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Novel Therapeutic Strategies in Acute Lymphoblastic Leukemia

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Abstract Chemotherapy cures only a minority of adult patients with acute lymphoblastic leukemia (ALL). In addition, relapsed ALL has a poor outcome with 5-year survival as low as 7 %. Hence, there is a need to develop effective therapies to treat relapsed disease and to combine these agents with chemotherapy to improve outcomes in newly diagnosed patients. ALL cells express several antigens amenable to target therapies including CD19, CD20, CD22, and CD52. Over the last decade, there has been a surge in the development of immune therapies which target these receptors and that have induced robust responses. In this manuscript, we review these novel immune agents in the treatment of B-ALL. As these new therapies mature, the challenge going forward will be to find safe and effective combinations of these agents with chemotherapy and to determine their place in the current treatment schema.

Keywords Acute lymphoblastic leukemia (ALL) · Immunotherapies · Monoclonal antibodies · Chimeric antigen receptor T cells (CART)

Topical Collection on *Acute Lymphocytic Leukemias*

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Introduction

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy in which uncontrolled proliferation of lymphoblasts (of B or T cell origin) occurs in the bone marrow, blood, and/or tissues. ALL has a bimodal distribution with roughly 60 % of cases diagnosed in patients younger than 20 years of age, accounting for nearly 80 % of childhood leukemias. The second peak is around the fifth decade of life and accounts for only 20 % of leukemia diagnoses overall in adults. According to the Surveillance, Epidemiology, and End Results Program (SEER), approximately 6250 new cases of ALL and 1450 deaths will occur in 2015 [1]. Currently, pediatric patients with ALL have dramatic cure rates with 95 % complete remission (CR) and estimated 5-year survival rates (EFS) of 80–85 % [2]. Although the current adult regimens have CR rates of ~85 %, the 3-year disease-free survival (DFS) and overall survival (OS) remain <40 % [3, 4]. Adult patients are at a higher risk of relapse secondary to high-risk disease factors at diagnosis which include adverse cytogenetics such as the Philadelphia chromosome (Ph+), chromosome defined as t(9;22) (q34;q11.2), 'Ph-like disease' identified recently by gene expression profiling which clusters with BCR-ABL1-positive ALL accounting for 15–20 % of adolescent and young adult (AYA) ALL and which is associated with unfavorable outcome [5], translocations involving the mixed lineage leukemia gene (MLL) on chromosome 11q23, persistent minimal residual disease (MRD) after treatment, and poor tolerance of intense and prolonged chemotherapy protocols. The incorporation of targeted agents into the treatment regimens of adult ALL has improved survival in several subsets of patients [6–9].

Multiagent cytotoxic chemotherapy has had a great success in pediatric age groups, but the same success has not been reproduced in adults despite modifications in the regimens.

Moreover, results are modest in the setting of relapsed or refractory ALL where the CR rates are 30–40 % in first salvage and drop down to 10–20 % in later salvages. However, for the majority of newly diagnosed adults, despite the ability to achieve a CR, these CR are seldom durable and only a few can be bridged to allogeneic stem cell transplantation (ASCT), with transplant rates ranging from a low of 5 % to as high as 40 % in some German trials [10, 11]. Three recent cytotoxic agents have been approved for patients with relapsed or refractory ALL, clofarabine, nelarabine, and vincristine sulfate liposomal, demonstrating respective CR rates in adult patients of 17, 31, and 20 % [12–14]. In this review, we will discuss alternative therapeutic agents, some of which are completely novel, others of which are more established in the treatment of other malignancies. We will discuss clinical trials with antibody-based therapy, including naked antibodies (rituximab, epratuzumab, alemtuzumab); the bispecific T cell engaging (BiTE) antibody, blinatumomab; the immunoconjugate, inotuzumab ozogamicin; and chimeric antigen receptor (CAR)T cell therapy. We will also briefly discuss NOTCH inhibitors, FMS-related targeted kinase-3 (FLT3), and other cell signaling inhibitors and proteasome inhibitors.

Monoclonal Antibodies

One of the most exciting groups of compounds under investigation in ALL is the monoclonal antibodies. Lymphoblasts express several cell surface antigens that can serve as targets for monoclonal antibodies. More than 95 % of B cell ALL express CD19 and more than 90 % express CD22, thereby making them attractive targetable sites. There are four different monoclonal antibody constructs that are currently been developed in ALL: (1) the naked antibodies, rituximab, epratuzumab, and alemtuzumab, that destroy and target cell through antibody-dependent cell-mediated cytotoxicity (ADCC); (2) inotuzumab ozogamicin and SGN 19a which are antibody drug conjugates; (3) SAR3419 and combotox which are antibody immunotoxins; and (4) the BiTE single-chain antibody, blinatumomab (Fig. 1). Details on clinical trials with these agents are listed in Table 1.

