18 Management of Relapsed and Refractory ALL

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18.1 Introduction

Acute lymphoblastic leukemia (ALL) is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood, and extramedullary sites. Treatment of ALL in children is one of the great success stories of combination chemotherapy. Unfortunately, adults fare much worse. Most current induction regimens obtain complete responses (CR) in 65–90% of newly diagnosed adult patients with ALL. However, up to 10% of patients will have disease that is refractory to initial treatment, and 40–70% of patients who do achieve CR will ultimately relapse [1]. Relapsed/refractory (R/R) ALL has been associated with a rather dismal prognosis, with 3- and 5-year overall survival (OS) historically reported to be 24% and 10%, respectively, in older studies [2–4]. The prognosis of patients with R/R ALL depends on several parameters, including duration of first remission, response to prior salvage therapy, disease burden at the time of relapse, and age of the patient [3].

Treatment of R/R ALL therefore represents a challenge. Treatment strategies such as variations of chemotherapy as a salvage therapy remain ineffective for many patients. The key therapeutic goal in treating R/R ALL is to induce a CR and for a patient to be able to proceed to hematopoietic stem cell transplant (HSCT), which ultimately remains the only known cure. Multiple advances in our understanding of biology of ALL over the past decade have led to significant breakthroughs in the development of novel immunotherapeutic approaches that hold the promise in improving the outcomes of patients. Table 18.2 and Fig. 18.1 highlight selective novel drugs and targets of interest for R/R ALL, which will be discussed throughout the course of this chapter. We will not discuss Philadelphia chromosome positive (Ph+) ALL and Ph-like ALL in this chapter as they are being discussed in Chaps. 16 and 17 in this book.

18.2 Immunotherapy

In 2017, three groundbreaking immunotherapies (blinatumomab, inotuzumab, and chimeric antigen receptor T cells) targeting various surface antigens on ALL cells for R/R B-ALL were FDA approved based on impressive outcomes observed in clinical trials. These approvals have changed the treatment paradigm for R/R ALL.

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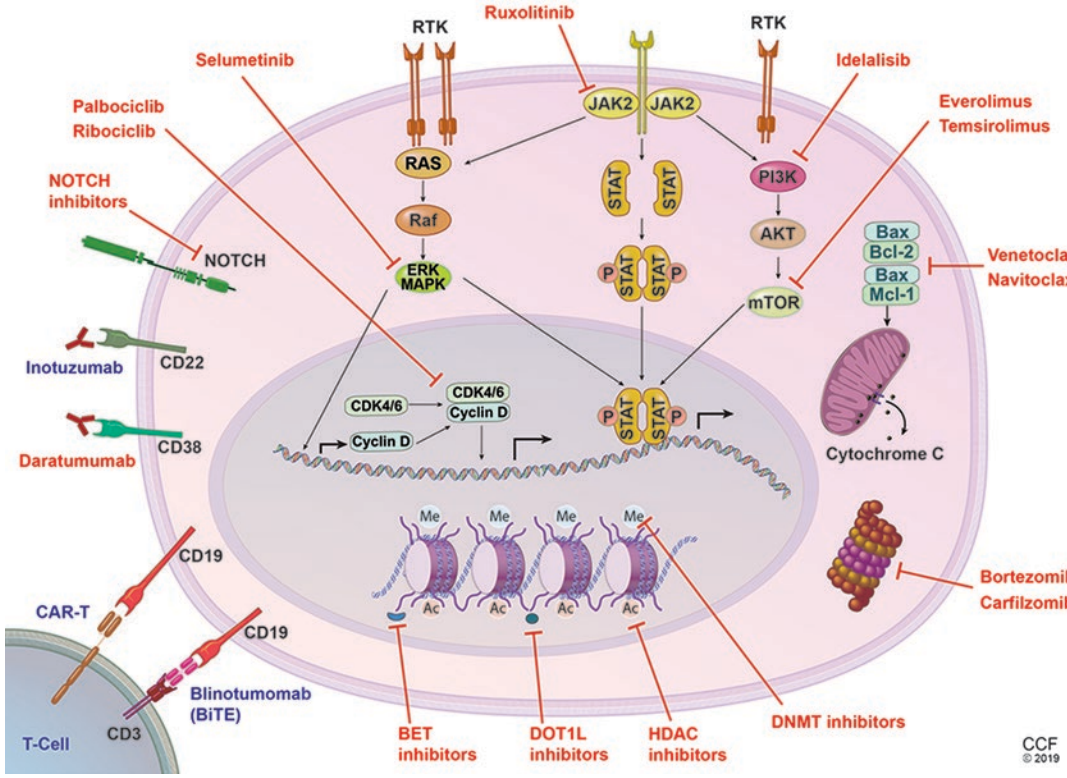

