapsed/refractory pre-B-ALL in August 2017. At present, studies are underway using InO in frontline therapy, in MRD, and in combination with various agents [85–88].

Both blinatumomab and InO have comparable response rates. However, due to a short half-life, blinatumomab requires a continuous infusion. The major adverse effects include infusion reactions as well as the potentially fatal cytokine release syndrome (CRS) and neurological toxicities. Neurological events can include tremor, dizziness, confusion, and aphasia. Significant CRS was reported in 2% of patients and generally occurs with the first treatment [73]. It is treated by interrupting/permanently discontinuing the infusion and using corticosteroids.

Conversely, InO can be given weekly. The most frequent adverse effect is myelosuppression. InO is associated with hepatotoxicity and most commonly grade 1 or 2 liver-related laboratory abnormalities. Importantly, the INO-VATE trial reported a higher rate of veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) in the InO arm (11% vs. 1%). Patients at increased risk of SOS include age ≥65 years, history of HSCT before InO treatment, history of liver disease, longer duration of InO exposure, and conditioning regimens containing two alkylating agents, especially those containing thiotepa. Studies have emphasized the importance of medical history and implementing risk reduction strategies in patients undergoing HSCT after InO [89].

CAR-T (Tisagenlecleucel)

CAR T-cell therapy is a revolutionary treatment in which T cells are genetically engineered to express chimeric antigen receptors specifically directed toward antigens on a patient's tumor cells and then infused back into the patient where they attack and kill the cancer cells.

In August 2017, the FDA approved the anti-CD19 CAR T-cell agent tisagenlecleucel for the treatment of patients up to 25 years of age with relapsed/refractory

B-ALL based on the results of the ELIANA global multicenter trial of 75 patients (3–21 years). Eighty-one percent of patients had an ORR within the first 3 months and 100% achieved MRD-negative status. Persistence of tisagenlecleucel in the blood was observed for as long as 20 months leading to a durable relapse-free survival rate of 80% at 6 months and 59% at 12 months, and only 9% of patients proceeded to allogeneic HSCT [90]. However, growing experience has revealed that remissions may be short in a substantial number of patients owing to poor persistence and/or resistance from antigen loss or modulation. Improved strategies and newer CAR-Ts are being developed to overcome this hurdle [91].

In a phase I trial, 53 adults with relapsed/refractory B-ALL received one infusion of 19-28z CAR-T cells, which expressed a second-generation CD19-specific CAR, and 83% of patients achieved CR. Median EFS was 6.1 months and median OS was 12.9 months. Other studies have also reported similar results, but it has not yet been approved in the adult population [92, 93].

Toxicities, which can be fatal, include CRS, B-cell aplasia, and cerebral edema. Tocilizumab, a recombinant humanized mAb against the interleukin-6 receptor (IL-6R), has been FDA approved for the treatment of severe/life-threatening CRS resulting from CAR T-cell therapy in patients ≥2 years of age. In clinical trials, 69% of patients with CAR T-cell therapy-related CRS had complete resolution within 2 weeks after receiving one to two doses of tocilizumab [94].

Venetoclax/Navitoclax

Venetoclax is a highly selective BCL-2 inhibitor. Navitoclax is a BCL-2/BCL-X_L/BCL-$_W$ inhibitor, but prolonged thrombocytopenia limits its continuous use at higher doses. The combination aims for synergistic activity against BCL-2 with reduction in the limiting adverse effect from navitoclax. A phase I, multicenter study (NCT03181126) is currently evaluating venetoclax+navitoclax and chemotherapy (PEG-asparaginase, vincristine, dexamethasone) in relapsed/refractory ALL. Based on preliminary data, the ORR was 56% (20/36) in the total population with best responses of CR/CRi/CR with incomplete platelet recovery (CRp) in 18 patients. Of the 18 patients with CR/CRi/CRp, 10 (56%) had undetectable MRD. The preliminary efficacy data is promising in this heavily pretreated population [95].

Clinical Case II

A 22-year-old man presents with fever, weight loss, fatigue, and abdominal pain. He has no past medical history. CBC at presentation is as follows: WBC 21 × 10^9/L, hemoglobin 7.1 g/dL, and platelets 33 × 10^9/L. Hepatosplenomegaly is present. Bone marrow biopsy is consistent with the diagnosis of precursor B-ALL. He is CD20- and cytogenetics show a normal male karyotype. RT-PCR for *BCR-ABL1*

and Ph-like signature testing is negative. FISH is negative for recurrent genetic abnormalities.

Approach to a Young Adult

At the intersection between children and older adults is the population of AYAs. Their disease biology, management, and psychosocial factors are unique and require a distinct approach.

Risk Stratification

In an analysis of 21,626 ALL cases diagnosed between 1990 and 2005 and treated with Children's Oncology Group (COG) regimen, survival rates decreased significantly with increasing age at diagnosis regardless of treatment era (94.1% for ages 1–10, 84.7% for ages 10–15, and 75.9% for ages 15–22 years in the 2000–2005 cohort) [1]. An explanation for this is the primary differences in the frequency of the recurrent genetic alterations between children and adults with ALL [96, 97]. The most significant of these is the poor-risk Ph chromosome which is observed in 2–5% of children vs. 30% of adults. iAMP21 is present in 2% of childhood ALL, is more frequent in older children and adolescents, and is associated with a higher risk of relapse. *IgH* rearrangements are more frequent in the AYA population and are also associated with unfavorable outcomes. Additionally, the t(12;21)(p13;q22)(ETV6–RUNX1), associated with good prognosis, is observed in 25% of children vs. 3% of adults. Similarly, a hyperdiploid karyotype (>50 chromosomes) is found in 30–40% of children vs. 2–10% of adults. Hence, as age increases, there is a progressive rise in the prevalence of ALL genetic subtypes with poor prognosis, whereas subtypes with favorable outcomes become less common [98]. Therefore, relative to children, AYAs tend to present with higher rates of unfavorable genetic abnormalities and thus have inferior outcomes.

