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Optimal approach to the treatment of young adults with acute lymphoblastic leukemia in 2020 ☆

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ABSTRACT

Akin to the introduction of tyrosine kinase inhibitors to Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL), pediatric-based asparaginase-heavy approaches have revolutionized the treatment of young adults with the Philadelphia chromosome-negative subset the past decades. Once again, we are approaching a new era. An era of precision medicine with immunotherapy and other molecularly targeted treatments that offers unique opportunities to customize treatment intensity with or without hematopoietic stem cell transplantation, reduce the burden of toxicities, and combat persistent residual disease. Recently approved agents for refractory/relapsed B-cell precursor ALL include the chimeric antigen receptor-modified T-cells, the anti-CD22 monoclonal antibody-drug conjugate, inotuzumab ozogamicin, and the bispecific anti-CD19 T-cell engager, blinatumomab. These agents are expected to move widely into the frontline setting along with the proteasome inhibitors, bortezomib and carfilzomib, as well as tyrosine kinase inhibitors for Philadelphia-like rearrangements that are especially frequent among young adults. To this add the BH3 mimetics, venetoclax and navitoclax, which are being widely explored in refractory/relapsed as well as frontline settings for B- and T-cell ALL. The promising anti-CD38 monoclonal antibody, daratumumab, is entering the scene of refractory/relapsed T-ALL, whereas the old purine analogue, nelarabine, is being evaluated in a new upfront setting. This review focuses on 2 main questions: How do we optimize frontline as well as salvage ALL treatment of young adults in the 2020s? Not least, how do we address the current burden of serious toxicities unique to young adults?

Introduction

Young adults belong in the adolescent and young adult (AYA) group according to international consensus [1]. When treated according to either pediatric-inspired or fully adopted pediatric regimens as opposed to traditional adult protocols, AYAs with Philadelphia chromosome (Ph)-negative B- and T-cell ALL have far superior outcomes [2-9] (Appendix, Tables A and B; Figure A). Generally, pediatric regimens contain more nonmyelosuppressive agents such as vincristine, asparaginase, and glucocorticoids; earlier and more intensive intrathecal prophylaxis; and longer maintenance. On the other hand, traditional adult treatment protocols are characterized by use of higher doses of cytarabine, cyclophosphamide, and daunorubicin as well as more frequent use of allogeneic hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1). Results from the prospective multicenter pediatric Nordic society Of Pediatric Hematology and Oncology (NOPHO) ALL2008 trial have recently been published, reporting an impressive 5-year event-free survival (EFS) of 74% and overall survival (OS) of 78% in adults up to the age of 45 years [10]. Accordingly, the US Cancer and Leukemia Group B (CALGB) pediatric-based 10403 trial for ALL patients aged 17 to 39 years has demonstrated 3-year EFS of 59% and OS of 73% [11]. Not to mention the US Dana-Farber Cancer Institute (DFCI) pediatric-inspired 06-254 trial for adults up to the age of 50 years with 3-year disease-free survival (DFS) of 73% and OS of 75% [12]. Other

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larger groups using a pediatric-inspired for young adults include the French Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) and the German Multicenter study group for adult ALL (GMALL). The GRAALL-2005 trial found a 5-year EFS of 52% and OS of 59% in adults up to the age of 59 years [13], and the GMALL 07/03 trial reported a 5-year OS of 65% in patients aged 15 to 35 years [14]. Although some young adults with Ph-positive ALL have been included in the pediatric-based trials during the past decades, a similar standard of care for the Ph-positive subset in young adults has not been standardized—apart from the addition of tyrosine kinase inhibitors (TKIs).

Despite the use of pediatric treatment strategies, the early response and the survival rates of young adults are still inferior to that of children with ALL [10]. Furthermore, they are burdened by a higher incidence of thromboembolism, pancreatitis, and osteonecrosis compared with children—even in risk group stratified analysis of patients treated according to the same protocol [10,15-17]. The explanation for this is multifactorial. First, adults rarely have the classical childhood good prognostic cytogenetic risk factors (high-hyperdiploidy >50 chromosomes and t(12;21)-translocation encoding *ETV6-RUNX1*) but a higher incidence of high-risk features (T-cell immunophenotype, *KMT2A* rearrangements, iAMP21, t(9;22)/Ph-translocation encoding the *BCR-ABL1* fusion transcript, and Ph-like aberrations) [10,18-21]. Ph-like ALL is especially common in young adults. Although somewhat different definitions of the Ph-like signature itself across European and North American study groups exist, it is a distinct subgroup of B-cell precursor (BCP)-ALL with a kinase-activated gene expression profile similar to Ph-positive ALL driven by various gene fusions, truncations, and insertions/deletions in kinase/cytokine signaling—rendering them targetable with TKIs [22]. Still, this subset is associated with low CR rate, minimal residual disease (MRD) persistence, and poor survival [23,24]. The incidence of Ph-like ALL reaches 20% among adolescents and almost 30% in young adults, whereas it is rare in elderly patients [19,23]. Second, age-dependent changes in body composition and drug distribution, comorbidities and co-medication, and hormonal changes may also influence treatment efficacy and toxicity in young adults [25]. Third, psychosocial issues and competing motives may jeopardize adherence to oral steroids and methotrexate/thiopurine-based maintenance therapy and, thus, increase relapse rates [26,27]. Finally, pediatric protocols have for decades fine-tuned all treatment phases and consequently optimized the use of traditional antileukemic drugs, whereas the lower incidence of ALL in the AYA group and the lower inclusion rate in research programs have slowed a similar learning trajectory.