Fig. 18.1 Therapeutic targets and drugs in ALL. Nodes to attack specific cell-surface antigens such as NOTCH, CD22, CD38 and CD19 on B-lymphoblasts. Nodes to modulate B-lymphoblasts epigenetics include chromatin post-translational modifications through DNA methyltransferase (DNMT) inhibitors and histone deacetylase inhibitors (HDACs) as well as transcription factor activation via BET bromodomain inhibitors and DOT1L inhibitors. Nodes to attack protein homeostasis by increasing unfolded protein stress include direct inhibition of the proteasome. Nodes to activate apoptosis at the mitochondrion by inhibition of Bcl-2 and Mcl-1. Nodes to target signal transduction involved in the regulation of key cell proliferation and differentiation pathways such as mTOR, PI3K, JAK2, ERK/MAPK, and CDK4/6. *ALL* Acute lymphoblastic leukemia; *BET* Bromo- and extra-terminal domain; *DOT1L* Disruptor of telomeric silencing 1-like; *Bcl-2* B-cell lymphoma 2; *Mcl-1* Myeloid cell leukemia 1; *mTOR* Mechanistic target of rapamycin; *PI3K* Phosphoinositide 3-kinase; *JAK2* Janus kinase 2; *ERK* Extracellular-signal-regulated kinase; *MAPK* mitogen-activated protein kinase; *CDK* cyclin-dependent kinase

18.3 Blinatumomab

Blinatumomab is a bispecific antibody directed to CD19 (B-cell differentiation antigen) and CD3 (T-cell antigen) receptors. Bivalent binding of CD19 to B-lymphoblasts and CD3 to T cells induces a synapse which leads to release of inflammatory cytokines, production of cytolytic proteins, and proliferation of cytotoxic T cells, resulting in lysis of B-lymphoblasts. This CD19/CD3-bispecific antibody construct is the first T-cell engaging and the first CD19-specific antibody approved by the FDA.

A phase II multicenter single-arm trial of R/R ALL treated 36 patients with blinatumomab in cycles of 4-week continuous infusion followed by a 2-week treatment-free interval with a dose-finding stage and an extension stage [5]. Within two cycles, CR or CR with partial hematologic recovery (CRh) was achieved in 69% (25/36) of patients, with the majority (88%) of responders achieving minimal residual disease (MRD) negative status (<0.001%). Median OS was 9.8 months, and median relapse-free survival (RFS) was 7.6 months [5]. This led to an international, multicenter, phase II single-arm study which enrolled

189 patients with R/R Ph-negative ALL. Eighty-one patients (43%) achieved CR ($n = 63$, 33%) or CRh ($n = 18$, 10%) within two cycles of treatment, most did so after one cycle ($n = 64$) [6]. No difference in CR/CRh rates was observed based on prior salvage therapies, prior allogeneic HSCT, or age. Median OS was 6.1 months and median RFS was 5.9 months. Notably, there was a correlation between tumor burden and response rates: in patients with <50% bone marrow blasts, the rate of CR/CRh was 73% compared to 29% in patients with ≥50% bone marrow blasts [6]. This study led to accelerated FDA approval of blinatumomab for R/R Ph-negative ALL.

Blinatumomab was compared to standard chemotherapy in patients with R/R Ph-negative ALL in a randomized, multicenter phase III TOWER trial [7]. Four hundred and five patients were randomized 2:1 to blinatumomab ($n = 271$) or standard salvage chemotherapy ($n = 134$). Blinatumomab was administered at the standard dose continuously over 4 weeks for up to five cycles, followed by up to 12 months of maintenance. Remission rates favored blinatumomab within 12 weeks after initiation of treatment: CR (34% vs. 16%, $p < 0.001$), CR plus CRh (44% vs. 25%, $p < 0.001$). Median OS significantly improved with blinatumomab (7.7 vs. 4.0 months; $p = 0.01$) at a median follow-up of approximately 12 months [7]. Adverse events (grade 3 or higher) were reported in 87% of patients in the blinatumomab arm and in 92% of the patients in the chemotherapy group. Unique to the blinatumomab arm was the occurrence of the cytokine release syndrome (CRS), reported in 14.2% (≥grade 3 in 5%) of patients receiving blinatumomab [7]. The mechanism of action of blinatumomab generates its unique side effect profile: Cytokine release syndrome and neurological toxicities are thought to be the result of T-cell stimulation, proliferation, and cytokine release.