Clinical Case II (Continued)

The patient is started on induction chemotherapy according to the pediatric-based C10403 protocol.

Treatment

Adult treatment regimens typically include intensive use of myelosuppressive agents and allogeneic HSCT in first remission. Conversely, pediatric regimens focus on the Berlin-Frankfurt-Munster (BFM) backbone of vincristine, daunorubicin, prednisone, asparaginase, early and frequent CNS prophylaxis with intrathecal ara-c/MTX, and prolonged maintenance therapy. Because an AYA patient may be viewed as either an older child or a younger adult, AYAs were historically treated with either pediatric or adult ALL protocols based on the population most often seen by the treating oncologist. These inconsistencies led to the first comparisons of pediatric and adult regimens in the AYA population (Tables 5.3a and 5.3b).

- *Berlin-Frankfurt-Munster (BFM) Regimen*

  Stock et al. [99] performed a retrospective comparison of 321 adolescents aged 16–20 years who were treated on consecutive trials in either the Children's Cancer Group (CCG) using the BFM pediatric-style regimen or the CALGB adult-style regimen from 1988 to 2001. CR rates were 90% and identical in both arms. However, CCG adolescents had a 63% EFS and 67% OS at 7 years vs. 34% and 46% ($P < 0.001$), respectively, in the CALGB. Comparison of the regimens demonstrated that CCG adolescents received earlier and more intensive CNS prophylaxis and higher cumulative doses of non-myelosuppressive agents. Subsequently, similar results were also reported by several other groups [100–102].
- *PETHEMA (Programa Español de Tratamiento en Hematología) Pediatric-Based Protocol ALL-96*

  Retrospective studies consistently demonstrated that AYAs have better outcomes when treated with pediatric protocols, but prospective studies were scarce,

Table 5.3a Adult versus pediatric regimens for adolescent and young adults

Country	Adult regimen	EFS	Pediatric regimen	EFS	Reference
USA	CALGB	34	CCG	63	[99]
France	LALA94	41	FRALLE93	67	[100]
UK	UK ALL XII	49	ALL97	65	[136]
Finland	FLGN	60	NOPHO	67	[137]
Netherland	HOVON	34	DCOG	69	[138]
Italy	GIMEMA	71	AEIOP	80	[139]

Table 5.3b Pediatric regimens for adolescent and young adults

Country	Regimen	EFS/DFS	Reference
USA	DFCI	72	[104]
Spain	PETHEMA ALL-96	60	[103]
France	GRAALL-2003	58	[105]
Netherlands/Belgium	HOVON 70	66	[101]

and this was accomplished by the ALL-96 protocol. Among 81 patients aged 15–30 years, the CR rate was 98%, and 6-year EFS and OS were 61% and 69%, respectively, with no differences between adolescents and young adults [103].

- *Dana-Farber Cancer Institute (DFCI) ALL Regimen*

  This trial assessed the feasibility of treating adult patients aged 18–50 years with the DFCI Pediatric ALL Consortium regimen. Eighty-five percent of patients achieved a CR after 1 month of intensive induction therapy. The 4-year DFS and 4-year OS were 69% and 67%, respectively. They concluded that a pediatric-like treatment strategy for young adults is feasible, is associated with tolerable toxicity, and results in improved outcomes compared with historical regimens in young adult patients with ALL [104].

- *Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)-2003 and GRAALL-2005 Regimen*

  The aim of GRAALL-2003 study was to test a pediatric-inspired treatment in adult patients up to the age of 60 years. In this trial, the CR rate was 94%. EFS and OS rates were 55% and 60%, respectively. In a subgroup analysis, patients ≥45 years had a similar incidence of relapse (30% vs. 32%) but significantly higher rates of chemotherapy-related deaths (23% vs. 5%) and deaths during first CR (22% vs. 5%) as compared with patients ≤45 years which makes this regimen better suited for the AYA population [105]. This was the basis for the C10403 trial including patients up to the age of 40 years.

  In an update on their data, the GRAALL-2005 was aimed to determine the upper age limit for treatment tolerability of a pediatric-inspired protocol of hyperfractionated cyclophosphamide (hyper-C) dose intensification in 787 patients. Randomization to the hyper-C arm vs. a standard dose of cyclophosphamide did not increase the CR rate or prolong EFS or OS. Overall, patients <55 years of age were able to tolerate this intensive pediatric-derived treatment [106].

- *C10403 Regimen*

  To address the feasibility and efficacy of using a pediatric regimen for AYA patients administered by adult treatment teams, a prospective study, C10403, was performed. The treatment arm employed interim maintenance with escalating doses of MTX (without leucovorin rescue) followed by asparaginase (Capizzi MTX) as in the PC arm of the Children's Oncology Group (COG) study AALL0232 [25]. From 2007 to 2012, 318 patients with median age 24 years (range: 17–39 years) were enrolled. Median EFS was 78.1 months, more than double the historical control of 30 months. Three-year EFS was 59% and 3-year OS was 73%. Thus, use of a pediatric regimen for AYAs up to age 40 was found to be feasible and effective, resulting in improved survival rates compared with historical controls [107].

  In all of the above studies, the upper age limit varied from 40 to 59 years, but a higher chemotherapy-related toxicity was observed with increasing age. Thus, young adults benefit from pediatric-inspired approaches but the upper age limit of applicability should be determined by individual protocols.