Novel targeted and personalized approaches

Refractory/relapsed setting

BCP-ALL

The bispecific anti-CD19/-CD3 T-cell engager antibody construct (BiTE antibody), blinatumomab, has been successful in several clinical trials of refractory/relapsed (R/R) ALL by engaging CD3-positive cytotoxic T-cells to kill CD19-positive B-cells. Of note, nearly all BCP-ALL blasts are CD19-positive [28]. In 2 blinatumomab single-arm phase II trials enrolling adults with R/R Ph-negative/-positive ALL, 36% to 43% of patients (median age 39-55 years) achieved CR/CR with partial hematologic recovery, of whom 40% to 44% proceeded to HSCT [29,30]. The median DFS and OS ranged 5.9 to 6.7 months and 6.1 to 7.1 months, respectively [29,30]. In an update from one of these trials enrolling adults with Ph-positive ALL (the ALCANTARA trial), outcomes with single-arm blinatumomab were compared with historical controls receiving standard of care chemotherapy in a propensity score analysis [31]. The response rate and hazard ratio for OS were 36%/0.81 (95% confidence interval [CI] 0.57-1.14) with blinatumomab and 25%/0.77 (95% CI 0.61-0.96) with standard of care, respectively. In the phase III TOWER trial randomizing heavily pretreated adults with R/R Ph-negative ALL to either blinatumomab or standard of care chemotherapy, the overall direction of the results favored blinatumomab with respect to overall response (44 vs 25%, $P < .001$); CR (34% vs 16%, $P < .001$); MRD negativity among responders (76% vs 48%); 6-month EFS (31% vs 12%); and median OS (7.7 months vs 4.0 months) [32]. Twenty-four percent underwent allogeneic HSCT in each arm [32]. In a recent update of the responders (in remission the following 5 months) evaluating administration of additional cycles of blinatumomab, OS and DFS seemed longer among those who received blinatumomab maintenance (median OS/DFS not reached/14.5 months) compared with those who did not (median OS/DFS 15.5/9.8 months) [33]. Severe neurotoxicity and cytokine release syndrome (CRS) were seen with blinatumomab induction in 9% and 5%, respectively [32]. Similar findings have been shown for childhood ALL [34]. Consequently, blinatumomab has been approved by the US Food and Drug Administration (FDA) for R/R pediatric/adult BCP-ALL. An overview of the supportive trials is provided in Table 1. To overcome resistance to blinatumomab and/or enhance efficacy, ongoing trials in the R/R setting combine blinatumomab with PD-1/CTLA-4 checkpoint inhibitors that turn on the antileukemic T-cell function or Bruton tyrosine kinase (BTK)-inhibitors that target B-cell receptor signaling (Table 2) [35].

Another agent with remarkable clinical results in the R/R setting is inotuzumab ozogamicin, which has been FDA approved as monotherapy for R/R Ph-negative/-positive adult BCP-ALL (Table 1). This monoclonal anti-CD22 antibody is conjugated to the cytotoxic antibiotic calicheamicin, which induces apoptosis in CD22-positive BCP-ALL by DNA double-strand cleavage. Of note, >90% of BCP-ALL blasts express CD22 [28]. Inotuzumab proved markedly superior to standard of care chemotherapy in the phase III INO-VATE randomized trial of adult R/R Ph-negative/-positive ALL with longer 2-year OS (23 vs 10%, $P = .01$) [36,37]. The CR rate was higher with inotuzumab (81% vs 29%, $P < .0001$), and among responders a greater proportion achieved MRD-negativity (78 vs 28%, $P < .0001$) and proceeded to HSCT (41 vs 11%, $P < .0001$) [36,37]. Patients achieving MRD-negativity had significantly superior survival when compared with MRD-positive patients at the end of inotuzumab therapy [38]. The risk of sinusoidal obstruction syndrome (SOS; 14% with inotuzumab vs 2% with chemotherapy [37]) has been a major concern, but is primarily restricted to post-HSCT patients treated with dual alkylator HSCT conditioning [36]. Interestingly, the SOS incidence was markedly reduced from 12% to 5% with the addition of blinatumomab to a combination of inotuzumab and mini-hyper-CVD (mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone), allowing a fractionated lower dose of inotuzumab in adults with R/R B-cell ALL (B-ALL) [39,40]. An overall response rate of 92% including 85% achieving MRD negativity along with 3-year EFS and OS of 31% and 42%, respectively, were demonstrated [40] Fifty-four percent received allogeneic HSCT in CR2 [40]. Several ongoing trials explore inotuzumab dose modifications and combinations with chemotherapy (Table 2). Of note is another anti-CD19 antibody-drug conjugate ADCT-402 (loncastuximab tesirine) that demonstrated antileukemic activity and was well tolerated without any evidence of SOS in a recent phase I study of R/R adult B-ALL [41].