A single-arm, multicenter, phase II BLAST study evaluated blinatumomab in patients with CR with MRD positivity after intensive chemotherapy. Seventy-eight percent (88/113) of patients achieved MRD negativity after the first cycle of blinatumomab treatment and 67% of patients subsequently proceeded to allogeneic HSCT [8]. This study demonstrated the ability of blinatumomab to eradicate MRD positivity and serve as a bridge to allogeneic HSCT, leading to FDA approval in this setting. Blinatumomab was also evaluated in R/R Ph-positive ALL. A cohort of 45 patients, who were R/R to first- or later-generation tyrosine kinase inhibitors (TKI), were treated in the phase II, single-arm, multicenter ALCANTARA trial [9]. Within two cycles of treatment, 36% (16/45) achieved CR/CRh, including 10 patients with T315I mutations. The majority of responders (14/16, 88%) achieved MRD negativity. Median OS was 7.1 months [9]. Phase II studies evaluating blinatumomab in combination with TKIs, including dasatinib (NCT02143414; NCT02744768) and ponatinib (NCT03263572), are ongoing. Preliminary data demonstrate that blocking PD-1, PD-L1, or CTLA-4 enhances effector T cells, thus improving blinatumomab's activity against B-lymphoblasts. Accordingly, trials of combination immunotherapy (pembrolizumab, nivolumab ± ipilimumab) and blinatumomab are currently ongoing (NCT03160079, NCT03512405, and NCT02879695).

Blinatumomab should be considered in patients with low disease burden (<50% blasts) R/R B-ALL. Suitable candidates should proceed to consolidation with allogeneic HSCT. Blinatumomab has not been well evaluated in R/R ALL patients with active CNS disease due to concerns of neurotoxicity with concurrent intrathecal therapy.

18.4 Inotuzumab Ozogamicin

Inotuzumab ozogamicin is a humanized monoclonal antibody–drug conjugate targeting CD22. It consists of a CD22-targeting immunoglobulin G4 humanized monoclonal antibody conjugated to calicheamicin, a cytotoxic agent that cleaves double-stranded DNA [10]. This drug was initially developed for the treatment of non-Hodgkin lymphoma (NHL), but further development was focused on CD22+ ALL. CD22 is an attractive targeting molecule for an antibody–drug conjugate in ALL: (1) CD22 is a B-cell restricted type I transmembrane protein expressed in >90% of B-ALL. (2) Following ligand binding or antibody crosslink-

ing, CD22 is rapidly internalized, thus making it an ideal target for cytotoxic drug delivery by antibody–drug conjugates [10]. Inotuzumab is currently approved for the treatment of R/R B-ALL by the US FDA and the European Medicines Agency.

Based on the demonstration of inotuzumab's safety and efficacy in lymphoma, Phase I and II trials with single-agent inotuzumab were conducted in R/R ALL with overall remission rates of 58–68% (CR/CR with incomplete count recovery (CRi)) and MRD negative rates of 72–84% [11, 12]. A phase III multicenter, open-label, randomized trial (INO-VATE study) compared inotuzumab to standard of care intensive chemotherapy for R/R CD22+ B-ALL in first or second salvage [13]. Inotuzumab was administered weekly for a total dose of 1.8 mg/m^2 per cycle (0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15 of a 21-day cycle), reduced to 1.5 mg/m^2 once patients achieved CR or CRi. Patients were allowed to proceed to stem cell transplant at the investigator's discretion. Patients randomized to the inotuzumab treatment arm had a significantly higher CR rate compared to standard chemotherapy (80.7% vs. 29.4%, $p < 0.001$). Of the patients who achieved CR/CRi, inotuzumab had a significantly higher rate of MRD negativity (78.4% vs. 28.1%, $p < 0.001$), and more patients proceeded directly to HSCT (41% vs. 11%) [13]. Remission duration was longer in the inotuzumab arm (median, 4.6 vs. 3.1 months, $p = 0.03$). Median OS was 7.7 months in the inotuzumab group and 6.7 months in the standard chemotherapy group, although the hazards ratio suggested improved OS at 0.77 ($p = 0.04$), likely reflecting a separation of the two survival curves at later time-points (2-year OS, 23% vs. 10%). This difference is likely explained by the greater proportion of patients proceeding to stem cell transplant in the inotuzumab arm. Treatment-related neutropenia, thrombocytopenia, infusion-related reactions, hepatic toxicities, including transaminitis and hyperbilirubinemia, and veno-occlusive disease (VOD) are unique adverse events of inotuzumab. In the phase III trial, the rate of VOD, a potentially fatal condition, was higher in the inotuzumab arm (11% vs. 1%). This complication occurred mainly in patients who undergo or had received a prior stem cell transplant especially if a dual-alkylator conditioning regimen was given [13].

Inotuzumab was evaluated in combination with hyper-fractionated reduced-dose cyclophosphamide, vincristine, dexamethasone (mini-hyper-CVD) in patients with R/R ALL with a median age of 35 years (range, 18–78 years), and the combination produced a CR rate of 78% with a 1 year OS rate of 46% [14]. Multiple clinical trials are currently underway to improve our understanding of how and when to best use inotuzumab: safety and efficacy of using a TKI and inotuzumab concurrently for treatment of relapsed Ph+ ALL (NCT02311998), inotuzumab in combination with intensive chemotherapy in the frontline setting (NCT03150693, NCT03488225), and using inotuzumab to eliminate MRD (NCT03441061).

Inotuzumab is effective in patients with high disease burden (>50% blasts) and can be used in combination with intrathecal therapy for patients with CNS disease.