CD20-Directed Therapy

Rituximab

Rituximab is humanized murine anti-CD20 monoclonal antibody, originally developed and approved for treatment of non-Hodgkin's lymphoma. Addition of rituximab to hyper-CVAD (R-hyper-CVAD: rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with cytarabine and methotrexate) in newly diagnosed Ph-negative CD20-positive ALL demonstrated an improved 3-year rates of CR duration (CRD), a lower relapse rate, and an improved OS, but only in younger patients under the age of 60 years compared with historical controls (3-year CRD of 70 vs. 38 %; $p < 0.001$ and OS of 75 vs. 47 %, $p = 0.003$). However, older patients with CD20-positive ALL did not seem to benefit from R-hyper-CVAD regimen [15]. The German Multicenter Study Group for ALL (GMALL) also reported an improvement in 3-year CR duration and OS survival rates (64 vs. 58 %, $p = 0.009$ and 75 vs. 54 %, no p value given) with the addition of rituximab to standard induction and consolidation chemotherapy in patients who are <55 years of age [16]. As a result of these studies, the French multicenter phase 3 study, Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL-R) 2005, explored the use of rituximab in patients under 60 years of age. They enrolled a total of 205 patients: 105 in the rituximab arm and 104 in the control arm. Preliminary results demonstrate improvement in 2-year event-free survival (65 vs. 52 %) with addition of rituximab to standard GRAALL chemotherapy [17•]. This study established rituximab combined with chemotherapy as a standard of care for patients with CD20-positive ALL.

Ofatumumab

Ofatumumab is a second-generation humanized anti-CD20 antibody that binds to a proximal small loop epitope of CD20, different from that of rituximab. Early results of a phase 2 study of ofatumumab combined with hyper-CVAD in pre-B CD20-positive ALL were highly effective, and at a median follow-up of 14 months, the 1-year DFS and OS rates were 94 and 92 %, respectively. The rates for CR and MRD negativity were both 96 % [18].

Obinutuzumab

Obinutuzumab is a novel type 2 glycoengineered humanized IgG1 CD20 monoclonal antibody. It is a third-generation anti-CD20 antibody that is superior to rituximab and ofatumumab in induction of cell death. As of now, there is no clinical trial data available for its use in ALL.

Anti-CD22 Antibodies

Epratuzumab

Epratuzumab is a naked unconjugated humanized immunoglobulin G1 (IgG1) directed against CD22. The Children's Oncology Group (COG) evaluated epratuzumab combined with standard COG reinduction chemotherapy and compared