The more recent revolutionizing avenue for BCP-ALL patients is the chimeric antigen receptor (CAR) T-cells, where autologous T lymphocytes are engineered to express CARs directed toward the B-cell specific antigens CD19 and CD22. The CD19-specific CAR T-cells, tisagenlecleucel, have been FDA approved for children and AYAs up to the age of 25 years in the R/R setting. The approval is based on results from the phase II ELIANA trial

Table 1
FDA-approved agents for ALL.

Agent	FDA approval	Trial basis	CT-identifier	ALL subtype	Age range, y	N	Treatment	Young adult-specific data	Selected adverse events grade ≥3
Nelarabine	Oct, 2005: R/R T-ALL	Phase II multicenter COG trial (single-arm) [174]	–	R/R T-ALL/LBL	0.6-21.7	153*	Nelarabine single-arm	CR (T-ALL): 35% (28/79).	Neurotoxicity (T-ALL+LBL): 18% (27/151).
		Phase II multicenter CALGB 19801 trial (single-arm) [61]	–	R/R T-ALL/LBL	≥16	39†	Nelarabine single-arm	CR/CRi (T-ALL): 31% (8/26).	Neurotoxicity (T-ALL+LBL): 18% (7/39).
Blinatumomab	Dec, 2014: BCP-ALL	Phase II multicenter trial (single-arm) [29]	NCT01466179	R/R Ph-neg CD19+ BCP-ALL	≥18	189	Blinatumomab single-arm	CR/CRh: 43% (39/90, <35y) and 46% (21/46, 35 to <55y).	Neurotoxicity: 13% (24/189). CRS: 2% (3/189).
	Sep, 2016: Pediatric R/R Ph-neg BCP-ALL	Phase I/II multicenter '205 trial (single-arm) [34]	NCT01471782	R/R Ph-neg/-pos CD19+ BCP-ALL	≤17	70‡	Blinatumomab single-arm	CR within the first 2 cycles: 39% (27/70); 33% (13/40, 7-17y). MRD response: 52% (14/27).	Neurotoxicity: 4% (3/70). CRS: 6% (4/70).
	July, 2017: Full approval for R/R Ph-neg/-pos pediatric/adult BCP-ALL	Phase III multicenter TOWER RCT [32]	NCT02013167	R/R Ph-neg CD19+BCP-ALL	18-80	405§	Blinatumomab vs standard of care chemotherapy	Remission rate (<35y): 43% (blinatumomab arm) vs 25% (chemotherapy arm); OR 2.27 (95% CI 1.15-4.50). Median survival (<35y): 9.9 (blinatumomab arm) vs 4.5 months (chemotherapy arm) (not significant).	Neurotoxicity: 9% (25/267; (blinatumomab vs 8% (9/109; chemotherapy arm). arm) CRS: 5% (13/267; blinatumomab arm) 0% (0/109; chemotherapy arm).
		Phase II multicenter ALCANTARA trial (single-arm) [30]	NCT02000427	R/R Ph-pos CD19+BCP-ALL	23-78	45‖	Blinatumomab single-arm	CR/CRh: 0% (0/5, <35y) and 47% (8/17, 35 to <55y).	Neurotoxicity: 7%. CRS: 0% (7% grade 1-2).
	March, 2018: Expanded approval for MRD+ BCP-ALL	Phase II multicenter BLAST trial (single-arm) [175]	NCT01207388	Ph-neg/-pos CD19+BCP-ALL in CR1/2 with MRD ≥0.1%	18-76	116¶	Blinatumomab single-arm	Complete MRD response (negativity) after cycle 1: 91% (29/32, <35y) and 71% (25/35, 35 to <55y).	Neurotoxicity: 11%. CRS: 2%.
Inotuzumab ozogamicin	Aug, 2017: R/R Ph-neg/-pos adult BCP-ALL	Phase III multicenter INO-VATE RCT [36,37]	NCT01564784	R/R Ph-neg/-pos CD22+ BCP-ALL	18-79	326#	Inotuzumab vs standard of care chemotherapy	CR/CRi rate (<55y) 75% (104/207; inotuzumab arm) vs 28% (103/207; (chemotherapy arm) ($P < .0001$). Median OS: 8.6 months (inotuzumab arm) vs 8.0 months (chemotherapy arm). 2-year OS (all included patients) 22.8% (inotuzumab arm) vs 10% (chemotherapy arm).	SOS: 14% (23/164) (inotuzumab arm) vs 2% (3/143) (chemotherapy arm).
Tisagenlecleucel	Aug, 2017: R/R BCP-ALL patients ≤25y	Phase II multicenter ELIANA trial single-arm [42,43]	NCT02435849	R/R CD19+ BCP-ALL	3-23	75	Tisagenlecleucel CTL019 (single-arm)	CR: 60% (45/75). CRi: 21% (16/75). All patients with MRD-negative CR.	CRS: 47%. Neurotoxicity: 13%.

