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REVIEW ARTICLE

ACUTE LYMPHOBLASTIC LEUKEMIA

Optimizing the treatment of acute lymphoblastic leukemia in younger and older adults: new drugs and evolving paradigms

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Abstract

In the past decade, the available treatments for patients with acute lymphoblastic leukemia (ALL) have rapidly expanded, in parallel with an increased understanding of the genomic features that impact the disease biology and clinical outcomes. With the development of the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin, the CD3-CD19 bispecific T-cell engager antibody blinatumomab, CD19 chimeric antigen receptor T-cell therapy, and the potent BCR-ABL1 tyrosine kinase inhibitor ponatinib, the outlook of ALL in both younger and older adults has substantially improved. The availability of highly effective drugs raised important questions concerning the optimal combination and sequence of these agents, their incorporation into frontline regimens, and the role of hematopoietic stem cell transplantation. In this review, we discuss the rapidly evolving paradigms in the treatment of ALL, highlighting both established and effective regimens, as well as promising new therapies that are being evaluated in ongoing clinical trials. We specifically focus on novel combination regimens in both the frontline and salvage settings that are leading to new standards of care in the treatment of ALL.

Introduction

Despite cure rates exceeding 90% in children with acute lymphoblastic leukemia (ALL), adults with ALL historically have had long-term survival of less than 40% [1, 2] However, major scientific and therapeutic advances in recent years have led to significant improvements in outcomes. This has been driven both by better risk stratification and selection of patients for hematopoietic stem cell transplantation (HSCT) in the first remission and by an expansion of effective treatment options [3–12]. In particular, the development of novel monoclonal antibodies (e.g., the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin (INO) and the CD3-CD19 bispecific T-cell engaging antibody blinatumomab), chimeric antigen receptor (CAR) T-cells for B-cell ALL, and later-generation BCR-ABL1 tyrosine kinase inhibitors (TKIs) such as ponatinib for Philadelphia chromosome (Ph)-positive ALL have led to major breakthroughs in the management of ALL. We now have an increasing number of effective therapeutic tools at our disposal, and in this review, we will discuss the emerging data of how to optimally sequence and combine these agents in both the frontline and relapsed/refractory settings.

Ph-positive B-cell ALL

Ph-positive ALL has historically been considered a poor-risk subtype of ALL and was associated with long-term survival rates <20% in the pre-TKI era [13–15]. Due to the aggressive natural history of this ALL subtype, HSCT in first remission was also routinely recommended to all fit patients. However, with the introduction of highly potent BCR-ABL1 TKIs, the outcomes of Ph-positive ALL now surpass those of Ph-negative ALL in several studies. The goal of therapy is now a complete molecular response (CMR) as assessed by the real-time quantitative reverse-transcription polymerase chain reaction of *BCR-ABL1* transcripts, which, if achieved, identifies patients who have excellent long-term survival and a high likelihood of cure without the need for HSCT (discussed in more detail in "The evolving role of HSCT for ALL" below) [16, 17]. Although there are currently no randomized studies to definitively support the preferential use of later-generation TKIs in adults, dasatinib was associated with superior

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event-free survival (EFS) and overall survival (OS) in a study of dasatinib versus imatinib-based therapy in children with newly diagnosed Ph-positive ALL [18]. A randomized phase III study comparing low-intensity chemotherapy with either imatinib or ponatinib is also ongoing in adults with newly diagnosed Ph+ ALL and may further clarify the role of later-generation TKIs in this disease (NCT03589326).

Intensive chemotherapy+ TKI

The introduction of imatinib to standard chemotherapy improved outcomes compared to chemotherapy alone and resulted in complete remission (CR) rates of 95% and long-term OS rates of 40–50% [5, 6, 19–21]. Subsequent studies with the combination of hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine) chemotherapy plus dasatinib resulted in similar high CR rates and 3-year OS rates of 64–69% [5, 22, 23]. Another study of intensive chemotherapy plus nilotinib showed a 2-year OS rate of 72% [24]. While T315I resistance mutations in *ABL1*—which confer resistance to all first- and second-generation TKIs—cannot be reliably detected at the time of diagnosis [25], they have been reported in up to 75% of patients who relapse after treatment with a first- or second-generation TKI, suggesting that these approaches may be suboptimal for many patients [23, 26].

Ponatinib is a highly potent pan-BCR-ABL1 TKI that is active in T315I-mutated Ph-positive leukemias [23, 26, 27]. A study of hyper-CVAD plus ponatinib has been reported in 86 patients with newly diagnosed Ph-positive ALL (median age: 46 years) with promising results. Initially, a dose of ponatinib 45 mg daily was used; however, after two deaths possibly due to ponatinib-induced cardiovascular toxicity were observed, the protocol was amended to use response-adapted dosing (i.e., 45 mg in cycle 1, 30 mg once CR is achieved, and 15 mg once CMR is achieved) without any further ponatinib-related mortality [28–30]. With this regimen, the CMR rate at 3 months was 74%, an important endpoint that strongly correlates with superior long-term OS in Ph-positive ALL [17]. Only 19 patients (22%) underwent HSCT in first remission. The 5-year OS rate was 74% for the entire population and was 83% for those who did not undergo HSCT. These data compare favorably to other series using first- or second-generation TKIs in similar populations, where 5-year OS rates of 40–50% have been reported [6, 22]. The superiority of ponatinib in the frontline management of ALL is further supported by both a meta-analysis and a propensity-matched score analysis, both of which showed an OS benefit with a ponatinib-based regimen [31, 32]. Presently, the selection of a first-, second-, or third-generation TKI for patients with newly diagnosed Ph+ ALL is variable across institutions and practitioners. However, considering the promising data with ponatinib and the risk of relapse and development of T315I mutations with earlier-generation TKIs, at our institution, we always prefer a ponatinib-based regimen for any patient without a clear contradiction to its use.