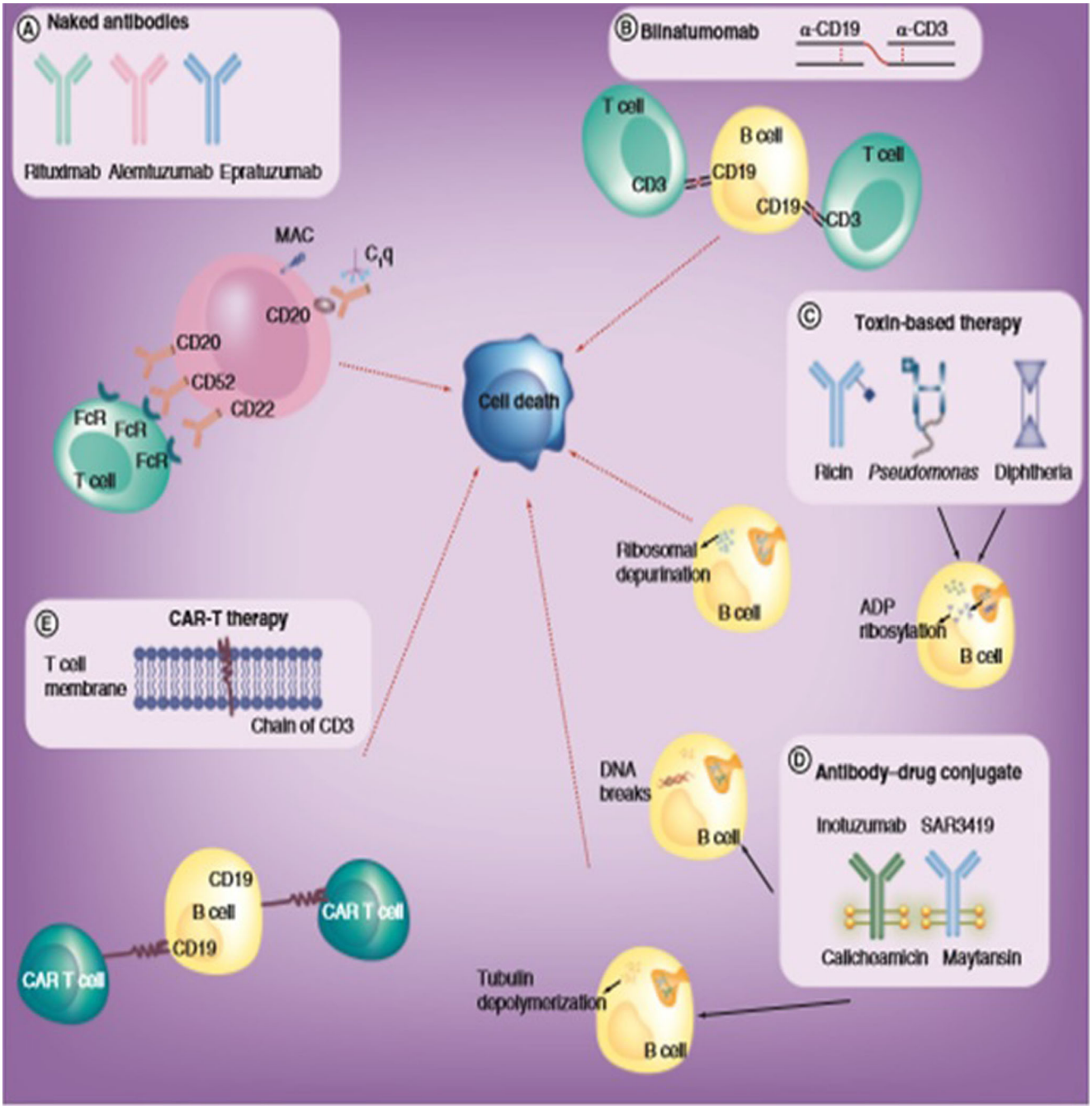

Fig. 1 Mechanisms of action monoclonal antibody conjugates. **a** Naked (unconjugated) antibodies. **b** Bispecific T cell engaging antibody. **c** Antibodies linked to toxins. **d** Antibodies linked to drugs. **e** Chimeric antigen receptor T cells. Image reproduced with permission of the rights holder: Parikh SA, Litzow MR. Future Oncology (2014)10(14)

the combination to historical controls with the same chemotherapy backbone. The CR rate was identical in both arms (65 vs. 66 %); however in those patients achieving a second CR, more patients achieved negative MRD status (42 vs. 25 %, $p = 0.001$) [19]. In adult ALL, the Southwest Oncology Group evaluated epratuzumab combined with clofarabine plus cytarabine in 31 patients experiencing first or later relapse. Overall, 16 patients (52 %) responded with 10 CR and 6 CR with incomplete recovery of neutrophils or platelets (CRi). The median survival was 5 months. Of the 16 responding patients, only 6 had MRD assessed. Of these, only one became MRD negative (<0.01 %), and this patient survived for 11 months [20]. A randomized phase III trial in children with relapsed ALL (IntReALL) evaluating chemotherapy with or without epratuzumab is currently recruiting patients and should better define the role of this antibody (NCT01802814).

Table 1 Monoclonal antibodies

Target	Drug	Clinical trial	Results	Reference	Ongoing clinical trials
CD20	Rituximab (R)	Phase III, GRAALL2005	2-year EFS 65 % with (R) vs. 52 % without (R) 2-year OS 75 vs. 63 %	17	GRAALL 2005 is ongoing (NCT00327678)
	Ofatumumab	Phase II, ofatumumab with hyper-CVAD	At 14 months–1-year DFS 94 % and OS 92 %	18	Hyper-CVAD + ofatumumab in CD20 + ALL (NCT01363128) is ongoing
	Obinutuzumab	Preclinical	None		None
CD22	Epratuzumab	Phase II, epratuzumab with clofarabine and cytarabine	RR (CR + CRi) 52 % Median survival 5 months Unclear OS benefit, may improve MRD	20	Phase III trial IntReALL (NCT01802814)
	Inotuzumab ozogamicin (IO)	1. Phase II, R/R ALL	ORR of 57 % Median survival 5.1 months	22	SWOG S1312 phase 1 study, IO + combination chemotherapy (CVP) in treating patients with relapsed or refractory acute leukemia (NCT01925131
		2. Weekly dosing: multicenter phase I/II study	ORR (CR/CRi) 68 % 86 % MRD	24	
		3. Phase III trial, compared with standard chemotherapy	ORR 80.7 vs. 33.3 % MRD negative 78 vs. 28 %	25	
		4. Patients >60 years: inotuzumab + low-intensity hyper-CVD	ORR (CR + CRi) 96 % MRD negative 96 % 1-year PFS 86 %, 1-year OS 81 %	26	
	Moxetumomab pasudotox	Phase I study	70 % patients showed reduction in blasts and four patients cleared. No CRs or PR	29	Moxetumomab pasudotox (CAT 8015, HA22) in children with B-lineage ALL and MRD prior to allogeneic HSCT (study terminated) NCT02338050
Anti-CD19	SAR3419	Phase II study as monotherapy	ORR 25.5 %, DOR 1.9 months–study terminated due to modest activity	33	
	Denintuzumab mafadotin (SGN-CD19a)	Phase 1 study	ORR (CR/CRi) 19 % with weekly regime and 35 % with three weekly regimen Median response 27 weeks Ph + ALL 50 % CR and 10 % PR	34	Phase II study in relapsed/refractory Ph + ALL is ongoing
	Combotox	Phase 1 study	CR in three patients, six patients decrease of >95 % blasts	35	Immunotoxin therapy and cytarabine in treating patients with R/R B cell ALL (NCT01408160)
	Blinatumomab	1. MRD-positive disease	80 % achieved MRD negative. Long-term data MRD-negative patients lived longer (35.2 vs. 7.1 months)	38	1. Phase III ECOG 1910 trial evaluating blinatumomab during consolidation in adults with newly diagnosed Ph-negative ALL (NCT02003222)
		2. Phase II study for R/R ALL in the salvage setting	ORR (CR/CRi) 69 % MRD negative 88 % Median OS 9.8 months Median DFS 7.1 months	41	2. TOWER trial: blinatumomab vs. investigators' choice of therapy in adult patients with R/R precursor B cell ALL (NCT0201367)
		3. Multicenter phase II study R/R ALL (NCT01466179)	ORR 43 % (33 % CR and 10 % CRh) MRD negative 82 %	42	