AYA, adolescents and young adults; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CALGB, Cancer and Leukemia Group B; COG, Children's Oncology Group; CRS, cytokine release syndrome; CT-identifier, ClinicalTrials.gov identifier; CR/CRh/CRi; complete remission/complete remission with partial hematologic recovery/complete remission with incomplete hematologic recovery; CRS, cytokine release syndrome; FDA, US Food and Drug Administration; HR, hazard ratio; LBL, Lymphoblastic lymphoma; MRD, minimal residual disease; N, number of patients; OR, odds ratio; OS, overall survival; Ph, Philadelphia chromosome; RCT, randomized controlled trial; R/R, refractory or relapsed, SAEs, serious adverse events; T-ALL, T-cell acute lymphoblastic leukemia; SOS, sinusoidal obstruction syndrome; y, years.

* N = 118 T-ALL. Intent-to-treat cohort N = 153, of whom N = 136 were used assessable for efficacy analyses; N = 151 who received at least 1 dose of nelarabine were included in the safety analyses.

† N = 18 aged 16 to 30 years; 26 T-ALL.

‡ 49 (phase I; dose-escalation)/44 (phase II); 70 received the recommended blinatumomab dosage of 5μg/m^2/d (first 7 days) followed by 15μg/m^2/d and were included in the efficacy and safety analyses.

§ N = 183 aged <35 years. N = 405 patients randomized; 376/405 received open-label trial treatment. Efficacy analyses based on the intent-to-treat cohort (N = 405), and safety analyses based on the as-treated cohort (N = 376).

‖ N = 22 aged <55 years.

¶ N = 36 aged 18.0 to 34.9 years and N = 41 aged 35.0 to 54.9 years. Intent-to-treat cohort N = 116; N = 103 after exclusion of patients with no central MRD assay result, assay sensitivity not reached, without hematologic CR or MRD ≤0.1% at study entry. Efficacy analyses based on the as-treated cohort (N = 103), and safety analyses based on the intent-to-treat cohort (N = 116).

N = 207 aged <55 years. Intent-to-treat cohort N = 326 (at second data cutoff); efficacy analyses are based on this cohort. N = 307 (at second data cutoff) received ≥1 dose of study treatment and were included in the safety population.

Table 2
Ongoing R/R approaches.