Clinical Case II (Continued)

The patient completes induction chemotherapy according to the C10403 protocol without significant complications. Bone marrow biopsy on day 28 demonstrates CR with no detectable MRD by MFC. At this stage, a decision was made not to proceed to HSCT. He continues therapy as per protocol. Following intensive post-remission consolidation, he moves on to starting maintenance therapy. At this time, he unfortunately loses his job and the associated health insurance. He is unable to bear the cost of medications and does not refill them. With multidisciplinary support for his socioeconomic situation, he is able to complete treatment.

Hematopoietic Stem Cell Transplant

The MRC UKALLXII/ECOG E2993 [63] was the largest prospective study of 1484 patients evaluating the role of allogeneic HSCT in first remission. Specific to AYAs, this trial enrolled 234 patients <20 years old and 301 patients 20–29 years old. A significant OS benefit in favor of allogeneic HSCT was seen only in those with standard-risk disease (62% vs. 52%; P = 0.02), defined as <35 years of age with no adverse biological features. The 5-year OS for patients aged 15–29 years was 45%.

Although these results suggest that allogeneic HSCT in first remission may be superior in young adults without high-risk features, the principal limitation of these studies was the use of adult treatment regimens in treating AYA patients. Hence, the comparison of 422 patients (18–50 years) reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) with 108 age-matched patients who received a DFCI pediatric-inspired regimen showed no difference of 4-year relapse rates (24% vs. 23%). Due to a high treatment-related mortality in allogeneic HSCT (37% vs. 6%, P < 0.0001), the 4-year OS was significantly better in non-transplanted patients (45% vs. 73%, P < 0.0001) [108]. Similarly, another retrospective study evaluated the CALGB 10403 regimen for post-remission therapy in 295 AYAs compared to a contemporary matched cohort of 217 AYAs undergoing allogeneic HSCT in first remission reported to the CIBMTR. The pediatric-inspired chemotherapy regimen was found to be superior in terms of OS, DFS, and non-relapse mortality [109].

Thus, in the current era of excellent outcomes in AYAs treated with intensified pediatric-based regimens, HSCT should be reserved for patients determined to be high risk based on molecular aberrations and MRD evaluation.

Psychosocial Support

Non-adherence to treatment regimens and missed appointments are a significant challenge in AYAs seen in up to 65% patients [110]. This is due to complex and prolonged regimens administered outpatient. The diagnosis and treatment at a

young age also has a significant impact on psychosocial functioning. Fear about prognosis, loss of independence, treatment-related toxicities, and financial issues can negatively impact quality of life. These patients are thus optimally treated in a supportive outpatient setting with a multidisciplinary approach unique to this patient population.

Clinical Case III

A 28-year-old man presents with a mediastinal mass and dyspnea on exertion. At presentation, CBC is as follows: WBC 50 × 10^9/L, hemoglobin 6.5 g/dL, and platelets 11 × 10^9/L. A bone marrow aspirate/biopsy shows 60% blasts positive for CD2, CD5, CD17, cytoplasmic CD3, CD10, weak CD4, and TdT, diagnostic of T-ALL. Cytogenetics are normal and cerebrospinal fluid examination is negative. He is treated with a combination of standard chemotherapy with nelarabine according to the COG AALL0434 protocol.

Risk Stratification

Factors that have been reported to increase the risk of relapse in patients with T-ALL include age, CNS involvement, an initial WBC count >100 × 10^9, a complex karyotype, CD13 expression, and CD1a-negativity. However these have been inconsistent across studies [111]. Karyotypic abnormalities are present in most patients with T-ALL, but there are no recurrent disease defining abnormalities. Recurrent gene mutations associated with prognosis have been identified in T-ALL. *NOTCH* gene mutations are present in 60% of cases [112] and *FBXW7* in 15% of cases [113]. These mutations are associated with a favorable prognosis, while mutations in *NRAS*, *KRAS*, or *PTEN* are associated with a higher incidence of relapse [114]. Similar to B-ALL, MRD is the most important prognostic factor in T-ALL as well [115]. Early T-cell precursor (ETP) ALL was recognized as a new provisional entity in the 2016 update to the World Health Organization classification of acute leukemia [116]. It comprises 15% of T-ALL and has a distinct biology. It has stem cell-like features and is associated with chemotherapy resistance. It requires intensified therapy with consideration of allogeneic HSCT particularly in patients with persistent MRD [117, 118].

Upfront Treatment

Childhood T-cell ALL is considered high risk with an inferior prognosis, and these patients are now treated in the high-risk arms of pediatric protocols with improved outcomes. In contrast, adult T-ALL has similar outcomes to B-ALL. In the

UKALLXII/ECOG 2993, the rate of CR for T-ALL and B-ALL was equivalent (94% vs. 93%; P = 0.5), and there was a trend toward improved 5-year OS in the patients with T-ALL (48% vs. 42%; P = 0.07). Similar results have been reported in other studies as well [5, 32, 34, 35, 111]. Hence, adult T-ALL patients are generally treated with the same regimens as those used for B-ALL. However, enhanced understanding of T-lineage biology and prognostic features has impacted the approach to treatment of T-ALL.

A vital aspect is the recognition of improved outcomes in young adults treated with pediatric regimens. These regimens heavily use asparaginase as compared to adult regimens and can explain the favorable outcomes [119]. The commonly used hyper-CVAD regimen does not incorporate asparaginase and may not be adequate for T-ALL treatment [120, 121]. Another important consideration is that T-ALL patients are more likely to have CNS involvement at presentation than B-ALL (9.6% vs. 4.4%; P = 0.001). Patients with CNS disease at diagnosis have inferior 5-year OS (42% vs. 29%) due to an increased risk of both systemic and CNS relapse [41]. Pediatric trials have demonstrated improved EFS in T-ALL when high-dose MTX is added as an intensification phase [122], and, hence, most T-ALL protocols have adopted high-dose MTX in addition to intrathecal chemotherapy. Additionally, the incorporation of dexamethasone (instead of prednisone) in frontline regimens has also been reported to decrease the risk of relapse in T-ALL [123].