18.5 CAR-T-Cell Therapy

Genetically engineered T cells expressing a chimeric antigen receptor (CAR-T) targeting specific antigens (CD19) present on B-lymphoblasts have generated promising results in children and adults with R/R disease. Tisagenlecleucel (CTL019) by Novartis, an autologous anti-CD19 CAR-T cell therapy, was recently approved (2017) by the US Food and Drug Administration (FDA) for patients up to the age of 25 years with B-ALL that is refractory or in second or greater relapse.

CARs are engineered molecules which consist of an extracellular binding domain (scFv), a transmembrane domain, a costimulatory domain (either 4-1BB or CD28), and intracellular CD3-ζ signaling domain. In this treatment strategy, a patient's own T cells (autologous) are transduced to express an anti-CD19 CAR that, when reintroduced into the patient, directs specific binding and killing of CD19+ B cells. Prior to CAR-T-cell infusion, patients typically receive chemotherapy in an effort to induce lymphodepletion to enhance CAR-T-cell expansion and persistence

Table 18.1 Selected CAR-T-cell therapy studies in relapsed and/or refractory B-ALL

Group/Reference	CAR design (costimulatory domain/vector)	Median age	Number of patients	Prior Allo-HSCT (%)	CR/CRi (%)	MRD-CR (%)	Allo-HSCT post CAR-T cell therapy (%)	CRS
UPenn/CHOP Maude et al. [17]	4-1BB/ lentivirus	14 (5–60)	30	18 (60)	27 (90)	22 (73)	3 (10)	100% (27% severe)
UPenn/CHOP Global, multicenter Maude et al. [18]	4-1BB/ lentivirus	11 (3–23)	75	46 (61)	61 (81)	61 (81)	8 (11)	40% (13% severe)
MSKCC Park et al. [19]	CD28/ retrovirus	44 (23–74)	53	19 (36)	44 (83)	32 (60)	17 (32)	43% (42% severe)
NCI Lee et al. [20]	CD28/ retrovirus	13 (5–27)	21	8 (38)	14 (67)	12 (57)	10 (48)	43% (5% severe)
FHCRC Turtle et al. [21]	4-1BB/ lentivirus	40 (20–73)	30	11 (37)	29 (97)	25 (83)	13 (43)	50% (50% severe)
FHCRC Gardner et al. [22]	4-1BB/ lentivirus	12 (1–25)	43	28 (65)	41 (95)	41 (95)	11 (26)	93% (23% severe)

MRD− minimal residual disease negative by flow cytometry, *CR* complete remission, *CRi* complete remission with incomplete blood count recovery, *HSCT* hematopoietic stem cell transplant, *CRS* cytokine release syndrome, *MSKCC* Memorial Sloan Kettering Cancer Center, *UPenn* University of Pennsylvania, *CHOP* Children's Hospital of Philadelphia, *NCI* National Cancer Institute, *FHCRC* Fred Hutchinson Cancer Research Center

in vivo [15]. The major studies published on CAR-T-cell therapy in B-ALL are summarized in Table 18.1. Important differences between these studies include different transduction methods, costimulatory domains, and lymphodepleting chemotherapy regimens.

Initial CAR-T-cell clinical trials included a phase I trial in 16 adult patients with R/R B-ALL treated with a CD19 CAR-T with a CD28 costimulatory domain. The remission rate was impressive, at 88%. Some patients underwent a subsequent allogeneic HSCT after CAR-T therapy [16]. Another phase I trial of CD19 CAR-T cell with a 4-1BB costimulatory domain in 30 patients (25 pediatric and 5 adults) with R/R B-ALL reported a 90% CR rate by morphology (73% MRD-negative CR), and prolonged B-cell aplasia in some patients up to 2 years [17]. Durable remissions up to 24 months are correlated with persistence of CAR-T cells.

In a phase II, single-arm, multicenter, global ELIANA study of 75 pediatric and young adult patients with R/R B-cell ALL, tisagenlecleucel (4-1BB costimulatory domain) resulted in an overall response rate (ORR) of 81% (CR 60% and CRi 21%). MRD by flow cytometry was negative in 95% of the responders by day 28 [18]. Most relapses were CD19 negative. With a median follow-up of 13.1 months, the OS at 12 months was 76%, and the median duration of CAR-T cell persistence was 168 days (range 20–617 days). This study illustrated the feasibility of utilizing centralized manufacturing of CAR-T cells to broaden access to CAR-T-cell therapies beyond a few specialized centers [18]. Encouraging results have been obtained with CAR-T cells developed and evaluated by investigators at the Memorial Sloan Kettering Cancer Center (MSKCC) with a CD28 costimulatory domain in a phase I single-center trial in adults with ALL (median age 44 years, range 23–74). Among the 53 adult patients with R/R B-ALL who received the CAR-T cell infusion, the CR rate was 83%, and with a median follow-up of 29 months, median EFS and OS were 6 and 13 months, respectively [19]. Better outcomes were observed in patients with low disease burden (≤5% bone marrow blasts) at the time of CAR-T-cell infusion. Most importantly, CAR-T-cell therapies are effective in treating relapsed B-ALL after allogeneic HSCT, an area of unmet need. It is feasible to collect and manufacture

donor-derived T cells from the recipient and safely infuse without induction of graft versus host disease (GVHD) [17–22].