ORR overall response rate, *CR* complete response, *CRi* complete response with incomplete blood count recovery, *CRh* complete response with partial hematologic recovery, *MRD* minimal residual disease, *OS* overall survival, *DOR* duration of response, *R/R* relapsed/refractory, *DFS* disease-free survival, *CVD* cyclophosphamide, vincristine and dexamethasone, *PR* partial response, *HSCT* hematopoietic stem cell transplantation

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (IO) is a humanized IgG4, anti-CD22 monoclonal antibody conjugated to calicheamicin, a natural product of *Micromonospora echinospora*, a potent cytotoxic compound that induces double-strand DNA breaks [21]. A single-institution phase 2 study in patients with relapsed and/or refractory ALL showed an ORR of 57 % and a median survival of 5.1 months. Nearly half the patients treated with IO were able to proceed to ASCT, including four patients who were receiving their second ASCT. Survival was similar whether patients underwent subsequent ASCT or not [22]. Two studies, a single-center study and a multicenter phase 1/2, have explored weekly dosing schedules with IO using 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15 repeated every 3–4 weeks. The single-center study evaluated 41 patients with CR and CRi rates at 20 and 32 %, respectively, with 78 % of responding patients achieving an MRD-negative status. The median survival was 9.5 months [23]. These results were similar to the multicenter trial where 72 patients were evaluated demonstrating an ORR (CR and CRi) of 68 with 86 % of patients achieving a negative MRD status [24]. These studies support weekly IO dosing as it is as effective as and possibly better tolerated than the every 3–4 weeks of dosing. IO was recently evaluated in a phase 3 trial compared with standard chemotherapy in patients with relapsed ALL in first or second salvage where it showed an improved ORR of 80.7 vs. 33.3 % ($p<0.0001$) in the IO arm vs. the standard chemotherapy arm. In addition, MRD-negative status was achieved in78% of patients with IO as against 28 % with standard chemotherapy arm [25].

IO has also demonstrated encouraging results in combination with low-intensity hyper-CVD (rituximab, dexamethasone, cyclophosphamide, vincristine, and intrathecal chemotherapy) in elderly patients. The regimen eliminates doxorubicin and uses cyclophosphamide and steroids at 50 % of the dose of the standard regimen and reduces methotrexate to 250 mg/m^2 on day 1 and cytarabine to 0.5 mg/m^2 for four doses (days 2 and 3) of even courses. IO 1.3 to 1.8 mg/m^2 was given once with each of the first four courses. Of the 28 patients treated with this combination, 27 patients (96 %) achieved a CR/CRi (21 CR/5 CRi). All patients achieving CR/CRi have also achieved flow cytometric MRD-negative status. The 1-year PFS and OS were 86 and 81 %, respectively [26•]. The 1-year survival rate was superior to previous results obtained with HCVAD ± rituximab in similar patient populations. Finally, SWOG S1312 is currently accruing patients, and this trial uses a standard dose of CVP with a dose escalation of IO given on a fractionated schedule. The advantage is the potential synergy with cyclophosphamide/prednisone and IO as well as the possibility that a lower dose of IO may lead to a lower risk of sinusoidal obstruction syndrome (SOS) [27].