Decision-making after remission requires an assessment of prognostic factors to determine whether to continue consolidation/maintenance chemotherapy or to consider allogeneic HSCT. Among the T-ALL patients in the UKALLXII/ECOG 2993, having a sibling donor halved the chance of relapse (25% vs. 51%; P < 0.0001) but modestly increased non-relapse mortality (22% vs. 12%; P = 0.06). Allogeneic HSCT is thus an effective therapy and can be considered for adult patients with high-risk T-ALL [111].

Nelarabine (nel) is a prodrug converted in vivo to ara-GTP especially in T cells. The COG AALL0434 [124] evaluated the safety and efficacy of nel when incorporated into COG augmented BFM (ABFM) chemotherapy in newly diagnosed T-ALL pediatric and young adult patients (1–30 years). The 4-year DFS for nel vs. no nel was 88.9 vs. 83.3% (P = 0.0332). Among patients randomized to escalating dose MTX (CMTX), the 4-year DFS was 92.2% vs. 89.8% (P = 0.3825), and for those randomized to high-dose MTX, 4-year DFS was 86.2% vs. 78% (P = 0.024) for nel vs. no nel. Overall toxicity and neurotoxicity were acceptable and not significantly different between all arms. The outcomes observed on this trial were markedly superior to any trial for children and young adults with T-ALL, and most groups have incorporated this as a new standard of care.

Recently, a phase II study of nel combined with hyper-CVAD in 67 adult patients (18–78 years) revealed [125] that it is safe and effective upfront, but compared to hyper-CVAD alone, there was no survival benefit with the addition of nel. The reason nel did not improve outcomes in adults could be the late incorporation of nel and the exclusion of asparaginase in the hyper-CVAD regimen.

Relapsed/Refractory Treatment

The goal in T-ALL is to prevent relapse through optimization of de novo therapy since treatment of relapsed disease is challenging and the salvage rates are dismal. Unlike B-ALL, where several novel agents have been approved for relapsed/refractory disease, there is a paucity of options beyond nelarabine and chemotherapy.

Nelarabine In October 2005, the FDA granted approval to nelarabine for relapsed/refractory T-ALL based on two phase II trials, one in pediatric and the other in adult patients. In the pediatric trial of 39 patients, 13% had a CR and 23% had a CRi. The adult trial of 28 patients demonstrated a CR in 18% and CR/CRi in 21% patients [126, 127].

Investigational Agents

New treatments for T-cell ALL are critically needed [128]. Gamma secretase is required for NOTCH1 signaling, and gamma secretase inhibitors are being developed. Ruxolitinib or other JAK/STAT pathway inhibitors may be an option especially for ETP-ALL. The BCL-2 inhibitor venetoclax is being investigated. T-ALL expresses CD30 and brentuximab could be used, while daratumumab, a mAb to CD38, has shown efficacy in preclinical trials [129]. A CD7-targeted CAR-T cell without self-destruction has also been developed. OBI-3424 is a highly selective prodrug that is converted by aldo-keto reductase family 1 member C3 (AKR1C3) to a potent DNA-alkylating agent and is under study as well [118]. These are discussed in a separate chapter.

Conclusion

The approach to management of ALL is one of the most complex and intensive strategies in cancer. The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades primarily among children. Improvements are largely due to advances in the understanding of the molecular biology and pathogenesis of the disease, incorporation of risk-adapted therapy, advent of new targeted agents, and the use of allogeneic HSCT. However, survival rates for adult patients remain inadequate and are especially guarded in older patients at approximately 20%. The approval and discovery of more effective and targeted therapies for ALL and moving novel therapies in the upfront setting will hopefully improve the outcomes for these patients.

Conflicts of Interest Shimoli V. Barot declares no conflicts of interest. Anjali S. Advani: honoraria, Pfizer; consulting/research funding, Amgen; consulting, GlycoMimetics; research support, MacroGenics, AbbVie, Pfizer, GlycoMimetics

References

1. 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; https://doi.org/10.1200/JCO.2011.37.8018.
2. Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. Cancer. 2015; https://doi.org/10.1002/cncr.29383.
3. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007; https://doi.org/10.1182/blood-2006-05-018192.
4. Siegel SE, Stock W, Johnson RH, et al. Pediatric-inspired treatment regimens for adolescents and young adults with Philadelphia chromosome–negative acute lymphoblastic leukemia: a review. JAMA Oncol. 2018; https://doi.org/10.1001/jamaoncol.2017.5305.
5. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood. 2005; https://doi.org/10.1182/blood-2005-04-1623.
6. Wetzler M, Dodge RK, Mrózek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the Cancer and Leukemia Group B experience. Blood. 1999; https://doi.org/10.1182/blood.V93.11.3983.
7. Moorman AV, Harrison CJ, Buck GAN, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007; https://doi.org/10.1182/blood-2006-10-051912.
8. Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings outcome. A Collaborative Study of the Group Francais de Cytogenetique Hematologique [published erratum appears in Blood 1996 Oct 1;88(7):2818]. *Blood*. 1996. https://doi.org/10.1182/blood.v87.8.3135.bloodjournal8783135.
9. Mancini M, Scappaticci D, Cimino G, et al. A comprehensive genetic classification of adult acute lymphoblastic leukemia (ALL): analysis of the GIMEMA 0496 protocol. Blood. 2005; https://doi.org/10.1182/blood-2004-07-2922.
10. Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. Blood. 2008; https://doi.org/10.1182/blood-2007-10-116186.
11. Gleißner B, Gökbuget N, Bartram CR, et al. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. Blood. 2002; https://doi.org/10.1182/blood.V99.5.1536.
12. 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; https://doi.org/10.1016/S1470-2045(08)70339-5.
13. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009; https://doi.org/10.1056/NEJMoa0808253.
14. Hoelzer D, Bassan R, Dombret H, et al. Acute lymphoblastic leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016; https://doi.org/10.1093/annonc/mdw025.
15. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012; https://doi.org/10.1016/j.ccr.2012.06.005.
16. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014; https://doi.org/10.1056/NEJMoa1403088.