The main unique adverse events with CAR-T-cell therapy are CRS, B-cell aplasia, and neurologic toxicity. The incidence of CRS across several different CAR-T-cell products for B-ALL are summarized in Table 18.1. The frequency of these side effects correlates with the disease burden and is less likely to occur in patients with ≤5% bone marrow blasts. The assessment and management of toxicities in patient receiving CAR-T-cell therapy is reviewed in Ref. [23]. CRS can present with a variety of symptoms ranging from flu-like symptoms to high fevers which can progress to life-threatening manifestations of severe hypotension, hypoxia, and end-organ damage. Life-threatening manifestations require interventions with anti-IL6R (tocilizumab)-directed therapy; and many trials are now incorporating tocilizumab earlier in the treatment course. Neurologic toxicity associated with CAR-T-cell therapies can also vary from headache, dizziness, memory loss, impaired speech (dysarthria, aphasia), alterations in mental status, seizures, and encephalopathy to coma [24].

Despite impressive long-term data with CAR-T-cell therapies, relapses across all studies remain a limitation of this therapy. Relapse occurs because of poor persistence of CAR-T cells and loss of the targeted CD19 epitope (antigen escape). Minimizing CD19-positive relapses may result from a better understanding of the biology of persistence. To improve CAR-T-cell persistence, a number of methods are being investigated: (1) inclusion of a 4-1BB costimulatory domain as opposed to CD28, (2) selection and separate manufacturing of bulk CD4+ T cells and central memory CD8+ T cells upfront and then administered in a controlled 1:1 ratio to the patient. CARs equipped with 4-1BB costimulatory domains appear to be associated with longer persistence compared to CD28 costimulatory domain CARs [25]. However, 4-1BB containing CARs are also associated with higher rates of CD19-negative relapse. Currently, dual B-cell antigen targeting (e.g., CD19 and CD22), aimed at preventing or treating CD19 antigen escape, is being tested in clinical trials and may result in the next generation of CAR-T-cell therapies [26].

The emergence of antigen loss and escape are frequent causes of resistance to CD19-targeted CAR-T-cell therapy. This has fueled the development of CARs directing alternative B-cell antigens. A first-in-human, phase I, intent-to-treat clinical trial using CD22 targeted CAR-T-cell therapy in 21 pediatric and adult patients with R/R B-ALL, 17 of whom had relapsed after prior anti-CD19-directed immunotherapy [26]. Twelve patients (12/21; 57%) achieved a CR. Dose-dependent activity was observed with improved responses at higher doses. Eleven out of 15 (73%) patients achieved morphologic CR with a dose of $\geq 1 \times 10^6$ CD22 CAR-T cells per kg body weight [26]. The same group demonstrated important preclinical data showing efficacy of a bispecific CD19/CD22 CAR in a murine model that led to initiation of two ongoing phase 1 clinical trials (NCT03330691; NCT03233854) [26].

18.6 Other Therapies

18.6.1 Vincristine Sulfate Liposome Injection (VSLI)

Liposomal vincristine (VSLI) constitutes encapsulating vincristine in a sphingomyelin/cholesterol envelope. This process enhances drug delivery to the target tissues and decreases neurotoxicity by reducing the percentage of free drug in the plasma leading to increased efficacy with acceptable toxicity. In a phase II single-arm, open-label trial of 65 patients with B- or T-ALL with second or greater relapse, who were previously treated with standard vincristine, the CR/CRh rate with VSLI was 20%, with an overall response rate of 35% [27]. Median OS was 4.6 months. VSLI was administered at a dose of 2.25 mg/m^2. It was well tolerated with a side effect profile similar to standard-formulation vincristine. VSLI received accelerated approval from the US FDA in 2012 for the treatment of adults with Ph-ALL in second or greater relapse or whose disease has progressed following at least two or more lines of treatment.