Lower-intensity therapy +TKI

Several investigators have evaluated the use of lower-intensity regimens for Ph-positive ALL, in an attempt to maintain efficacy but reduce the risk of treatment-related mortality. These studies are summarized in Table 1. The use

Table 1 Prospective studies of lower-intensity therapy plus a tyrosine kinase inhibitor in adult ALL.

Regimen	*N*	Age in years, median [range]	CR rate (%)	CMR rate (%)	HSCT rate (%)	OS rate (%)
Low-intensity chemotherapy						
+ imatinib [7]	135	49 [18–59]	98	28	62	46 (5-year)
+ dasatinib [26]	71	69 [59–83]	96	24	10	36 (5-year)
+ dasatinib [34]	60	42 [19–60]	100	19	42	58 (3-year)
+ nilotinib [33]	79	65 [55–85]	94	58	16	47 (4-year)
+ nilotinib [140]	60	47 [18–59]	98	Not reported	73	96 (1-year)
Corticosteroids						
+ imatinib [37]	30	69 [61–83]	100	4	Not reported	74 (1-year)
+ dasatinib [35]	53	54 [24–77]	100	23	42	69 (20-month)
+ ponatinib [36]	42	69 [27–85]	95	46	Not reported	88 (1-year)
Blinatumomab						
+ dasatinib [41]	63	54 [24–82]	98	60[a]	38	95 (1-year)

CR complete remission, *CMR* complete molecular response, *HSCT* hematopoietic stem cell transplant, *OS* overall survival.

[a]Includes patients with "positive non-quantifiable" results.

of low-intensity, minimal chemotherapy in combination with a TKI has been largely explored in older patients who are at particularly high risk for complications with standard intensive approaches. For example, the EWALL-PH-01 study evaluated low-intensity chemotherapy plus dasatinib in older adults with newly diagnosed Ph-positive ALL [26]. Although the CR rate was high (96%), responses were not durable, and the 5-year OS rate was 36%. A study of low-intensity chemotherapy plus nilotinib in a similar population yielded a CR rate of 94% and a 4-year OS rate of 47% [33]. Chemotherapy-free regimens with corticosteroids plus a TKI have also been evaluated in older adults with Ph-positive ALL. These regimens are generally well-tolerated but are associated with short durations of response and suboptimal CMR rates (4% with imatinib, 23% with dasatinib, and 46% with ponatinib) [34–37].

Blinatumomab is highly effective in relapsed or refractory Ph-positive ALL, with a CR/CR with incomplete hematologic recovery (CRi) rate of 36% and median OS of 7.1 months in a population of heavily pretreated patients (e.g., 50% with prior exposure to ponatinib, 44% with prior HSCT, and 27% with T315I mutation) [38]. Retrospective analyses have also shown the safety and efficacy of blinatumomab in combination with a BCR-ABL1 TKI, with a CR rate of 50% and molecular response rate of 75% reported in one study [39, 40]. Building upon this work, the D-ALBA study evaluated the combination of blinatumomab and dasatinib in patients of all ages with newly diagnosed Ph-positive ALL (median age: 54 years) [41]. Patients initially received dasatinib monotherapy for 85 days, followed by up to five cycles of blinatumomab in combination with dasatinib. Among 63 patients treated, the CMR plus positive non-quantifiable (PNQ) rate was 29% after dasatinib monotherapy and 60% after two cycles of blinatumomab. Twenty-four patients (38%) underwent HSCT in first remission. With a median follow-up of 18 months, the disease-free survival (DFS) and OS rates were 88% and 95%, respectively. These early results are encouraging and support the further exploration of blinatumomab plus TKI combinations in Ph-positive ALL. A study of blinatumomab plus ponatinib for adults of all ages with Ph-positive ALL is ongoing and may further improve outcomes and decrease reliance on HSCT in first remission (NCT03263572).

Other novel therapies

INO has shown single-agent activity in Ph-positive ALL in subgroup analyses of larger trials [8, 42]. The combination of INO plus bosutinib was evaluated in 18 patients with relapsed/refractory Ph-positive ALL or chronic myeloid leukemia in lymphoid blastic phase [43]. The overall response rate was 83% and the CMR rate was 56%, resulting in a promising median OS of 15.4 months. Preclinical evidence also suggests that Ph-positive ALL is highly dependent on Bcl-2 for survival, supporting a potential role for venetoclax in this setting [44]. Initial results in nine patients from a phase I/II study of the oral combination of ponatinib, venetoclax and dexamethasone showed a CR/CRi rate of 56% and CMR rate of 44% in a heavily pretreated population of patients with relapsed/refractory Ph-positive ALL (78% with prior ponatinib, 56% with prior blinatumomab, and 67% with prior HSCT) [45]. With a median follow-up of 13.2 months, the median OS was not reached and none of the five responding patients had relapsed.