17. 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; https://doi.org/10.1200/JCO.2016.69.0073.
18. Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood. 2017; https://doi.org/10.1182/blood-2016-07-726588.
19. Hunger SP, Mullighan CG. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. Blood. 2015; https://doi.org/10.1182/blood-2015-02-580043.
20. Roberts KG. The biology of Philadelphia chromosome-like ALL. Best Pract Res Clin Haematol. 2017; https://doi.org/10.1016/j.beha.2017.07.003.
21. Gottlieb AJ, Weinberg V, Ellison RR, et al. Efficacy of daunorubicin in the therapy of adult acute lymphocytic leukemia: a prospective randomized trial by cancer and leukemia. Blood. 1984; https://doi.org/10.1182/blood.v64.1.267.bloodjournal641267.
22. 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; https://doi.org/10.1182/blood-2002-08-2454.
23. Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TOB. 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; https://doi.org/10.1111/j.1365-2141.2005.05509.x.
24. Pui CH. Central nervous system disease in acute lymphoblastic leukemia: prophylaxis and treatment. Hematology Am Soc Hematol Educ Program. 2006; https://doi.org/10.1182/asheducation-2006.1.142.
25. 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; https://doi.org/10.1200/JCO.2015.62.4544.
26. Hunger SP. Glucocorticoid selection for pediatric ALL. Blood. 2016; https://doi.org/10.1182/blood-2016-02-701664.
27. Clavell LA, Gelber RD, Cohen HJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med. 1986; https://doi.org/10.1056/NEJM198609113151101.
28. Wetzler M, Sanford BL, Kurtzberg J, et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B study 9511. Blood. 2007; https://doi.org/10.1182/blood-2006-09-045351.
29. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood. 2002; https://doi.org/10.1182/blood.V99.3.863.
30. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: Cancer and Leukemia Group B study 8811. Blood. 1995; https://doi.org/10.1182/blood.v85.8.2025.bloodjournal8582025.
31. Pui CH, Cheng C, Leung W, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med. 2003; https://doi.org/10.1056/NEJMoa035091.
32. Larson RA, Dodge RK, Linker CA, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood. 1998;
33. Stock W, Johnson JL, Stone RM, et al. Dose intensification of daunorubicin and cytarabine during treatment of adult acute lymphoblastic leukemia: results of Cancer and Leukemia Group B study 19802. Cancer. 2013; https://doi.org/10.1002/cncr.27617.
34. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004; https://doi.org/10.1002/cncr.20668.

35. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000; https://doi.org/10.1200/jco.2000.18.3.547.
36. Hunault-Berger M, Leguay T, Thomas X, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. Haematologica. 2011; https://doi.org/10.3324/haematol.2010.027862.
37. Goekbuget N, Beck J, Brueggemann M, et al. Moderate intensive chemotherapy including CNS-prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): results of a prospective trial from the German Multicenter Study Group for Adult ALL (GMALL). Blood. 2012; https://doi.org/10.1182/blood.v120.21.1493.1493.
38. Ribera JM, García O, Oriol A, et al. Feasibility and results of subtype-oriented protocols in older adults and fit elderly patients with acute lymphoblastic leukemia: results of three prospective parallel trials from the PETHEMA group. Leuk Res. 2016; https://doi.org/10.1016/j.leukres.2015.11.012.
39. Poch Martell M, Atenafu EG, Minden MD, et al. Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. Br J Haematol. 2013; https://doi.org/10.1111/bjh.12561.
40. Bleyer WA, Poplack DG. Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Semin Oncol. 1985; https://doi.org/10.5555/uri:pii:0093775485900065.
41. Lazarus HM, Richards SM, Chopra R, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. Blood. 2006; https://doi.org/10.1182/blood-2005-11-4666.
42. Reman O, Pigneux A, Huguet F, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis and/or at first relapse: results from the GET-LALA group. Leuk Res. 2008; https://doi.org/10.1016/j.leukres.2008.04.011.
43. Omura GA, Moffitt S, Vogler WR, Salter MM. Combination chemotherapy of adult acute lymphoblastic leukemia with randomized central nervous system prophylaxis. Blood. 1980; https://doi.org/10.1182/blood.v55.2.199.bloodjournal552199.
44. Jabbour E, Thomas D, Cortes J, Kantarjian HM, O'Brien S. Central nervous system prophylaxis in adults with acute lymphoblastic leukemia: current and emerging therapies. Cancer. 2010; https://doi.org/10.1002/cncr.25008.
45. Sancho JM, Ribera JM, Oriol A, et al. Central nervous system recurrence in adult patients with acute lymphoblastic leukemia: frequency and prognosis in 467 patients without cranial irradiation for prophylaxis. Cancer. 2006; https://doi.org/10.1002/cncr.21948.
46. Cortes J, O'Brien SM, Pierce S, Keating MJ, Freireich EJ, Kantarjian HM. The value of high-dose systemic chemotherapy and intrathecal therapy for central nervous system prophylaxis in different risk groups of adult acute lymphoblastic leukemia. Blood. 1995; https://doi.org/10.1182/blood.v86.6.2091.bloodjournal8662091.
47. Pui CH, Mahmoud HH, Rivera GK, et al. Early intensification of intrathecal chemotherapy virtually eliminates central nervous system relapse in children with acute lymphoblastic leukemia. Blood. 1998; https://doi.org/10.1182/blood.v92.2.411.414k34_411_415.
48. Dekker AW, van't Veer MB, Sizoo W, et al. Intensive postremission chemotherapy without maintenance therapy in adults with acute lymphoblastic leukemia. Dutch Hemato-Oncology Research Group. J Clin Oncol. 1997;15(2):476–82.
49. 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; https://doi.org/10.1111/j.1365-2141.2009.07712.x.
50. Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. N Engl J Med. 2016; https://doi.org/10.1056/NEJMoa1605085.
51. 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; https://doi.org/10.1200/JCO.2009.26.9456.