18.6.2 BCL-2 Inhibitors

Dysregulation of the B-cell leukemia/lymphoma-2 (BCL-2) family of proteins of the intrinsic apoptotic pathway can promote cancer and impair responses of malignant cells to therapies. ALL blast cells express higher levels of BCL-2 and BCL-xL than normal B and T cells [28], and therefore, dual inhibition may be beneficial. Venetoclax is a highly selective BCL-2 inhibitor, and navitoclax is an investigational, orally bioavailable small molecule inhibitor of BCL-2, BCL-xL, and BCL-w [29].The addition of navitoclax to venetoclax has demonstrated synergistic effects in preclinical models and might mitigate the dose-limiting thrombocytopenia associated with navitoclax alone [30]. Trials have recently been launched to explore the activity of BCL-2 inhibitors in ALL. These include a phase 1, multicenter, open-label, dose escalation study of venetoclax plus navitoclax as a chemo-sensitizing agent in pediatric and adult patients (aged ≥4 years) with R/R B-and T-ALL (NCT03181126). Patients receive daily oral venetoclax on day 1 and received oral navitoclax on day 3. Treatment continued for two cycles. Investigators could administer chemotherapy (peg-asparaginase, vincristine, and dexamethasone) at their discretion. Preliminary data presented recently showed that of the nine patients treated, five patients achieved a response (CR/CRi/CRp). Of the remaining four patients, one patient had a partial response and three patients had stable disease in this heavily pretreated group [31]. The combination treatment is relatively well tolerated with no grade 4 adverse events reported. Grade 3 or less adverse events include nausea and vomiting, back pain and muscle spasms. Other trials looking at BCL-2 inhibitors include: venetoclax ± chemotherapy in pediatric and young adult patients with R/R ALL (NCT03236857).

18.7 Relapsed and Refractory T-ALL

Survival of patients with newly diagnosed T-cell ALL has significantly improved but survival remains quite poor for those patients who relapse. For adults with T-ALL treated on the E2993/UKALL12 study who achieved a CR, the incidence of relapse at 5 years was 42% [32]. Most T-ALL disease recurrences occur within the first 2 years of diagnosis, and relapsed disease remains very difficult to salvage, with survival rates <7% at 5 years [2]. There is no single standard of care salvage chemotherapy regimen used in treatment of patients with relapsed and refractory T-ALL. Nelarabine and liposomal vincristine are both US Food and Drug Administration (FDA)-approved drugs for the treatment of relapsed and/or refractory T-ALL. The notably minimal armamentarium of molecularly targeted therapies for T-ALL stands in sharp contrast to the remarkable progress that has been made in B-ALL although other avenues are being explored, as mentioned above with BCL-2 inhibitors.

Nelarabine, a purine nucleoside analog, has single-agent activity in T-ALL. It was granted accelerated approval by the US FDA in 2005 for the treatment of patients with R/R T-ALL. Today, nelarabine remains the only therapy approved specifically for R/R T-ALL. In two phase II trials of adult patients with R/R T-ALL or lymphoblastic lymphoma treated with nelarabine monotherapy, the CR rate was 31–36%, with 1-year OS rate of 24–28% [33, 34]. Neurotoxicity, including neuropathy, mental status changes, and seizures, has been reported in up to 18% of patients, but is usually mild and reversible (grade 3 and 4 in ≦5% of patients) [33, 34]. In two small retrospective series, nelarabine was studied in combination with etoposide and cyclophosphamide as a treatment in the salvage setting in R/R T-ALL [35, 36]. Seven pediatric patients (2–19 years of age) with R/R T-ALL were treated sequentially with nelarabine and etoposide/cyclophosphamide, 71% (5/7) patients achieved a CR after receiving 1–2 cycles [35]. All patients in the study experienced neurotoxicity, grade 2–3 sensory and motor neuropathies. This was reversible in most cases. In a study of five adult patients (50–63 years of age) treated with the same regimen, 60% (3/5) achieved CR after 1–2 cycles, and two of these patients were successfully bridged to allogeneic HSCT [36].

Activating mutations in *NOTCH1* were discovered in a majority (60%) of T-ALL cases

15 years ago [37, 38]. Notch signaling plays a crucial role in normal T-cell development, hematopoiesis, and cell growth and proliferation [38]. After ligand binding, Notch receptors undergo a series of cleavages, first by a metalloprotease and subsequently by the γ-secretase complex [39]. After cleavage, the intracellular domain of Notch protein translocates into the nucleus and activates transcription of a variety of genes. Given that Notch signaling is frequently activated in T-ALL, a large number of preclinical studies and clinical trials have investigated the efficacy of targeting Notch in T-ALL. γ-Secretase inhibitors (GSIs) prevent the ability of Notch signaling to activate transcription by blocking intramembrane proteolytic processing of Notch1 by the γ-secretase complex, thereby preventing translocation to the nucleus [40]. Encouraging preclinical data led to the early phase clinical trials of GSIs for R/R T-ALL. Unfortunately, this has not translated successfully into the clinic. These trials were disappointing due to limited anti-leukemic effects and systemic toxicity, namely gastrointestinal toxicity [41]. Current research aims to identify alternative approaches that prevent or overcome resistance to GSIs, inhibit downstream effectors of Notch signaling, and improve the specificity of agents targeting mutant Notch1 [42].