Ph-negative B-cell ALL

Frontline therapy

With the development of new, highly effective monoclonal antibodies in the treatment of relapsed/refractory B-cell ALL (discussed later in more detail), these agents are now being incorporated into frontline regimens and for measurable residual disease (MRD)-positive disease, with a goal of deepening responses, reducing reliance on HSCT, and increasing the cure fraction of patients with newly diagnosed ALL. Interim results of a phase II study of the sequential combination of hyper-CVAD plus blinatumomab in younger patients with Ph-negative B-cell have been reported [46]. Patients receive four cycles of standard hyper-CVAD alternating with high-dose methotrexate and cytarabine followed by four cycles of blinatumomab consolidation (except for patients with high-risk disease features [e.g., low hypodiploidy, complex cytogenetics, Ph-like ALL, *KMT2A* rearrangement, or persistent MRD positivity], who receive blinatumomab after two cycles of chemotherapy). Maintenance is with alternating blocks of 3 months of POMP (prednisone, vincristine, methotrexate, and 6-mercaptopurine) and one cycle of blinatumomab for 15 total cycles (18 months). Compared to the standard hyper-CVAD regimen [47], the number of cycles in induction/consolidation and the duration of the maintenance period have both been reduced by half. Thirty-eight patients have been treated (median age: 37 years). All patients achieved CR and 97% achieved MRD negativity by flow cytometry at some point over the course of therapy. Twelve patients (32%) underwent HSCT in first remission due to presence of one or more high-risk disease features. With a median follow-up of 24 months, the 2-year OS rate was 80%, which compares favorably with historical data with standard hyper-CVAD [1]. Notably, no relapses have so far been observed in patients without a baseline high-risk feature nor in any patient beyond 2

years, suggesting encouraging long-term durability of these responses. The protocol has now been amended to incorporate INO in order to further deepen responses and improve outcomes. Multicenter, randomized studies incorporating these novel monoclonal antibodies into frontline ALL therapy in younger adults with ALL are also being conducted, including studies of chemotherapy ± blinatumomab (NCT02003222) and chemotherapy ± INO (NCT03150693).

The treatment of older adults (generally defined as age ≥60 years and older) with Ph-negative ALL is particularly challenging [48]. These patients historically have a long-term OS rate of 20% or less when treated with intensive chemotherapy, due to a higher incidence of adverse-risk cytogenetic and molecular features and poorer tolerance of conventional therapies, including high rates of induction mortality and death in CR [48–52]. Data from prospective studies specifically designed for older adults with Ph-negative ALL are summarized in Table 2. In an attempt to deliver lower-intensity, tolerable therapy that is capable of achieving durable responses in this population, we conducted a phase II study of mini-hyper-CVD plus INO, with or without blinatumomab, in older adults with newly diagnosed Ph-negative B-cell ALL [53, 54]. Patients receive four cycles of mini-hyper-CVD alternating with mini-methotrexate and cytarabine in combination with INO (cycle 1 with INO 0.6 mg/m^2 on day 2 and 0.3 mg/m^2 on day 8, cycles 2–4 with INO 0.3 mg/m^2 on days 2 and 8; total cumulative INO dose of 2.7 mg/m^2), followed by four cycles of blinatumomab consolidation, and then alternating blocks of three cycles of POMP with one cycle of blinatumomab for 16 cycles as maintenance. Seventy patients have been treated (median age 68 years [range 60–81 years]). The CR/CRi rate was 98% and MRD negativity rates after one cycle and at any time over the course of therapy were 78% and 96%, respectively. The 3-year OS rate was 56%, which is superior to historical outcomes in this older population in a propensity score matched analysis [55]. The 3-year OS rate was 65% in the 60–69-year-old age group and 43% in the ≥70 age group. Due to high rate of death in remission observed in patients ≥70 years of age compared to those aged 60–69 years (57% versus 22%, respectively), the protocol has now been amended to eliminate chemotherapy for patients ≥70 years of age; these patients will now receive only a combination of INO and blinatumomab.

Other groups have also evaluated the combination of INO or blinatumomab with low-intensity chemotherapy in older adults with newly diagnosed Ph-negative B-cell ALL. The SWOG 1318 trial evaluated blinatumomab for 4–5 cycles followed by POMP maintenance in 31 patients. The CR rate was 66% and 1-year OS rate was 65% [56]. The GMALL group also evaluated INO induction followed by conventional chemotherapy in 31 patients >55 years of age. All patients achieved CR/CRi, with 74% of evaluable patients achieving MRD negativity [57]. The estimated 1-year OS rate was 82%. An ongoing Alliance study is evaluating a chemotherapy-free sequential therapy with INO and blinatumomab in adults ≥60 years of age with Ph-negative B-cell ALL (NCT03739814), although no results are yet publicly available.

Treatment of relapsed/refractory disease

The outcomes of relapsed/refractory ALL are poor, with a historical CR rate of 20–40%, median OS of 6 months, and cure rates of <10% [58, 59]. However, the development of INO, blinatumomab and the CD19 CAR T-cell product tisagenlecleucel have significantly altered the treatment landscape for these patients. Data from the pivotal studies

Table 2 Prospective studies in older adults with Philadelphia chromosome-negative ALL.