Phase	CT-identifier	Accrual date	Est. completion date	ALL subtype	Age range, y	Regimen
I	NCT02879695	May, 2017	Nov, 2021	R/R Ph-neg/-pos CD19+ BCP-ALL	≥16	single-arm blinatumomab + nivolumab +/− ipilimumab*
II	NCT02997761	Jun, 2017	Jan, 2021	R/R Ph-neg/-pos CD19+ B-ALL	≥18	single-arm blinatumomab + ibrutinib†
I/II	NCT03512405	Aug, 2019	Apr, 2022	R/R Ph-neg/-pos CD19+ B-ALL	≥18	single-arm blinatumomab + pembrolizumab*
I/II	NCT03160079	Apr, 2017	Aug, 2023	R/R Ph-neg/-pos CD19+ B-ALL	≥18	single-arm blinatumomab + pembrolizumab*
II	NCT03263572	Nov, 2017	Nov, 2023	R/R Ph-pos CD19+ B-ALL	≥18	single-arm blinatumomab + ponatinib to methotrexate/cytarabine backbone
II	NCT03518112	Apr, 2018	Dec, 2035	R/R Ph-neg CD19+ B-ALL	≥18	single-arm blinatumomab + mini-hyperCVD
II	NCT03739814	Nov, 2018	Feb, 2021	R/R Ph-neg CD22+ B-ALL	≥18	single-arm inotuzumab followed by blinatumomab
Ib/II	NCT03851081	Mar, 2020	Dec, 2022	R/R Ph-neg/-pos CD22+ B-ALL	≥18	single-arm inotuzumab + liposomal vincristine
I	NCT01925131	Apr, 2014	Jan, 2023	R/R CD22+ B-ALL	≥18	single-arm inotuzumab + CVP
II	NCT03094611	Nov, 2017	Nov, 2023	R/R CD22+ B-ALL	≥12	single-arm low dose inotuzumab
IV (RCT)	NCT03677596	Jul, 2019	Aug, 2025	R/R CD22+ B-ALL, HSCT eligible	18-75	inotuzumab approved dose vs lower dose
I	NCT03962465	Nov, 2019	Nov, 2025	R/R CD22+ BCP-ALL	18-55	single-arm inotuzumab + aBFM re-induction +/− pegaspargase
I	NCT03991884	Sep, 2019	Feb, 2026	R/R Ph-neg/-pos CD22+ B-ALL	≥18	single-arm dose-escalated inotuzumab + DA-EPOCH chemotherapy
I	NCT02746952	Aug, 2016	Oct, 2020	R/R CD19+ B-ALL	16-69	single-arm allogeneic CD19 CAR-T TCR/CD52-deficient RQR8+‡
I/II	NCT03614858	Sep, 2017	Jan, 2021	R/R CD19/22+ B-ALL	6-65	single-arm CD19/22 CAR-T
I	NCT04004637	Jun, 2019	Jun, 2021	R/R CD7+ T-ALL	7-70	single-arm gene-edited CD7-specific CAR-T
I	NCT02650414	Jan, 2016	Dec, 2022	R/R CD22+ B-ALL	<25	single-arm autologous CD22 CAR-T
I	NCT04173988	Nov, 2019	Jul, 2022	R/R Ph-neg/-pos CD19+ BCP-ALL	1-18	single-arm allogeneic CD19 CAR-T
I	NCT04204161	Oct, 2019	Oct, 2024	R/R CD19/22+ B-ALL	≤18	single-arm autologous CD19/22 CAR-T
I	NCT01853631	Feb, 2014	Feb, 2033	R/R CD19+ B-ALL	≤75	single-arm autologous/allogeneic CD19 CAR-T CD28+ CD137+/− §
I/II	NCT02028455	Feb, 2014	Sep, 2035	R/R CD19+ BCP-ALL	<27	single-arm autologous/allogeneic CD19 CAR-T + EGFRt‖
I	NCT03081910	Nov, 2017	Jun, 2036	R/R CD5+ T-ALL	≤75	single-arm autologous gene-edited CD5-specific CAR-T CD28+
I	NCT03690011	Mar, 2021	May, 2038	R/R CD7+ T-ALL	≤75	single-arm autologous gene-edited CD7-specific CAR-T CD28+
II	NCT01700946	Apr, 2013	Apr, 2021	R/R CD20+ BCP-ALL	≤21	rituximab + standard of care chemotherapy + infusion of haploidentical NK cells
II	NCT03384654	May, 2018	Aug, 2021	R/R BCP-/T-ALL	≤30	daratumomab + chemotherapy
III (RCT)	NCT01802814	May, 2014	Nov, 2023	R/R B-/T-ALL	<18	ALL-REZ BFM 2002/ALL-R3 chemotherapy backbone +/− epratuzumab
II	NCT03136146	Aug, 2017	Aug, 2026	R/R Ph-neg/-pos CD20+ BCP-ALL	>1	rituximab/ofatumumab + clofarabine-based chemotherapy
Ib	NCT02303821	Feb, 2015	May, 2020	R/R B-/T-ALL	1-21	single-arm carfilzomib + induction chemotherapy
II (RCT)	NCT03590171	Sep, 2017	Aug, 2023	Relapsed B-/T-ALL	≤17	BFM ALL-R3 chemotherapy backbone +/− bortezomib
I	NCT03181126	Nov, 2017	Oct, 2020	R/R Ph-neg/-pos/-like B-/T-ALL	≥4	single-arm venetoclax + navitoclax + chemotherapy
I/II	NCT03576547	Jun, 2018	Jan, 2020	R/R Ph-pos B-ALL	≥18	venetoclax + ponatinib + dexamethasone
Ib/II	NCT03504644	Apr, 2018	Apr, 2021	R/R B-/T-ALL	≥18	venetoclax + liposomal vincristine
I	NCT03236857	Nov, 2017	Apr, 2022	R/R ALL	≤25	venetoclax +/− chemotherapy
Ib	NCT03319901	Oct, 2017	Apr, 2023	R/R B-/T-ALL	≥18	single-arm venetoclax + chemotherapy
I/II	NCT03808610	Apr, 2019	Dec, 2024	R/R B-/T-ALL	≥18	venetoclax + low dose chemotherapy
I/II (RCT)	NCT04029688	Jan, 2020	May, 2024	R/R BCP-ALL	≤30	idasanutlin + venetoclax/chemotherapy¶
I	NCT03218683	Aug, 2017	Jan, 2022	R/R ALL	18-85	single-arm monotherapy AZD-5991#
I/II	NCT03705507	May, 2018	May, 2022	R/R Ras pathway-mutated BCP-/T-ALL	<18/≥18	selumetinib + dexamethasone**
I	NCT03515200	Apr, 2018	Sep, 2022	R/R Ph-neg/-pos/-like BCP-ALL	<22	palbociclib + chemotherapy††
II	NCT02420717	Jul, 2015	Jul, 2024	R/R Ph-like BCP-ALL	≥10	ruxolitinib/dasatinib + hyper-CVAD

aBFM, augmented Berlin-Frankfurt-Münster; B-ALL, B-cell acute lymphoblastic leukemia; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CAR-T; chimeric antigen receptor T-cells; CT-identifier, ClinicalTrials.gov identifier; CVP, cyclophosphamide + vincristine + prednisone; DA-EPOCH, dose-adjusted etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin; Est., estimated; hyperCV(A)D, hyperfractionated cyclophosphamide + vincristine + (adriamycin) + dexamethasone; MPAL, mixed phenotype acute leukemia; Ph, Philadelphia chromosome; RCT, randomized-controlled trial; R/R, refractory or relapsed; SWOG, SouthWest Oncology Group; T-ALL, T-cell acute lymphoblastic leukemia; y, years. Clinical trials arranged according to the main agent of interest and in accordance with estimated completion date in increasing order.

* Check-point inhibitors: pembrolizumab/nivolumab (monoclonal anti- PD-1 antibodies), ipilimumab (monoclonal anti- CTLA-4 antibody).

† Ibrutinib, a BTK-inhibitor.

‡ Allogeneic 'off-the-shelf' gene-edited CAR-T with a RQR8 transgene (potentially antineoplastic) resistant to the anti-CD52+ monoclonal antibody alemtuzumab used for lymphodepletion.