In a recent publication, samples collected from patients enrolled in the COG ALL1231 study of T-ALL were noted to have consistent expression of CD38 at the time of diagnosis, after completion of 1 month of induction chemotherapy, and most importantly at the time of relapse [43]. The study also reported efficacy of daratumumab (a monoclonal antibody which binds to an epitope of CD38) in 14 of 15 T-ALL patient-derived xenografts studied. An international multicenter phase II study is currently evaluating daratumumab in combination with chemotherapy for children and young adults (≤30 years) with relapsed and/or refractory T- or B-cell ALL (NCT03384654).

One member C3 (AKR1C3) of aldo-keto reductase family belongs to a superfamily of oxidoreductases that are broadly expressed in human tissues. AKR1C3 is expressed at high levels in T-ALL [44]. OBI-3424 is a first-in-class novel highly selective small-molecule prodrug converted by AKRC13 to a DNA alkylating agent. This selective mode of activation distinguishes OBI-3424 from traditional alkylating agents. OBI-3424 exerted profound in vivo efficacy against a broad range of T-ALL patient-derived xenografts (PDXs) and significantly reduced leukemia infiltration in the bone marrow [45]. OBI-3424 is being studied in a phase I/II clinical trial in patients with solid tumors, such as hepatocellular carcinoma (HCC) and castrate-resistant prostate cancer (CRPC), which has begun enrollment. A clinical trial in T-ALL is scheduled to begin soon.

The dramatic and promising results of cellular and antibody-based immunotherapies in the B-ALL have generated much interest in the development of targeted immunotherapies for the treatment of T-ALL. It is challenging to target T-cell malignancies using CAR-T cells because of the shared expression of target antigens between CAR-T cells and T-lineage tumor cells [46–50]. In this regard, CAR-Ts against pan T-cell antigens have two major drawbacks: (1) CAR-T cells self-targeting/fratricide and (2) T-cell aplasia, leading to life-threating immunodeficiency. Numerous preclinical studies demonstrated that T cells transduced with CD3, CD5, CD7 or TCR CARs, the most expressed pan-T-cell antigens, efficiently eliminate T-ALL blasts in vitro and are able to control the disease in vivo [46–50], leading to phase I clinical trials with CAR T-cells for T-ALL (NCT03081910, NCT03690011, NCT03590574). Many creative approaches are being evaluated including CRISPR/Cas9 gene editing to prevent the antigen (CD7) expression on the surface of CAR-T cells to overcome the issue of fratricide/self-targeting [48].

There are many other targets and therapies including proteasome inhibitors, CXCR4 inhibitors, CDK 4/6 inhibitors, signal transduction inhibitors, and epigenetic therapies which are currently in development for treatment of R/R B and/or T-ALL. They are not discussed in this chapter extensively given the limited space. They are outlined in Table 18.2 and illustrated in Fig. 18.1.

Table 18.2 Selected emerging and approved therapies for relapsed and/or refractory ALL

Drug class/mechanism (References)	Agent	Patient population and notes	Phase
Monoclonal antibodies			
CD19 [5–9]	Blinatumomab (bispecific T-cell engager)	FDA approved for R/R Ph-negative B-ALL and B-ALL in CR with MRD+ disease	
		R/R B-ALL (blinatumomab in combination with pembrolizumab)	I/II (NCT03160079, NCT03512405)
		R/R B-ALL (blinatumomab in combination with nivolumab ± ipilimumab)	I (NCT02879695)
		R/R B-ALL (blinatumomab in combination with ibrutinib)	II (NCT02997761)
		B-ALL (blinatumomab maintenance following allogenic-HSCT)	II (NCT02807883)
CD22 [11–14]	Inotuzumab	FDA approved for R/R Ph-negative B-ALL	
		R/R and newly diagnosed CD22+ B-ALL (inotuzumab followed by blinatumomab)	II (NCT03739814)
		R/R Ph+ B-ALL (safety and efficacy of combination of bosutinib and inotuzumab)	I/II (NCT02311998)
		B-ALL in CR with MRD+ (tolerability and efficacy if using inotuzumab to eliminate MRD+ disease)	II (NCT03441061)
CD38 [43]	Daratumumab	1–30 years old with R/R T- or B-ALL (daratumumab in combination with chemotherapy)	II (NCT03384654)
Chimeric antigen receptors T cells (CAR-T)			
CD3, CD5, CD7, and T-cell receptor beta (TCR B) [46–50]		≤75 years old with relapsed T-ALL or T-cell lymphoma	I (NCT03081910, NCT03690011, NCT03590574)
CD19 [16–22]	Tisagenlecleucel	(FDA) for patients under 25 years old with refractory or those with second or later relapsed B-ALL	
CD19/CD22 dual-targeted [26]		1–30 years old with R/R CD19+ B-ALL ≥18 years with R/R B-cell malignancies	I (NCT03241940, NCT03330691, NCT03233854)
CD38		12–70 years with relapsed B-ALL after CD19 CAR-T adoptive cellular immunotherapy with CAR-T cells targeting CD38	I/II (NCT03754764)
BH3-mimetics (targeting apoptosis)			
BCL-2 inhibitors [28, 30, 31]	Venetoclax	≥18 years old with R/R T-or B-ALL (venetoclax in combination with liposomal vincristine)	Ib/II (NCT03504644)