Reference (regimen)	*N*	Age in years, median [range]	CR/CRi rate (%)	Early death rate (%)	OS rate (%)
Sancho et al. 2007 [141]	33	65 [56–77]	58	36	39 (2-year)
Gökbuget et al. 2008 [142]	54	66 [56–73]	85	0	61 (1-year)
Hunault-Berger et al. 2011 [143]					
Arm 1	31	68 [55–77]	72	6	35 (2-year)
Arm 2	29	66 [60–80]	90	10	24 (2-year)
Gökbuget et al. 2012 [144]	268	67 [55–85]	76	14	23 (5-year)
Ribera et al. 2016 [145]	56	66 [56–79]	74	13	Not reported
Kantarjian et al. 2017/Short et al. 2020 [53, 54] (mini-hyper-CVD + INO ± blinatumomab)	70	68 [60–81]	98	0	56 (3-year)
Advani et al. 2018 (SWOG 1318: blinatumomab + POMP)	31	75 [66–84]	66	0	65 (1-year)
Stelljes et al. 2020 (INITIAL-1: INO + chemotherapy)	31	64 [56–80]	100	0	82 (1-year)

CR/CRi complete remission or complete remission with incomplete hematologic recovery, *OS* overall survival, *CVD* cyclophosphamide, vincristine, and dexamethasone, *INO* inotuzumab ozogamicin, *POMP* 6-mercaptopurine, vincristine, methotrexate, and prednisone.

Table 3 Pivotal trials of novel agents approved for B-cell ALL.

Drug	Study population	Mechanism of action	FDA approval	*N*	Age in years, median [range]	CR/CRi rate (%)	MRD negativity[a] (%)	Median OS, months
Inotuzumab ozogamicin [8]	R/R CD22 + ALL	Anti-CD22 ADC	R/R B-cell ALL	109	47 [18–78]	81	78	7.7
Blinatumomab [9]	R/R Ph-negative ALL	CD3-CD19 bispecific antibody	R/R B-cell ALL	271	41 [18–80]	44	76	7.7
Blinatumomab [10]	R/R Ph-positive ALL	CD3-CD19 bispecific antibody	R/R B-cell ALL	45	55 [23–78]	36	88	7.1
Blinatumomab [11]	MRD + B-cell ALL	CD3-CD19 bispecific antibody	MRD+(>0.1%) B-cell ALL	113	45 [18–76]	N/A	78	36.5
Tisagenlecleucel [12]	R/R CD19 + ALL	Anti-CD19 CAR T-cell	CD19 + B-cell ALL that is refractory or in 2nd or later relapse in patients ≤25 years of age	75	11 [3–23]	81	100	19.1

FDA food and drug administration, *CR* complete remission, *CRi* complete remission with incomplete hematologic recovery, *MRD* measurable residual disease, *OS* overall survival, *R/R* relapsed/refractory, *ADC* antibody-drug conjugate, *Ph* Philadelphia chromosome, *CAR* chimeric antibody receptor.

[a]MRD negativity rate is among responders only.

leading to the approvals of these agents are summarized in Table 3. In the randomized, phase III INO-VATE study which compared INO to conventional chemotherapy in adults with relapsed/refractory CD22 + B-cell ALL, INO was associated with a significantly higher rate of CR/CR with incomplete hematologic recovery CRi (81% versus 29%, $P < 0.001$), a higher rate of HSCT realization (41% versus 11%; $P < 0.001$), and longer median OS (7.7 months versus 6.7 months; $P = 0.04$) [8, 60, 61]. The rate of veno-occlusive disease (VOD) with INO was 11%, predominantly after HSCT and with the use of dual-alkylator conditioning. In a similar randomized, phase III study in adults with relapsed/refractory Ph-negative B-cell ALL (TOWER study), blinatumomab was associated with a higher CR rate (34% versus 16%; $P < 0.001$) and a longer median OS (7.7 months versus 4.0 months; $P = 0.01$) compared to standard of care chemotherapy [9]. Consistent with the toxicity profile observed in previous phase I/II studies, severe neurotoxicity or cytokine release syndrome (CRS) was observed in 10% and 5% of blinatumomab-treated patients, respectively.

Despite the improvement in OS compared with conventional chemotherapy, outcomes with INO or blinatumomab monotherapy are suboptimal (median OS 7.7 months in both studies; 2-year OS rates of 20–30%). Combination therapies with low-intensity chemotherapy and the incorporation of both agents may lead to more durable responses. Mini-hyper-CVD plus INO, with or without blinatumomab, has also been evaluated in relapsed/refractory Ph-negative B-cell ALL [62–64]. In the most recent update, 96 patients were treated (67 without blinatumomab and 29 with blinatumomab) [64]. The CR/CRi rate was 80% (91% for patients in first salvage), and 46% patients proceeded to HSCT. The 3-year OS rate was 33% for the entire cohort and 42% for patients in first salvage. Ten patients (10%) developed VOD; the rate of VOD was lower in patients treated with a fractionated schedule of INO compared with a larger single dose of INO each cycle (3% versus 13%, respectively). The survival outcomes with this regimen compare very favorably to reported data with either INO or blinatumomab monotherapy, suggesting the benefit of adding of low-dose chemotherapy to these monoclonal antibodies and to their use in combination rather than as sequential single agents. The results observed in patients who received this regimen in first salvage are particularly encouraging and support the consideration of this regimen early in the treatment course, ideally at first relapse, when long-term OS rates of >40% can still be achieved. In light of these promising data, we generally treat all patients in first salvage who have not previously been exposed to INO or blinatumomab with a combination of INO and blinatumomab (e.g., mini-hyper-CVD + INO + blinatumomab), and we never use these agents as monotherapy in any line of salvage.