52. Hoelzer D, Gökbuget N. Chemoimmunotherapy in acute lymphoblastic leukemia. Blood Rev. 2012; https://doi.org/10.1016/j.blre.2011.08.001.
53. Maiti A, Kantarjian HM, Ravandi F, et al. Updated results of frontline ofatumumab-hyper-CVAD in adults with CD20+ acute lymphoblastic leukemia. J Clin Oncol. 2017; https://doi.org/10.1200/jco.2017.35.15_suppl.7033.
54. Bazarbachi AH, Yilmaz M, Ravandi F, et al. A phase 2 study of hyper-CVAD plus ofatumumab as frontline therapy in CD20+ acute lymphoblastic leukemia (ALL): updated results. J Clin Oncol. 2018; https://doi.org/10.1200/jco.2018.36.15_suppl.7041.
55. Awasthi A, Ayello J, Van de Ven C, et al. Obinutuzumab (GA101) compared to rituximab significantly enhances cell death and antibody-dependent cytotoxicity and improves overall survival against CD20+ rituximab-sensitive/-resistant Burkitt lymphoma (BL) and precursor B-acute lymphoblastic leukaemia. Br J Haematol. 2015; https://doi.org/10.1111/bjh.13764.
56. Gökbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012; https://doi.org/10.1182/blood-2011-09-377713.
57. 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; https://doi.org/10.1001/jamaoncol.2017.0580.
58. Bassan R, Brüggemann M, Radcliffe HS, Hartfield E, Kreuzbauer G, Wetten S. A systematic literature review and metaanalysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. Haematologica. 2019; https://doi.org/10.3324/haematol.2018.201053.
59. Hefazi M, Litzow MR. Recent advances in the biology and treatment of B-cell acute lymphoblastic leukemia. Blood Lymphat Cancer Targets Ther. 2018; https://doi.org/10.2147/blctt.s170351.
60. https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-next-generation-sequencing-based-test-detect-very-low-levels-remaining-cancer
61. Raff T, Gökbuget N, Lüschen S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. Blood. 2007; https://doi.org/10.1182/blood-2006-07-037093.
62. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol. 2004; https://doi.org/10.1200/JCO.2004.10.050.
63. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008; https://doi.org/10.1182/blood-2007-10-116582.
64. Ram R, Gafter-Gvili A, Vidal L, et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission: systematic review and meta-analysis. Cancer. 2010; https://doi.org/10.1002/cncr.25136.
65. Gupta V, Richards S, Rowe J. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. Blood. 2013; https://doi.org/10.1182/blood-2012-07-445098.
66. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J. 2017; https://doi.org/10.1038/bcj.2017.53.
67. O'Brien S, Schiller G, Lister J, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. J Clin Oncol. 2013; https://doi.org/10.1200/JCO.2012.46.2309.

68. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol. 2006; https://doi.org/10.1200/JCO.2005.03.8554.
69. Kantarjian H, Gandhi V, Cortes J, et al. Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. Blood. 2003; https://doi.org/10.1182/blood-2003-03-0925.
70. Advani AS, Gundacker HM, Sala-Torra O, et al. Southwest Oncology Group Study S0530: a phase 2 trial of clofarabine and cytarabine for relapsed or refractory acute lymphocytic leukaemia. Br J Haematol. 2010; https://doi.org/10.1111/j.1365-2141.2010.08387.x.
71. Bassan R, Fumagalli M, Chiaretti S, et al. Phase II trial with sequential clofarabine and cyclophosphamide for refractory and relapsed Philadelphia-negative adult acute lymphoblastic leukemia. Results of the GIMEMA LAL 1610 protocol. Leuk Lymphoma. 2019; https://doi.org/10.1080/10428194.2019.1639170.
72. Topp MS, Gökbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol. 2014; https://doi.org/10.1200/JCO.2014.56.3247.
73. 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; https://doi.org/10.1016/S1470-2045(14)71170-2.
74. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017; https://doi.org/10.1056/NEJMoa1609783.
75. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018; https://doi.org/10.1182/blood-2017-08-798322.
76. Tisagenlecleucel vs blinatumomab or inotuzumab for patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. https://ClinicalTrials.gov/show/NCT03628053
77. Blinatumomab added to prephase and consolidation therapy in precursor B-acute lymphoblastic leukemia in adults. https://ClinicalTrials.gov/show/NCT03541083
78. Sequential chemotherapy and blinatumomab to improve minimal residual disease response and survival in acute lymphoblastic leukemia. https://ClinicalTrials.gov/show/NCT03367299
79. Blinatumomab and pembrolizumab for adults with relapsed/refractory B-cell acute lymphoblastic leukemia with high marrow lymphoblasts. https://ClinicalTrials.gov/show/NCT03160079
80. Blinatumomab in treating patients with B-cell acute lymphoblastic leukemia with minimal residual disease. https://ClinicalTrials.gov/show/NCT02458014
81. Combination chemotherapy with or without blinatumomab in treating patients with newly diagnosed BCR-ABL-negative B lineage acute lymphoblastic leukemia. https://ClinicalTrials.gov/show/NCT02003222
82. DiJoseph JF, Armellino DC, Boghaert ER, et al. Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. Blood. 2004; https://doi.org/10.1182/blood-2003-07-2466.
83. 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; https://doi.org/10.1002/cncr.32116.
84. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016; https://doi.org/10.1056/NEJMoa1509277.
85. Inotuzumab ozogamicin and vincristine sulfate liposome in treating patients with relapsed or refractory CD22+ B-cell acute lymphoblastic leukemia. https://ClinicalTrials.gov/show/NCT03851081