The adverse events with IO include liver function abnormalities, thrombocytopenia, and veno-occlusive disease (VOD) especially in patients who proceed to ASCT. The majority of abnormal liver function tests are reversible. The antibody conjugation of IO is similar to gemtuzumab ozogamicin, a humanized anti-CD33 monoclonal antibody attached to calicheamicin used for treatment of relapsed CD33+ AML, and this is associated with elevated liver function tests and VOD, especially among patients who had allogeneic hematopoietic stem cell transplantation (HSCT). In one of the studies with IO, elevations of liver function tests were common adverse events (e.g., increased AST and hyperbilirubinemia in 41 and 22 % in patients treated at MTD, respectively). However, grade 3 or 4 elevations of liver function tests were uncommon. One patient had VOD, and he had a medical history significant for VOD-like syndrome with prior therapy [28]. Further studies are needed to define risk of hepatotoxicity and VOD with IO. Currently, all studies with IO exclude patient with active hepatitis, patients with cirrhosis or other serious liver disease, or with suspected alcohol abuse.

VOD after allogeneic HSCT remains a major concern, and this may partly be attributable to preparative regimens containing double alkylating agents. In a recent study in multiply relapsed ALL, more patients were able to achieve CR with IO, with nearly half of the patients experiencing eradication of MRD, and this has allowed for more patients to be eligible for transplantation and better transplantation outcomes [29]. The rate of NRM at 6 months was 32 % with five deaths attributed to VOD. The rates of VOD after transplantation vary widely in literature, ranging from 0 to 38 % based on the intensity of the conditioning regimen [30, 31]. Total-body irradiation (TBI) regimens have historically been associated with higher rates of VOD up to 54 % [32], and thiotepa combined with other alkylating agents is also associated with high rates of VOD [33]. In this study, the VOD rates were 19 % as majority of these patients were heavily pretreated, and majority received myeloablative conditioning regimens including three patients who received TBI-based preparative regimens [29]. Hence, great care needs to be taken in selecting the transplantation regimen and avoiding myeloablative double alkylator combinations that have historically been associated with increased risk for hepatic injury.

Moxetumomab Pasudotox (HA22) and BL22

The immunoconjugate BL22 (CAT 3888) is a monoclonal antibody directed against CD22 fused to a 38-kDa fragment *Pseudomonas aeruginosa* exotoxin A (RFB4[dsFv]-PE38). In a phase I study in 23 patients with childhood ALL, 16 (70 %) showed reductions of leukemic blasts and 4 patients had clearance of peripheral blasts, but no objective CRs or partial responses were noted [34].

HA22 is a second-generation immunoconjugate similar to BL22 with a 15-fold increase in binding affinity to surface CD22. This was initially called high-affinity BL22 (HA22) and later named moxetumomab pasudotox. In a phase 1 study in children with relapsed refractory ALL, among the 21 children and young adults, 17 were evaluable for analysis. Among these, 24 % achieved CR, 6 % had partial response (PR), and 47 % had hematologic improvement for an overall activity rate of 70 % [35]. Currently, studies are underway with higher doses of moxetumomab in pediatric and adult ALL patients.

Anti-CD19 Antibodies

CD19 is ubiquitously expressed on B cells and is known to internalize on binding of antibody. This makes it an attractive target for immunoconjugate therapy.

SAR3419 (Coltuximab Ravtansine)

SAR3419 is a humanized anti-CD19 monoclonal antibody conjugated to maytansin DM4, a potent tubulin inhibitor that binds to the same site as vincristine. Maytansinoids are far more potent than vinca alkaloids and are associated with excessive systemic toxicity such that the development of these compounds was halted early. In preclinical models, SAR3419 significantly delayed the progression of four of four CD19-positive B cell precursor ALL and three of three mixed lineage leukemia xenografts and induced objective responses in all but one xenograft but was ineffective against T-lineage ALL xenografts [36]. In phase 1 studies in patients with relapsed refractory B cell lymphoma, the dose-limiting toxicity was reversible severe blurred vision associated with reversible corneal changes [37]. The phase 2 study in adult patients with relapsed or refractory ALL was stopped early due to very modest activity [38].

Denintuzumab Mafadotin (SGN-CD19A)

SGN-CD19A is a novel humanized anti-CD19 monoclonal antibody conjugated to the microtubule—disrupting agent monomethyl auristatin F (MMAF) via a maleimidocaproyl (mc) linker. In a phase 1 dose escalation study of SGN-CD19A, among the 71 adult patients with relapsed or refractory B-ALL and highly aggressive lymphomas including B cell lymphoblastic lymphoma and Burkitt lymphoma, 59 B-ALL patients were evaluable for response. Six patients (19 %) treated weekly achieved composite CR (CR or CRi), and eight patients (35 %) treated every 3 weeks achieved composite CR. The median response was 27 weeks. Fifty-four percent of patients across both schedules achieved cytoreduction of greater than 50 %. In the subset of patients with Ph-positive B-ALL, four of the eight patients (50 %) achieved CR and one patient (10 %) a PR. SGN-CD19A was generally well tolerated with superficial microcystic keratopathy as the most common toxicity, observed in 40 patients (56 %); symptoms were less severe than the associated corneal findings. Keratopathy was managed with topical steroids and dose modifications and improved/resolved within a median of 3 weeks (1–17 weeks) in patients with sufficient follow-up [39].