Over the past decade, five generations of CAR T-cell products have been developed, each differing in the type and number of co-stimulatory domains, which influence their in vivo expansion and persistence [65]. Tisagenlecleucel, which is currently the only CAR T-cell approved for ALL, was evaluated in a phase I/IIa study in 75 children and young adults with relapsed/refractory CD19 + ALL, 61% of whom had undergone prior HSCT [12]. Among 75 evaluable patients, the CR/CRi rate was 81% (66% using the intention-to-treat population), all of whom achieved MRD negativity. CRS and neurotoxicity were observed in 70% and 40% of patients, respectively. The 18-month OS rate was 70% [66]. The FDA subsequently approved tisagenlecleucel for patients up to 25 years of age with refractory ALL or in second or later salvage. In a later analysis of real-world data with tisagenlecleucel, similar outcomes were observed; however, patients with high disease burden (i.e., bone marrow blasts ≥5% or extramedullary disease) were noted to have worse survival than those with minimal disease (1-year OS rate: 58% versus 85%, respectively; $P < 0.001$) [67]. Promising results were also observed in a phase I study of 19–28z CAR T-cells in adults with relapsed/refractory CD19 + B-cell ALL (median age: 44 years [range, 23–74 years]) [68]. Lower pretreatment disease burden was associated with longer survival (median OS 20.1 months for patients with <5% bone marrow blasts versus 12.4 months for those with ≥5% bone marrow blast; $P = 0.02$) and lower rates of CRS, suggesting that this may be a particularly attractive strategy for the treatment of MRD-positive disease or as consolidation. As one obstacle to the timely delivery of current autologous CAR T-cell therapies is the need to leukapherese T-cells from the patient to manufacture the CAR T-cell product, there is interest in the development of allogeneic "off-the-shelf" CAR T-cells that can bypass this process. In phase I studies of children and adults with relapsed/refractory B-cell ALL, the allogeneic anti-CD19 UCART19 product resulted in a CR/CRi rate of 67% and a 6-month OS of 55% [69]. CAR T-cells targeting alternative antigens, including CD22 or dual CD19/CD22 CAR T-cells, are also being evaluated in clinical trials [70–72]. As CD19-negative relapses are common in patients treated with CD19 CAR T-cells, these novel constructs may retain efficacy even in patients with prior exposure to CD19-directed therapies. Given the current toxicity profile of CAR T-cells, the efficacy of INO and blinatumomab combinations, and the lack of an approved CAR product for patients >25 years of age, INO and blinatumomab-based therapies should generally be used earlier in the treatment algorithm than CAR T-cells (and ideally in first salvage). In the future, these modalities are likely to be complementary and may be used in combination or in sequence as part of a curative HSCT-free "total therapy" for ALL.

Other novel therapies

Several novel monoclonal antibody therapies and small molecule inhibitors are also in clinical development, some of which have shown promising data in the relapsed/refractory setting. Preclinical studies suggest that B-lineage ALL cells are highly sensitive to Bcl-2 inhibition with venetoclax and to Bcl-xL inhibition with navitoclax, with potential synergy between these two agents [73–75]. In a heavily pretreated population of 36 patients with relapsed/refractory ALL, the combination of venetoclax and navitoclax with chemotherapy resulted in an overall response rate of 50%, with 60% of responders achieving MRD negativity [76]. Ongoing studies are also evaluating chemotherapy plus venetoclax combinations in both the frontline and salvage settings (NCT03319901, NCT03504644, and NCT03808610). Alternative antibody constructs and combinations that may overcome some of the limitations of our currently available therapies are being explored. For example, ADCT-402 is an anti-CD22 antibody conjugated to the cytotoxic agent tesirine (SG3249) and is associated with less hepatotoxicity than INO. In a phase I study, this agent was safe and showed preliminary efficacy; ADCT-402 is now being evaluated in a dose-expansion study (NCT02669264) [77]. T-cell exhaustion and increase in regulatory T-cells are an established mechanism of resistance to blinatumomab; therefore combinations with immune checkpoint inhibitors are being explored in an effort to maintain or restore blinatumomab immune-related activity (NCT03160079, NCT02879695) [78]. Early data suggest that menin inhibitors may be a promising emerging therapy for patients with *KMT2A*-rearranged leukemias, which historically have been one of the most refractory and aggressive forms of ALL in children and adults [79].

T-cell ALL

T-cell ALL accounts for approximately 25% of ALL cases. Progress in the treatment of T-cell ALL has notably lagged behind that of B-cell ALL, where advances have been made through the development of effective monoclonal antibodies and CAR T-cell therapies. Nelarabine is a T-cell-specific purine analog that achieves CR rates of 30–40% in relapsed/refractory T-cell ALL, although these responses are generally short-lived [80–82]. Given the benefit of nelarabine in the salvage setting, several studies have evaluated its use in combination with standard chemotherapy. In a randomized phase III study of children and young adults age 1–31 years with newly diagnosed T-cell ALL, the addition of nelarabine to the pediatric-inspired Augmented Berlin–Frankfurt–Muenster (BFM) regimen resulted in significant improvement in the 5-year DFS compared with chemotherapy alone (88.2% versus 82.1%,

respectively; $P = 0.029$) [83]. Nelarabine treatment was also associated with fewer central nervous system (CNS) relapses (1.3% versus 6.9%, respectively; $P = 0.0001$). Promising results have also been observed with the combination of hyper-CVAD plus nelarabine in adults with newly diagnosed T-cell ALL, particularly in patients with non-early T-cell precursor (ETP) ALL, in whom the addition of nelarabine may be particularly beneficial [84, 85]. This study has now been amended to include both venetoclax and pegasparagainse, which may further improve outcomes. Despite the positive data in T-cell ALL, it remains unclear whether nelarabine benefits patients with T-cell lymphoblastic lymphoma [86].