§ Adding proteins that stimulate T-cells; second-/third-generation CAR-T.

‖ T-cells transduced to express CD19 CAR and truncated EGFR (EGFRt) that has no signaling capacity; second-generation CAR-T.

¶ Idasanutlin, a small molecule MDM2 inhibitor.

AZD-5991, a mcl-1 inhibitor.

** Selumetinib, a MEK-inhibitor.

†† Palbociclib, a CDK4/-6 inhibitor.

of single-arm tisagenlecleucel including 61% with prior allogeneic HSCT [42,43] (Table 1). Eighty-one percent of patients achieved CR/CR with incomplete hematologic recovery, of whom all obtained MRD eradication [43]. The 1.5-year EFS and OS were 66% and 70%, respectively; with the majority of leukemic relapses being CD19-negative [44]. Similar striking responses have also been reported both in heavily pretreated children and adults (some blinatumomab-refractory and post-HSCT) with CR rates up to 90% and MRD eradication in 60% to 80% of the responders [45-47]. However, CAR-T therapy has been challenged by inability to harvest enough lymphocytes from heavily treated patients, manufacturing waiting time, loss of persistence of CAR-T-cells, CD19 antigen escape/relapse, and severe CRS (in up to 48% [44]) and acute neurotoxicity (in up to 13% [44]). Clinical trials using different viral genetic transfer methods, CAR platform co-stimulatory domains, tandem/bispecific, and 'off-the-shelf' donor-derived CAR-T-cells are ongoing (Table 2). Recent findings from a phase I/II trial of autologous bispecific CD19/CD22 CAR-T-cells demonstrated a 100% MRD-negative CR rate in six R/R B-ALL patients aged 17 to 44 years [48]. No neurotoxicity was observed. One CD19-negative relapse with diminished CD22 site density was detected five months after treatment [48].

Naked monoclonal antibodies have also found their way into several drug combination trials in the R/R setting. The monoclonal anti-CD20 antibodies, rituximab and ofatumumab (~40% of BCP-ALL blasts express CD20 [28]), as well as the monoclonal anti-CD22 antibody, epratuzumab, are being tested (Table 2). Of note, the SWOG S0910 study of epratuzumab combined with clofarabine/cytarabine in adults with R/R BCP-ALL demonstrated a promising response rate of 52% compared with historical data of 17% (clofarabine/cytarabine) [49]. Only responses of very short duration have been reported with the monoclonal anti-CD52 antibody, alemtuzumab [50].

Mainly pediatric trials are exploring the proteasome inhibitors, carfilzomib and bortezomib, added to a pediatric chemotherapy backbone (Table 2). Bortezomib in combination with vincristine, dexamethasone, asparaginase, and doxorubicin has provided encouraging results with a CR rate of 80% in a phase II trial of 20 relapsed BCP-ALL patients aged 1 to 22 years [51]. However, no response was seen in 2 included T-cell ALL (T-ALL) patients.

As preliminary BH3 profiling has confirmed dependence of patient-derived ALL cells on bcl-xl and/or bcl-2 [52–54], addition of BH3 mimetics seems promising, that is, the bcl-2 inhibitor venetoclax and the bcl-2/bcl-xl/bcl-w inhibitor navitoclax. Preliminary results from an ongoing phase I study combining venetoclax, navitoclax, and chemotherapy in 36 heavily pretreated children and adults with R/R ALL (including prior HSCT and CAR-T treatment) have demonstrated a 50% response rate. To this adds MRD eradication in 56% of the responders [54]. Accordingly, several prospective trials are evaluating combined therapy with bcl-2 inhibitors in adult R/R ALL (Table 2).

Philadelphia chromosome-like B-ALL

Young adults with Ph-like ALL have a significantly lower MRD eradication rate compared with the non-Ph-like comparator. Furthermore, outcomes remain poor even after MRD eradication [55]. Ph-like B-ALL has been characterized by a wide range of genomic alterations listing >70 kinase mutations with various fusion partners, the commonest being *ABL*-class and *CRLF2/JAK* pathway-associated translocations [20-23,56,57]. Trials adding JAK inhibitors to a chemotherapy backbone (eg, the JAK1/2 inhibitor ruxolitinib) are ongoing, as *CRLF2* rearrangements are involved in activation of JAK-STAT signaling (Table 2). Worryingly, neither continued expression of mutant JAK2 nor JAK2 enzymatic activity was required for maintenance of leukemia survival in B-ALL mouse models [58]. For patients with *ABL*-class fusions, TKIs have been successfully added but so far documented only by case reports of refractory *EBF1-PDGFRB* (*ABL*-class rearrangements) BCP-ALL [59,60]. To this add several ongoing trials involving the addition of second and third-generation TKIs (primarily dasatinib and ponatinib) (Table 2).

T-ALL

More than a decade ago, the CALGB 19801 study of single-arm nelarabine, a purine analogue, for R/R T-ALL/-lymphoblastic lymphoma demonstrated a CR rate of 31%, median DFS of 20 weeks, and 1-year OS 28% [61]. Although this trial led to the FDA approval of nelarabine for adult R/R T-ALL (Table 1), novel and effective drugs for T-ALL have been somewhat unexplored since then.