Combotox

Combotox is an immunoconjugate, a 1:1 mixture of RFB4-dgA and HD37-dgA which are immunotoxins that target the CD22 and CD19 antigens, respectively. In a phase 1 dose escalation study using combotox in children with refractory or relapsed B-lineage ALL, 17 children were enrolled. Three patients experienced CR, six additional patients experienced a decrease of >95 % in their peripheral blood blast counts, and one experienced a decrease of 75 %. The maximum tolerated dose was 5 mg/m^2 [40]. Unfortunately, in adult patients, the peripheral blast counts rebounded rapidly after the last dose of combotox, suggesting that continued combotox administration at lower doses may lead to more durable remissions [41]. Combination studies with combotox and cytarabine are ongoing in adult patients with relapsed or refractory B cell ALL (NCT01408160).

Blinatumomab (MT103 or MEDI-538)

Blinatumomab is a BiTE antibody with variable regions recognizing both CD3 and CD19, with the anti-CD3 engaging cytotoxic T cells and the anti-CD19 recognizing lymphoblasts. On binding to CD19, the cytotoxic T cells become activated and induce cell death via the pore-forming perforin system. Because of this mechanism, the drug causes significant lymphopenia [42]. The first study with blinatumomab was used as a continuous infusion in patients with B cell ALL in morphologic remission but detectable MRD. Of the 20 evaluable patients with MRD data, 16 (80 %) achieved a negative MRD status after 1 cycle of blinatumomab at a dose of 15 mcg/m^2/day, including three of the five patients who were Ph+ [43]. Long-term data from 116 patients were recently reported [44]. Ninety patients received HSCT after blinatumomab. Sixty-two (53 %) patients are still being followed, 35 patients relapsed, and 26 patients died in CR (23 of them after subsequent HSCT). Median OS with a median follow-up of 29.5 months was 36. 5 months (95 % CI, 19.1 months to not reached (n.r.); 40.4 vs. 12.0 ($p = 0.001$)) in patients with or without MRD complete response in cycle 1 (patients with MRD, 88 and without MRD, 35). Of the 110 patients evaluable for relapse free survival (RFS), and duration of remission (DOR), the median RFS was 18.9 months [24.6 vs.11.0 months ($p = 0.005$)] in patients treated in first CR vs. later, and 35.2 vs. 7.1 ($p = 0.002$) in patients alive and relapse free after 45 days with or without MRD complete response in cycle 1.

Median DOR was n.r. vs. 15.0 months in patients treated in first CR vs. later remission and n.r. vs. 15 months in patients with DOR ≥ 45 days with or without MRD complete response in cycle 1. Further statistical analyses showed no difference for OS or DFS for patients undergoing HSCT vs. no HSCT. However, DOR was longer for HSCT vs. no HSCT (HR, 0.36; 95 % CI 0.17 to 0.77; $p = 0.008$). All patients experienced one adverse event; most common events included tremor (30 %), aphasia (13 %), dizziness (8 %), ataxia, and paresthesias. This long-term study thus far demonstrates that patients who achieved MRD negativity lived significantly longer than those who did not achieve MRD-negative status [44].

There are two multicenter trials and one German trial which have studied blinatumomab in the salvage setting. The largest is the phase 2 study which enrolled 189 adult patients with Ph-negative precursor B cell ALL. Patients had to have at least 10 % blasts and either primary refractory disease or relapse within 12 months of chemotherapy or ASCT. Prior ASCT was noted in 34 % of patients, and 39 % had received two or more lines of prior therapy. Patients who had CNS involvement, testicular involvement, autoimmune disease, active GVHD, recent transplantation, and significant liver or renal dysfunction were excluded [45•]. After 2 cycles, 81 patients (43 %) had achieved CR or CRh: 63 (33 %) patients had CR and 18 (10 %) patients had CRh. Thirty two (40 %) of patients who achieved CR/CRh underwent subsequent allogeneic HSCT. The most frequent grade 3 or worse complications were febrile neutropenia (25 %), neutropenia (16 %), and anemia. Three (2 %) patients had grade 3 cytokine release syndrome (CRS) [45•]. No baseline features predicted response to blinatumomab except for low burden disease at the time of treatment. CD19 negative and extramedullary relapse have been observed after blinatumomab therapy [43, 46].

Blinatumomab has also been studied in morphologic relapsed and refractory B-ALL. The initial study explored three dose levels, and a reduced dose (5 μg/m^2/day) was used in the first week to reduce infusion reactions. Twenty five of the 36 evaluable patients achieved CR/CRi (69 %), and 22 (88 %) achieved MRD-negative status. The median OS and DFS were 9.8 and 7.1 months, respectively. The final dose selected for future studies was 5 μg/m^2/day during week 1 and 15 μg/m^2/day during the following 3 weeks [47].