Approximately 15–20% of cases of T-cell ALL have an ETP immunophenotype, which is associated with poor prognosis [87, 88]. ETP ALL is characteristically negative for CD1a and CD8 surface expression, negative or dim for CD5 (i.e., <75% expression), and expresses one or more stem cell or myeloid antigens [89]. Compared with non-ETP ALL, ETP ALL has a lower frequency of *NOTCH1* mutation, a higher rate of MRD positivity after conventional chemotherapy, and a worse OS, although the poor outcome of ETP ALL may be negated by HSCT in first remission [87–91]. ETP ALL has significant epigenetic and genetic overlap with myeloid malignancies such as acute myeloid leukemia, including an enrichment of *RAS* and receptor tyrosine kinase mutations (e.g., *FLT3*); the biological similarity to myeloid malignancies (and dissimilarities with non-ETP ALL) may at least partially explain the resistance of ETP ALL to standard ALL therapies [91, 92]. Preclinical studies suggest that ETP ALL may be particularly sensitive to Bcl-2 and/or Bcl-xL inhibition; venetoclax or navitoclax-based strategies are being explored in this ALL subtype [93].

One factor that has limited progress in the management of T-cell ALL is the challenge of manufacturing effective and stable CAR T-cell therapies for this ALL subtype. The process of constructing and delivering T-cell-targeting CAR T-cells is limited by both fratricide of the product due to shared antigens between the leukemic blasts and CAR T-cells and by potential leukemic contamination of autologous T-cell products. One potential solution is CRISPR/Cas9 editing to delete CD7 from allogeneic donor T-cells while transducing them with a CD7-targeting CAR [94]. This and other innovative manufacturing processes have led to the development of CD5 and CD7 CAR T-cells that are currently under study in clinical trials (NCT03081910; NCT03690011).

Special considerations

Adolescents and young adults

The AYA age group is typically defined as between 16 and 39 years of age [95]. Pediatric-inspired, asparaginase-containing regimens are preferentially used as frontline therapy in AYAs at some centers, with CR rates of 85–90% and long-term OS rates of 60–70% achieved in several studies [96–103]. Because of the asparaginase-related toxicities, tolerability declines with increasing age. Thus, the ideal age cutoff for treatment with a pediatric-inspired asparaginase-containing regimen versus a regimen like hyper-CVAD is not settled. In a non-randomized study comparing Augmented BFM and hyper-CVAD in AYAs with newly diagnosed ALL, response rates were similar in both groups and long-term survival was identical, with a 5-year OS rate of 60% in both arms [104]. As expected, myelosuppression was more common with hyper-CVAD, whereas thrombotic events, pancreatitis, and hepatotoxicity were more common with Augmented BFM. Interestingly, these data are similar to that achieved with the recently reported CALGB 10403 regimen which was studied in 318 AYAs with newly diagnosed ALL (median age: 24 years [range, 17–39 years]) [105]. This optimized pediatric-inspired regimen resulted in a CR rate of 89% and a 5-year OS of approximately 60%. Similar long-term results have been attained outside the U.S. in the UKALL 2003 and NOPHO ALL2008 studies in the AYA population [99, 103]. Together these data suggest that either pediatric-inspired or adult regimens such as hyper-CVAD may be appropriate options for the frontline treatment of AYAs with ALL. In the absence of a definitive randomized study, the selection of therapy should therefore be based on the clinician's comfort level with the regimen and consideration of the toxicity profile for the particular patient.

Ph-like ALL

Ph-like ALL is a genetically heterogenous subtype of ALL that has a gene expression profile similar to Ph-positive ALL but lacks the classic *BCR-ABL1* translocation [106–108]. Ph-like ALL is observed in up to one-third of young adults with B-cell ALL, with an incidence that declines in older adults. It is particularly prevalent among patients of Hispanic ethnicity [109]. In adults, the majority of Ph-like ALL cases are associated with rearrangement of cytokine receptor-like factor 2 (*CRLF2*), approximately 50% of which have concomitant activating mutations of Janus kinases (*JAK1*, *JAK2*, or *JAK3*). In patients without *CRLF2* rearrangement, a variety of kinase-activating alterations have been described, including rearrangements in *ABL* class genes (e.g., *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB*), *EPOR*, or *JAK2*, as well as sequence mutations involving *FLT3*, *IL7R*, and *SH2B3* [110]. Ph-like ALL is associated with lower rates of MRD negativity and poor OS, particularly when driven by *CRLF2* rearrangement with a *JAK1/2* mutation [111]. The addition of TKIs targeting the specific driver translocation may be beneficial in

the subgroup of patients with potentially targetable fusions (e.g., dasatinib for *ABL* gene alterations) [112, 113]. Given the high incidence of JAK/STAT pathway activation in Ph-like ALL, there has been interested in ruxolitinib as an adjunct therapy. However, preclinical data suggest that lymphoblasts are not dependent on continued activation of JAK/STAT signaling for survival, and initial studies with chemotherapy plus ruxolitinib combinations have been disappointing [114, 115]. In the relapsed/refractory setting, blinatumomab therapy achieved similar survival outcomes for patients with Ph-like ALL and non-Ph-like ALL and therefore may abrogate the negative impact of this poor-risk phenotype in frontline chemotherapy combinations.