86. Inotuzumab ozogamicin and conventional chemotherapy in patients aged 56 years and older with ALL. https://ClinicalTrials.gov/show/NCT03460522
87. Inotuzumab ozogamicin in treating patients with B-cell acute lymphocytic leukemia with positive minimal residual disease. https://ClinicalTrials.gov/show/NCT03441061
88. Inotuzumab ozogamicin and frontline chemotherapy in treating young adults with newly diagnosed B acute lymphoblastic leukemia. https://ClinicalTrials.gov/show/NCT03150693
89. 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; https://doi.org/10.1016/S2352-3026(17)30103-5.
90. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018; https://doi.org/10.1056/NEJMoa1709866.
91. Shah NN, Fry TJ. Mechanisms of resistance to CAR T cell therapy. Nat Rev Clin Oncol. 2019; https://doi.org/10.1038/s41571-019-0184-6.
92. 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; https://doi.org/10.1056/NEJMoa1709919.
93. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014; https://doi.org/10.1056/NEJMoa1407222.
94. 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; https://doi.org/10.1634/theoncologist.2018-0028.
95. Lacayo NJ, Pullarkat VA, Stock W, et al. Safety and efficacy of venetoclax in combination with navitoclax in adult and pediatric relapsed/refractory acute lymphoblastic leukemia and lymphoblastic lymphoma. Blood. 2019;134(Supplement_1):285. https://doi.org/10.1182/blood-2019-126977.
96. Ribeiro RC, Abromowitch M, Raimondi SC, Murphy SB, Behm F, Williams DL. Clinical and biologic hallmarks of the Philadelphia chromosome in childhood acute lymphoblastic leukemia. Blood. 1987; https://doi.org/10.1182/blood.v70.4.948.bloodjournal704948.
97. Harrison CJ, Moorman AV, Barber KE, et al. Interphase molecular cytogenetic screening for chromosomal abnormalities of prognostic significance in childhood acute lymphoblastic leukaemia: a UK Cancer Cytogenetics Group Study. Br J Haematol. 2005; https://doi.org/10.1111/j.1365-2141.2005.05497.x.
98. Roberts KG. Genetics and prognosis of ALL in children vs adults. Hematology. 2018; https://doi.org/10.1182/asheducation-2018.1.137.
99. 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; https://doi.org/10.1182/blood-2008-01-130237.
100. 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; https://doi.org/10.1200/JCO.2003.02.053.
101. Rijneveld AW, Van Der Holt B, Daenen SMGJ, et al. Intensified chemotherapy inspired by a pediatric regimen combined with allogeneic transplantation in adult patients with acute lymphoblastic leukemia up to the age of 40. Leukemia. 2011; https://doi.org/10.1038/leu.2011.141.
102. Gökbuget N, Beck J, Brandt K, et al. Significant improvement of outcome in adolescents and young adults (AYAs) aged 15–35 years with acute lymphoblastic leukemia (ALL) with a pediatric derived adult ALL protocol; results of 1529 AYAs in 2 consecutive trials of the German Multicenter Study Group for Adult ALL (GMALL). Blood. 2013; https://doi.org/10.1182/blood.v122.21.839.839.
103. 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; https://doi.org/10.1200/JCO.2007.13.7265.
104. 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; https://doi.org/10.1038/leu.2014.229.
105. 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; https://doi.org/10.1200/JCO.2008.18.6916.
106. Huguet F, Chevret S, Leguay T, et al. Intensified therapy of acute lymphoblastic leukemia in adults: report of the randomized GRAALL-2005 clinical trial. J Clin Oncol. 2018; https://doi.org/10.1200/JCO.2017.76.8192.
107. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood. 2019; https://doi.org/10.1182/blood-2018-10-881961.
108. Seftel MD, Neuberg D, Zhang MJ, et al. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. Am J Hematol. 2016; https://doi.org/10.1002/ajh.24285.
109. Wieduwilt MJ, Stock W, Advani AS, et al. Superior survival with post-remission pediatric-inspired chemotherapy compared to myeloablative allogeneic hematopoietic cell transplantation in adolescents and young adults with Ph-negative acute lymphoblastic leukemia in first complete remission: comparison of CALGB 10403 to patients reported to the CIBMTR. Blood. 2019;134(Supplement_1):261. https://doi.org/10.1182/blood-2019-128560.
110. Kondryn HJ, Edmondson CL, Hill J, Eden TOB. Treatment non-adherence in teenage and young adult patients with cancer. Lancet Oncol. 2011; https://doi.org/10.1016/S1470-2045(10)70069-3.
111. Marks DI, Paietta EM, Moorman AV, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). Blood. 2009; https://doi.org/10.1182/blood-2009-08-231217.
112. Weng AP, Ferrando AA, Lee W, et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science (80-). 2004; https://doi.org/10.1126/science.1102160.
113. Yeh CH, Bellon M, Pancewicz-Wojtkiewicz J, Nicot C. Oncogenic mutations in the FBXW7 gene of adult T-cell leukemia patients. Proc Natl Acad Sci U S A. 2016; https://doi.org/10.1073/pnas.1601537113.
114. Mansour MR, Sulis ML, Duke V, et al. Prognostic implications of NOTCH1 and FBXW7 mutations in adults with T-cell acute lymphoblastic leukemia treated on the MRC UKALLXII/ECOG E2993 protocol. J Clin Oncol. 2009; https://doi.org/10.1200/JCO.2009.22.0996.
115. 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; https://doi.org/10.1182/blood-2011-03-338707.
116. Coustan-Smith E, Mullighan CG, Onciu M, et al. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol. 2009; https://doi.org/10.1016/S1470-2045(08)70314-0.
117. Genescà E, Morgades M, Montesinos P, et al. Unique clinico-biological, genetic and prognostic features of adult early T cell precursor acute lymphoblastic leukemia. Haematologica. 2019; https://doi.org/10.3324/haematol.2019.225078.
118. Luskin MR, DeAngelo DJ. T-cell acute lymphoblastic leukemia: current approach and future directions. Adv Cell Gene Ther. 2019; https://doi.org/10.1002/acg2.70.
119. Amylon MD, Shuster J, Pullen J, et al. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. Leukemia. 1999; https://doi.org/10.1038/sj.leu.2401310.