Based on the encouraging results of this phase II trial [47], blinatumomab was FDA approved for treatment of Philadelphia chromosome-negative (Ph−) relapsed refractory B cell precursor ALL in December 2014. A single cycle consists of 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval. A treatment course consists of up to 2 cycles for induction followed by three additional cycles for consolidation treatment (up to a total of 5 cycles). Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for ≥4 h), supervision by a health care professional or hospitalization is recommended. Premedication with dexamethasone 1 h prior to the first dose of each cycle, prior to a step dose (e.g., cycle 1, day 8), or when restarting an infusion after an interruption of ≥4 h is indicated. If the patient develops grade 3 CRS, the dose is withheld until it is completely resolved and then restarted at 9 mcg/day escalating to 28 mcg/day after 7 days if toxicity does not recur. For grade 4 CRS, the drug is permanently discontinued [48].

Currently, a phase 3 randomized trial [Eastern Cooperative Oncology Group (ECOG) E1910] is evaluating the role of blinatumomab during consolidation in adults with newly diagnosed Ph chromosome-negative B cell ALL (NCT02003222). The phase III open-label TOWER study is evaluating blinatumomab vs. investigators' choice of chemotherapy in adult patients with relapsed or refractory precursor B cell ALL and has completed recruiting patients (NCT0201367) [49].

Chimeric Antigen Receptor T Cell Therapy

The chimeric antigen receptor is a hybrid molecule composed of antigen-binding domains fused to T cell activation and costimulatory domains [50]. The T cells are genetically modified to express the hybrid protein and endowed with a new antigen specificity in addition to the antigen specificity encoded by the endogenous T cell receptor. In ALL, most of the CART to date have focused on CD19, although the NIH is developing CD22 CART. Although not the first target to be studied, CART cell therapies directed against CD19 are the most mature to date. The majority of CART cell-directed therapies are led primarily by three research institutes—University of Pennsylvania (U Penn), the National Cancer Institute (NCI), and Memorial Sloan Kettering Cancer Center (MSKCC). While both the NCI and MSKCC are using a second-generation CAR with CD3ζ and CD28 intracellular signaling domains that is retrovirally transduced into T cells [51, 52], U Penn has selected a second-generation CAR with CD3ζ and 4-1BB stimulatory domains using a lentiviral transduction system [53].

To date, the CART cell therapies have shown remarkable efficacy in B cell ALL. The group at MSKCC first reported CD19 CART cell treatment of an adult patient with B-ALL during his second remission. The patient remained in remission for 8 weeks before undergoing allogeneic HSCT. Although impossible to know if the CART cell treatment helped maintain remission, he did have persistent B cell aplasia prior to transplant, likely indicating activity of the CART cells [54]. This group then published their experience targeting B-ALL with CD19-targeted CART cells. The series involved five adult patients with relapsed B-ALL after salvage chemotherapy, but prior to allogeneic HSCT. All five patients became MRD negative within 8–59 days after infusion. Only four of the five patients were eligible for HSCT. The fifth patient was ineligible

for HSCT or additional CART cell therapy and relapsed after 90 days [55]. The same group published their results from 16 patients with relapsed/refractory B-ALL, including the 5 from their previous study and 11 new patients. Eighty-eight percent of patients had a CR (75 % MRD negative) [56]. Recently, this group updated the results from 33 adult patients treated with CD19-directed CART cell product. They reported 13/16 patients who had morphological disease and 16/16 patients with MRD-positive disease at the time of infusion who were in CR after infusion (91 % CR, 82 % MRD negative) [57]. These results were updated again at American Society of Hematology (ASH) meeting in 2015. Of the 43 patients evaluable for follow-up, median OS of all patients was 8.5 months and patients who achieved a CR with MRD negativity was 10.8 months which clearly predicts better survival in patients who attain MRD negativity. This study so far has not shown a significant difference in survival with allo-HSCT post CART cell infusion (OS at 6 months was 70 % in patients who underwent post-CAR allo-HSCT as compared with 64 % in patients who did not get allo-HSCT after CART cells) [58].

The U Penn and NCI have also reported their experience with CART cells in patients with ALL, but mostly in children and with fewer adults treated. The initial report from U Penn was in two children. Both patients were in second relapse, one after both allogeneic HSCT and blinatumomab. After treatment, both patients went into morphologic remission by 1 month. The patient without allogeneic stem cell transplant achieved CR with MRD negativity of now over 2-year duration. However, the other patient with prior allogeneic HSCT ultimately relapsed 2 months after therapy with CD19-negative leukemia cells [59]. The U Penn group has recently published their experience in treating 30 children and adults with relapsed/refractory ALL with CD19-targeted CART cells. Ninety percent (27/30) of treated patients achieved a CR, with MRD negativity in 22/27 patients. Of note, two patients had CNS blasts present prior to treatment, and these cleared with CART cell infusion with no CNS relapses. Of the 27 patients who achieved a CR, 7 relapsed between 1.5 and 8.5 months following treatment; among these, 3 patients had CD19-negative disease [60•].