CD20-positive B-cell ALL

CD20 positivity (typically defined as CD20 expression in ≥20% of lymphoblasts) is observed in 30–50% of precursor B-cell ALL [116]. Over 10 years ago, it was shown that the addition of rituximab improved the duration of remission and OS rates in younger patients age <60 years with newly diagnosed CD20 + B-cell ALL [117]. These findings were later confirmed by the GRAALL-R 2005 randomized phase III trial comparing standard chemotherapy, with or without 16–18 doses of rituximab, in patients 18–59 years of age with newly diagnosed CD20+ Ph-negative ALL [118]. Patients randomized to receive rituximab had a superior 2-year EFS (65% versus 52%, respectively; $P = 0.038$) and 2-year OS rates (71% versus 64%, respectively; $P = 0.095$). There was no added toxicity observed in the rituximab arm. Although there is a lack of convincing data for the benefit of anti-CD20 antibody therapy in older adults with B-cell ALL, it is common practice at our center and others to incorporate an anti-CD20 antibody for these patients, as the potential for added toxicity with this approach is minimal.

Ofatumumab is another anti-CD20 antibody with higher complement-dependent cytotoxicity and a slower dissociation rate compared with rituximab [119]. The combination of hyper-CVAD plus ofatumumab was evaluated in 69 patients with newly diagnosed Ph-negative B-cell ALL with CD20 expression ≥1% [120]. The 4-year OS rate was 68% in the entire population and 74% among AYA patients. These results compare favorably with historical expectations with rituximab-based regimens, particularly in AYAs, and suggest a potential benefit to anti-CD20 therapy with ofatumumab even in patients with dim CD20 expression.

Management of MRD

Persistent or recurrent MRD has been shown to be a negative predictor for relapse and survival in ALL across many retrospectives and prospective studies [4, 121–126]. This observation was subsequently confirmed in a large meta-analysis of 39 studies in adults and children, including >13,000 individual patients [3]. In adults, the 10-year EFS rates for MRD-negative versus MRD-positive patients were 64% and 21%, respectively, highlighting the substantial impact of MRD status on clinical outcomes. Eradication of MRD has therefore become an important therapeutic goal in the treatment of ALL, and this principle has been incorporated into consensus treatment guidelines [127]. In particular, early eradication of MRD is imperative, as studies have consistently shown that outcomes are superior for patients who achieve early MRD-negativity, ideally after the first course of induction chemotherapy [4, 128]. Highly sensitive next-generation sequencing-based MRD assays may further improve our prognostication and may potentially identify patients at a very low risk of relapse [129].

In an effort to improve outcomes for patients with MRD-positive disease, blinatumomab was evaluated in a single-arm phase II study in patients with B-cell ALL and MRD levels ≥0.1% after chemotherapy [11]. Among the 116 patients treated, the MRD clearance rate was 80% after 2 cycles of blinatumomab, which translated to a 4-year OS rate of 45%. These outcomes compare very favorably to historical expectations of patients with MRD-positive disease and led to the approval of blinatumomab in this setting, making it the first approved MRD-directed therapy for any leukemia. The role of HSCT after achieving MRD-negativity with blinatumomab is presently not well-established, as a post-hoc analysis of this study suggested that OS was similar whether or not patients proceeded to HSCT [11]. This was due to increased treatment-related mortality in the HSCT group that offset the increased relapse rate in the non-transplanted group. Thus, decisions for HSCT after MRD-directed blinatumomab therapy should be individualized based on a patient's risk of relapse and of HSCT-related mortality. Ongoing prospective studies are also evaluating INO in the context of MRD-positive disease (NCT03610438 and NCT03441061). Unfortunately, established MRD-directed therapies for patients with T-cell ALL are presently lacking.

The evolving role of HSCT for ALL

With an increased understanding of the pathobiology of ALL and its genomic landscape, our risk assessment has improved, further refining our determination of who may benefit from HSCT in the first remission versus in whom HSCT may be safely deferred. Patients without adverse-risk cyto-molecular characteristics often have favorable outcomes without HSCT, whereas HSCT is typically recommended for younger, fit patients with adverse-risk features when treated with conventional chemotherapy. Genetic features associated with particularly poor clinical outcomes

and in whom HSCT is routinely advised include: *KMT2A*/t(4;11) rearrangement, low-hypodiploid/near-triploidy, complex karyotype (defined as ≥5 abnormalities), Ph-like ALL (especially *CRLF2*-rearranged with *JAK1/2* mutation), and ETP ALL [127]. The persistence of MRD (even in the absence of an adverse-risk baseline feature) has also historically been an indication for HSCT in first remission [130]. Although MRD-positive patients appear to benefit from HSCT, their outcomes remain suboptimal even when HSCT is performed [97, 124, 125, 127, 131–133]. As previously discussed, the role of HSCT for MRD-positive disease is less clear in the era of blinatumomab, as survival appears similar in patients who clear MRD with blinatumomab therapy, regardless of whether or not subsequent HSCT is performed [11]. The role of HSCT in patients with one or more baseline high-risk features who rapidly achieve MRD negativity is less clear. In children, disease risk is largely defined by the early response and MRD status, irrespective of most cytogenetic/genetic features [134]. Our own approach, which is consistent with consensus guidelines, is to consider both very high-risk baseline features (e.g., poor-risk cytogenetics, ETP ALL, Ph-like ALL with CRLF2 rearrangement, etc.) and early MRD assessment when evaluating a patient's appropriateness for HSCT in the first remission.