Ongoing trials are combining bcl-2 inhibitors with a chemotherapy backbone (Table 2), as 60% of R/R adult T-ALL patients achieved bone marrow blasts <5% in a small study evaluating venetoclax combination therapy [62]. Interestingly, the early T-cell progenitor ALL subset that is associated with high risk of relapse was conversely bcl-2 dependent in preclinical studies [63]. Additionally, the mcl-1 inhibitor S63845 has shown synergy with venetoclax in zebrafish models of T-ALL [64] but awaits to be explored in a clinical trial setting. Another promising agent for T-ALL blasts with high CD38 surface expression is daratumumab, an anti-CD38 monoclonal antibody [65] (Table 2). To this add reports of significantly higher levels of AKR1C3 expression in T-ALL xenografts [66], for which the selective prodrug OBI-3424 that is converted by AKR1C3 to a potent DNA-alkylating agent is being studied [67]. Promising in vivo efficacy against T-ALL patient-derived xenograft models for both daratumumab and OBI-3424 have been presented [65,67], and the results of clinical trials are awaited. Moreover, given presence of activating *Notch1* mutations in > 50% of T-ALL, gamma secretase inhibitors (GSIs) that block activation of Notch receptors have been explored [68,69]. A phase I trial enrolling adults with R/R T-ALL has suggested anti-leukemic activity of the GSI BMS-906024 but at the expense of gastrointestinal toxicity [70]. Additionally, targeted pharmacological inhibition of the Notch-mediated E3 ubiquitin ligase F-box protein SKP2 critical for T-ALL leukemogenesis antagonized disease in murine and xenograft T-ALL models and may represent a new therapeutic target [71]. Noteworthy as well are the histone methyltransferase disrupter of telomeric silencing 1-like (DOT1L) small-molecule inhibitors, which are particularly promising agents in KMT2A rearranged and T-ALL. The DOT1L enzyme indirectly contributes to leukemogenesis by upregulating the *HOXA5* gene—through H3K79 methylation [72]. A phase I trial for advanced acute leukemias has provided promising pharmacodynamic evidence of reduction in H3K79 methylation during dose escalation of the DOT1L inhibitor, pinometostat (EPZ-5676) [73]. Furthermore, preclinical studies of the mitogen-activated protein kinase (MEK) 1/2 inhibitor selumetinib have demonstrated significant sensitivity against Ras pathway-mutated ALL [74], which is currently being tested in a phase I/II clinical trial of R/R Ras pathway-mutated ALL (Table 2).

Last but not least, gene-edited 'off-the-shelf' donor CAR-T-cells against T-ALL are being tested in phase I trials, in which the antigen CD7 (present in ~95% of T-ALL) has been deleted using CRISPR/Cas9 editing with subsequent transduction of CD7 targeting CAR [75] (Table 2). Most recently, preliminary results from a phase I study of CD7 CAR-T-cells for heavily pretreated adult R/R T-ALL demonstrated CR in all patients (N = 5) including one relapse (median follow-up of 3 months). No evidence of graft-vs-host disease or CRS was found [55,76].

Frontline setting

The markedly superior outcomes for patients with early response including MRD negativity have inaugurated various up-

front prospective trials integrating novel agents to achieve early response and deepen remission [77].

BCP-ALL

Most recently, blinatumomab has undergone expanded FDA approval for the treatment of MRD-positive (≥.001) Ph-negative/-positive BCP-ALL (Table 1). The approval was based on results from the phase II BLAST trial of single-arm blinatumomab, in which 78% of adults (median age 45 years) achieved MRD eradication [78]. When compared with MRD nonresponders, patients with MRD eradication had longer DFS (23.6 vs 5.7 months, $P = .002$) and OS (38.9 vs 12.5 months, $P = .002$) [78]. An ongoing single-arm phase II trial exploring the addition of blinatumomab to a hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone) backbone in ALL patients aged 18 to 59 years recently demonstrated CR rate and MRD eradication in 100% and 96%, respectively [79]. Thirty percent proceeded to HSCT due to high-risk features. One-year DFS and OS were 76% and 89%, respectively [79]. In addition to blinatumomab, ongoing trials are adding both inotuzumab ozogamicin and CAR-T-cells to the upfront treatment of de novo B-ALL in combination with other antileukemic agents or as monotherapy (Table 3). In the ALLTogether1 study, intermediate risk Ph-negative ALL patients with positive MRD at the end of consolidation will be randomized to chemotherapy with or without inotuzumab prior to maintenance therapy (NCT03911128).