At the NCI, 20 patients with relapsed/refractory ALL were treated with CD19-directed CART cells. Fourteen patients had a CR (70 %) with 12 of the 14 having a MRD-negative CR. Two patients relapsed after 3 and 5 months with CD19-negative ALL [61].

CART cell therapy is an exciting new development in the treatment armamentarium of ALL, but this is more technically intensive than other therapies and can be associated with significant CRS which needs early identification and aggressive medical management including hemodynamic support, treatment with tocilizumab (an IL-6 inhibitor), and in life-threatening conditions steroids though it may also minimize or eliminate the CART cell activity. The likelihood of developing severe CRS is tightly correlated with tumor burden, thus providing a simple means to anticipate patients who are at risk of developing severe CRS. This has proven true in pediatric patients [59, 60•, 61]. In a study of 33 adult patients who all had high tumor burden, severe CRS requiring vasopressors or mechanical ventilation for hypoxia occurred in seven patients which was effectively managed with IL-6 inhibitor and or corticosteroid therapy [62]. Other toxicities such as B cell aplasia and neurological toxicities including seizures and aphasia have also been reported.

Other Targeted Agents

Several different mutated genes have been identified as possible targets, and novel agents are already in clinical trials (Table 2). The classic examples are the tyrosine kinase

Table 2 Novel experimental agents

Target	Drug	Preclinical/trial
MLL (q11.23)	DOT1L inhibitors	Phase 1 [72].
	FLT3 inhibitors	Lestaurtinib—phase 1 and randomized trials [63, 64]
		Quizartinib—phase 1 (results pending)
Notch 1 (T-ALL)	γ secretase inhibitors (GSI)	Phase 1 [73]
JAK	JAK inhibitors	Preclinical [74]
mTOR	Everolimus, temsirolimus	Preclinical [75]
CRLF2	JAK and HSP 90 inhibitors	Preclinical [76]
PI3Kδ (pre-B)	Idelalisib	Preclinical [77]
PI3Kδ,γ (pre-T)	IPI-145	Phase II (study withdrawn)
PI3K and mTOR (dual)	BEZ 235	Preclinical [78], phase 1 [66] (ongoing)
PP2A mutations	Fingolimod (FTY720)	Preclinical [79]
Proteasome inhibitors	Bortezomib	Phase 1 [67, 68], phase II [69] (ongoing)
Hypomethylating agents	Decitabine	Phase 1 [80]

inhibitors (TKIs) such as imatinib, dasatinib, nilotinib, and ponatinib for BCR-ABL1-positive ALL, the NOTCH 1 and DOT1L pathway inhibitors, and the JAK inhibitors among others.

The FLT3 inhibitor, lestaurtinib, has been tried as a single agent and co-administered with chemotherapy [63, 64]. A phase III trial, COG P9409, is ongoing using combination chemotherapy with or without lestaurtinib in newly diagnosed ALL (NCT00557193). Similarly, a phase I study using another potent FLT3 inhibitor, quizartinib, as a single agent in children with relapsed/ refractory MLL rearranged and high hyperdiploid ALL has just been concluded (NCT01411267).

Other agents which are in preclinical and phase I and II trials include Bruton's tyrosine kinase inhibitors [65], phosphoinositol 3-kinase inhibitor in primary T-ALL [66], proteasome inhibitor bortezomib as a single agent [67, 68], and in combination [69, 70]. Recently, cytokine receptor-like factor 2 (CRLF2), JAK1, JAK2 deletions, and mutations in IKZF1 have been found to have unfavorable outcomes in ALL, and therefore, inhibitors of intracellular JAK2, PI3K/mTOR, and MEC as well as membranous CRLF2 provide potentially promising new research directions [71].

Conclusion

ALL treatment has advanced significantly, and it is clear that the current status of frontline treatment is being redefined. However, cure is often challenging, toxic, and will not occur in the majority of adult patients. Together with the range of new agents available to treat ALL, the natural course of this disease is likely to improve as these novel therapies hold promise for more effective treatment in the future. The overall goal of achieving safe and effective cure may be possible as more of these agents begin to move to the frontline setting in combination with chemotherapy and may even replace toxic chemotherapies. Furthermore, MRD monitoring is modifying treatment strategies. This review highlights only some of the new and recent developments in treatment of ALL, and the challenge for the future is to determine in what setting these agents are most active to limit their toxicity and to improve their efficacy.

Compliance with Ethical Standards

Conflict of Interest Ajoy Dias, Saad J. Kenderian, and Gustavo F. Westin each declare no potential conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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