120. Kota VK, Hathaway AR, Shah BD, et al. Poor outcomes with hyper CVAD induction for T-cell lymphoblastic leukemia/lymphoma. Blood. 2015; https://doi.org/10.1182/blood.v126.23.3762.3762.
121. Kozlowski P, Åström M, Ahlberg L, et al. High relapse rate of T cell acute lymphoblastic leukemia in adults treated with Hyper-CVAD chemotherapy in Sweden. Eur J Haematol. 2014; https://doi.org/10.1111/ejh.12269.
122. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). Blood. 2011; https://doi.org/10.1182/blood-2010-06-292615.
123. 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; https://doi.org/10.1182/blood-2015-09-670729.
124. Dunsmore KP, Winter S, Devidas M, et al. COG AALL0434: a randomized trial testing nelarabine in newly diagnosed t-cell malignancy. J Clin Oncol. 2018; https://doi.org/10.1200/jco.2018.36.15_suppl.10500.
125. Abaza Y, Kantarjian HM, Faderl S, et al. Hyper-CVAD plus nelarabine in newly diagnosed adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma. Am J Hematol. 2018; https://doi.org/10.1002/ajh.24947.
126. 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; https://doi.org/10.1200/JCO.2005.03.426.
127. Cohen MH, Johnson JR, Justice R, Pazdur R. FDA drug approval summary: nelarabine (Arranon®) for the treatment of T-cell lymphoblastic leukemia/lymphoma. Oncologist. 2008; https://doi.org/10.1634/theoncologist.2006-0017.
128. Durinck K, Goossens S, Peirs S, et al. Novel biological insights in T-cell acute lymphoblastic leukemia. Exp Hematol. 2015; https://doi.org/10.1016/j.exphem.2015.05.017.
129. Bride KL, Vincent TL, Im SY, et al. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. Blood. 2018; https://doi.org/10.1182/blood-2017-07-794214.
130. Zhang X, Rastogi P, Shah B, Zhang L. B lymphoblastic leukemia/lymphoma: new insights into genetics, molecular aberrations, subclassification and targeted therapy. Oncotarget. 2017;8(39):66728–41. https://doi.org/10.18632/oncotarget.19271.
131. Labar B, Suciu S, Zittoun R, et al. Allogeneic stem cell transplantation in acute lymphoblastic leukemia and non-Hodgkin's lymphoma for patients ≥ 50 years old in first complete remission: results of the EORTC ALL-3 trial. Haematologica. 2004;
132. Gokbuget N, Hoelzer D, Arnold R, et al. Treatment of adult all according to protocols of the German Multicenter Study Group for Adult ALL (GMALL). Hematol Oncol Clin North Am. 2000; https://doi.org/10.1016/S0889-8588(05)70188-X.
133. Takeuchi J, Kyo T, Naito K, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. Leukemia. 2002; https://doi.org/10.1038/sj.leu.2402526.
134. Thiebaut A, Vernant JP, Degos L, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation: a follow-up report of the French protocol LALA 87. Hematol Oncol Clin North Am. 2000; https://doi.org/10.1016/S0889-8588(05)70190-8.
135. Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J Clin Oncol. 2002; https://doi.org/10.1200/JCO.2002.07.116.
136. Ramanujachar R, Richards S, Hann I, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer. 2007; https://doi.org/10.1002/pbc.20749.

137. Usvasalo A, Räty R, Knuutila S, et al. Acute lymphoblastic leukemia in adolescents and young adults in Finland. Haematologica. 2008; https://doi.org/10.3324/haematol.12466.
138. de Bont JM, van der Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld R, Pieters R. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands [1]. Leukemia. 2004; https://doi.org/10.1038/sj.leu.2403538.
139. Testi AM, Valsecchi MG, Conter V, et al. Difference in outcome of adolescents with acute lymphoblastic leukemia (ALL) enrolled in pediatric (AIEOP) and adult (GIMEMA) protocols. Blood. 2004; https://doi.org/10.1182/blood.v104.11.1954.1954.
140. Moorman AV. New and emerging prognostic and predictive genetic biomarkers in B-cell precursor acute lymphoblastic leukemia. Haematologica. 2016;101(4):407–16. https://doi.org/10.3324/haematol.2015.141101.
141. Wei G, Wang J, Huang H, et al. Novel immunotherapies for adult patients with B-lineage acute lymphoblastic leukemia. J Hematol Oncol. 2017;10:150. https://doi.org/10.1186/s13045-017-0516-x.