(continued)

Table 18.2 (continued)

Drug class/mechanism (References)	Agent	Patient population and notes	Phase
		≤25 years old with R/R malignancies, including T-or B-ALL	I (NCT03236857)
	Navitoclax	≥4 years old with R/R T-or B-ALL (navitoclax in combination with venetoclax and chemotherapy)	I (NCT03181126)
Proteasome			
Proteasome inhibitors	Bortezomib	≥18 years old with R/R B- or T-ALL (bortezomib in combination with chemotherapy)	II (NCT01769209)
	Carfilzomib	1–21 years old with R/R B-or T-ALL (carfilzomib in combination with induction chemotherapy)	Ib (NCT02303821)
Neddylation inhibitors	Pevonedistat	16–39 years old with R/R B-or T-ALL (pevonedistat in combination with induction chemotherapy)	I (NCT03349281)
Chemokine receptors			
CXCR4 inhibitors	BL-8040	≥18 years old with R/R T-ALL (BL-8040 in combination with nelarabine)	IIa (NCT02763384)
IL7-JAK-STAT-CRLF2			
JAK inhibitors	Ruxolitinib	≥10 years with R/R Ph-like ALL (combination of ruxolitinib or dasatinib with chemotherapy)	II (NCT02420717)
		13–75 years old with R/R early T-precursor ALL (ruxolitinib in combination with chemotherapy)	I/II (NCT03613428)
PI3K/AKT/mTOR			
PI3K inhibitors	Idelalisib	≥18 years old with R/R B-ALL or ≥ 65 years old with newly diagnosed B-ALL for whom standard therapies are not recommended	I/II (NCT03742323)
mTOR inhibitors	Everolimus	18 months to 21 years old with relapsed B-or T-ALL (everolimus in combination with chemotherapy)	I (NCT01523977)
	Temsirolimus	1–21 years old with R/R B-or T-ALL (temsirolimus with etoposide and cyclophosphamide)	I (NCT01614197)
MAPK-RAS			
MEK inhibitors	Selumetinib	All ages with R/R B- or T-ALL with RAS pathway mutations (selumetinib in combination with dexamethasone)	I/II (NCT03705507)
Cell cycle regulation			
CDK4/CDK6 inhibitors	Palbociclib	≤21 years old with R/R B-or T-ALL (palbociclib in combination with chemotherapy)	I (NCT03515200)
		≥15 years with R/R B-or T-ALL (palbociclib in combination with dexamethasone)	I (NCT03132454)

Table 18.2 (continued)

Drug class/mechanism (References)	Agent	Patient population and notes	Phase
	Ribociclib	1–30 years old with R/R B-or T-ALL (ribociclib in combination with everolimus and dexamethasone)	I (NCT03740334)
Epigenetic drugs			
DNA methyltransferase 1 (DNMT1) inhibitors	Decitabine and 5-azacitidine		
Histone deacetylase (HDAC) inhibitors	Vorinostat and Romidepsin		
Bromodomain-containing protein 4 (BRD4) inhibitors	Birabresib	≥18 years old with R/R B- or T-ALL	I (NCT01713582)
DOT1-like histone lysine methyltransferase inhibitors	Pinometostat	≥18 years old with R/R B- or T-ALL with rearrangement of the MLL gene	I (NCT01684150)
Cytotoxic therapies			
Antimetabolites [33–36]	Nelarabine	FDA approved for treatment of R/R T-ALL	
Alkylators [44, 45]	OBI-3424 (AKR1C3 inhibitor)	A first-in-class novel highly selective small-molecule prodrug that is converted by AKRC13 enzyme to a DNA alkylating agent	
Vinca alkaloid	Liposomal vincristine (VSLI)	FDA approved for R/R Ph-negative B-ALL	

R/R relapsed and/or refractory, *CD* cluster of differentiation, *CAR* chimeric antigen receptor, *mTOR* mammalian target of rapamycin, *CDK* cyclin-dependent kinase, *AKR1C3* aldo-keto reductase 1c3

18.8 Conclusion

The treatment of ALL is evolving rapidly owing to the increased understanding of the genetic heterogeneity of ALL, which has contributed to the development of numerous novel therapies. Monoclonal antibodies, immunomodulators, CAR-T-cell therapies, and small molecule inhibitors targeting key molecular pathways are exciting additions to the therapeutic armamentarium of ALL. Some of the active agents in the salvage setting are currently being actively investigated for frontline use. Although the efficacy of these therapies is impressive, they are not without toxicity, both physical and financial. Current active and future clinical trials will hopefully guide us in determining how to best incorporate these novel therapies into the existing treatment algorithms to improve the cure rates of R/R ALL.

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