The role of HSCT in the management of Ph-positive ALL is also evolving. Initial studies in the pre-TKI era or with early-generation TKIs suggested a benefit to HSCT in first remission [20, 135]. In one retrospective study of patients with Ph-positive, ALL who received intensive chemotherapy plus a BCR-ABL1 TKI and did not undergo HSCT in first remission, achievement of CMR within 3 months was the only independent predictor of OS [17]. Importantly, patients who achieved CMR within 3 months had excellent outcomes, with a 4-year OS rate of 66%, suggesting that HSCT may be safely deferred in the first remission in patients who achieve CMR within 3 months. This approach is supported by consensus recommendations [127]. The need for routine HSCT may be further reduced with the use of potent later-generation TKIs such as ponatinib in the frontline setting. With the hyper-CVAD plus ponatinib regimen, a 5-year OS rate of 83% has been reported in non-transplanted patients [30]. With the introduction of blinatumomab into frontline regimens, the hope is that we will increase CMR rates and further reduce our reliance on HSCT in first remission for Ph-positive ALL.

Conclusions and future directions

With the availability of highly effective drugs for the treatment ALL, it is important to now consider how to best optimize our combination regimens in order to maximize efficacy and minimize potential toxicity. New regimens are now being explored in both the frontline and salvage settings that substantially reduce the dose and/or duration of chemotherapy, or even eliminate it entirely, as in the case of blinatumomab plus a TKI for Ph-positive ALL. In older adults (e.g., ≥60 years of age), the frontline incorporation of INO and/or blinatumomab is allowing for safe and effective therapy using lower-intensity chemotherapy backbones in this more frail population. While intensive chemotherapy is still widely considered an integral part of the management of younger patients with Ph-negative ALL, it is possible that we may also shift towards less intensive approaches with INO- and blinatumomab-based combination therapy in the near future. As we continue to see promising data emerge with these novel combination regimens, the field is also shifting towards relying less on HSCT in first remission for most patients. While there are particular ALL subtypes that confer very high risks of relapse with conventional therapies and for which HSCT is routinely recommended (e.g., *KMT2A* rearranged, low hypodiploidy with *TP53* mutation, Ph-like ALL with CRLF2 rearrangement and *JAK1/2* mutation, etc.), as we gain clinical experience with INO and blinatumomab combinations in the frontline setting, this calculus could shift. The introduction of new, effective therapies in specific subsets, such as menin inhibitors for *KMT2A*-rearranged leukemias, might also influence our risk assessment and selection of patients for HSCT.

An important mechanism by which we should evaluate potentially promising new agents and regimens is their ability to achieve very deep levels of MRD negativity. Several studies have suggested that the achievement of MRD negativity using an ultrasensitive next-generation sequencing assay is associated with an exceptionally low risk of relapse [129, 136–138]. Preliminary data suggests that the concordance between these next-generation sequencing MRD assays in the bone marrow and peripheral blood is very high, suggesting that they could allow for accurate and non-invasive disease monitoring [139]. Achievement of MRD negativity by these highly sensitive assays could also allow for early assessment of clinical efficacy of new drugs and might also identify patients who would benefit from treatment de-escalation, including deferral of HSCT in the first remission. Even in first salvage, a substantial proportion of patients treated with novel monoclonal antibody-based combination regimens (e.g., mini-hyper-CVD plus INO and blinatumomab) have long-term survival without subsequent HSCT [63], and therefore a robust assessment of MRD might identify patients with relapsed/refractory ALL who might be cured without HSCT. A similar approach could be used to select patients treated with blinatumomab for MRD-positive disease who are likely to benefit from consolidative HSCT.

Compared with the previous decade in which ALL treatment was almost entirely limited to varying combinations of cytotoxic therapies, we now have several highly effective tools at our disposal for the treatment of ALL. Prospective studies are ongoing to identify the optimal combinations and sequences of these agents; in parallel, clinical trials are evaluating promising novel monoclonal antibody constructs, autologous and allogeneic CAR T-cells, and small molecule inhibitors. As the field evolves, the goal of ALL therapy increasingly is to combine our most effective agents safely into the frontline setting, and with the development of new targeted agents and optimization of our existing combination regimens, hopefully, our objective of achieving cure across ALL subtypes and in patients of all ages will soon become a reality.

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Compliance with ethical standards

Conflict of interest NJS has served as a consultant for Takeda Oncology and AstraZeneca, reports receiving research grants from Takeda Oncology and Astellas Pharma Inc., and has received honoraria from Amgen. EJ has research grants with Amgen, AbbVie, Spectrum, BMS, Takeda Oncology, Pfizer, and Adaptive.

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