Addition of the naked CD20 monoclonal antibody, rituximab, into frontline treatment of young adults with Ph-negative CD20-positive B-ALL (>20% CD20 expression on blasts) improved 2-year EFS from 52% to 65% ($P = .038$) in the GRAALL-2005/R randomized study [80]. Enhanced efficacy of asparaginase therapy by rituximab mediated removal of B-cell depleting antiasparaginase antibodies has been one explanation for the observed reduction in relapse, as allergic reactions to asparaginase were less common in the rituximab group [80]. Noteworthy is that the ongoing UKALL14 phase III trial randomizes adults with B-ALL irrespective of their CD20 expression level (NCT01085617). Ofatumumab is a more potent second-generation CD20 monoclonal antibody [81]. Preliminary results from the recently completed frontline phase II trial with addition of ofatumumab to hyper-CVAD backbone for B-ALL showed response in 98% including MRD eradication in 63% at the time of CR and in 93% overall. The 2-year OS was 81% with no difference in CD20 expression level [82]. Another anti-CD20 monoclonal antibody, obinotuzumab, is being tested in frontline treatment combined with zanubrutinib, a BTK-inhibitor interfering with B-cell receptor signaling (Table 3). The proteasome inhibitors, bortezomib and carfilzomib, are being explored in the upfront setting as well (Table 3).

Philadelphia chromosome-like B-ALL

Addition of dasatinib and ponatinib to a chemotherapy backbone treating Ph-like ALL patients with *ABL*-class fusions is currently being evaluated (Table 3). The TKI imatinib is used in the frontline ALLTogether1 study for Ph-like B-ALL with *ABL*-class fusions (NCT03911128). For Ph-like ALL with *CRLF2* rearrangements and/or other JAK pathway mutations, JAK inhibitors (primarily ruxolitinib) combined with chemotherapy are being tested (Table 3). Novel approaches combining blinatumomab or the new histone deacetylase inhibitor, chidamide, with TKIs/JAK inhibitors and chemotherapy in clinical trials are also being investigated (Table 3). Preliminary results from the single-arm study of chidamide addition to a pediatric-inspired regimen with dasatinib in Ph-like ALL patients aged 14 to 55 years demonstrated CR rates of 77% (60% with MRD eradication) and an estimated 2-year EFS of 70% (NCT03564470) [83]. Ultimately, upfront Ph-like profiling is paramount for newly diagnosed ALL and can guide treatment in patients with very high white blood cell counts, high MRD at the end of induction, or induction failure [19]. In addition, ongoing trials are incorporating a personalized approach basing the choice of TKI (dasatinib, idelalisib, ponatinib, sorafenib, sunitinib, or ruxolitinib) on individual TKI activity profiling (Ph-like adult frontline: NCT02779283; Ph-positive adult R/R: NCT01620216).

Last, targeted pharmacological inhibition by BI2536/BI6727 (volasertib) of the Notch-mediated Polo-like kinase I (PLK1), with the highest expression in the Ph-like B-ALL, effectively induced cell death in B-ALL patient-derived xenograft models and awaits to be tested in clinical trials [84].

T-ALL

The Children's Oncology Group (COG) AALL0434 study of frontline augmented BFM chemotherapy treatment with or without addition of nelarabine in T-ALL patients aged 1 to 30 years reported 4-year DFS of 89% vs 83% ($P = .03$), respectively [85]. However, the benefit of nelarabine was lees convincing with longer follow-up [86]. Importantly, no increased incidence of neurotoxicity was reported in the nelarabine arm, as the agent has been associated with severe dose-limiting neurotoxicity in previous trials [87]. Upfront addition of nelarabine to chemotherapy regimens for T-ALL is currently being evaluated (Table 3).

Treatment intensity

Philadelphia chromosome-negative ALL

It remains unknown, if further intensification of pediatric(-inspired) regimens can improve the outcomes of young adults even further. On the other hand, intensification may introduce a higher risk of treatment-related death, second malignant neoplasm, unacceptable persistent toxicities, and excess costs [13]. Yet, under-treatment will increase relapse rates [88]. Trials testing risk-adapted chemotherapy regimens, including reduced intensity for low-risk AYA patients, are ongoing: COG includes ALL patients aged 1 to 30 years (NCT01190930) and the new ALLTogether Consortium across 14 European countries (NCT03911128) will include children aged 1 to 18 years in all countries and young adults in several countries. The risk-adapted modification of dose intensity will be guided by MRD measured during the first months of therapy, as this is the most important risk factor in both children and adults with ALL [89-93]. Novel advances in MRD detection including next generation sequencing (NGS)-based MRD assays have increased sensitivity and specificity, thus competing with the traditional polymerase chain reaction (PCR)- and flowcytometry-based methods for MRD detection [94-96]. Although it remains to be shown that the detection of very low MRD levels improves treatment stratification. Trials using NGS-MRD are currently tested in the R/R ALL setting (NCT02551718).

Philadelphia chromosome-positive ALL

The common goal of ALL therapy is to achieve and maintain early response as well as to deepen remission. Especially for the Ph-positive subset, early complete molecular response (CMR) has been associated with markedly improved survival [97]. To date, no separate trial for AYA Ph-positive ALL exists. Although the addition of TKIs to Ph-positive ALL therapy has become the standard of care, the optimal choice of treatment backbone remains unclear. The current use of backbone varies with the approach being either intensive (pediatric) or less intensive (adult).

Frontline addition of imatinib, a first-generation TKI, to a standard ALL regimen significantly doubled long-term OS from 20% to 40% in Ph-positive ALL patients (median age 42 years) [98]. Further improvement was seen in phase II trials combining second-generation TKIs (dasatinib/nilotinib) with chemotherapy demon-

Table 3
Ongoing frontline approaches.

Phase	CT-identifier	Accrual date	Est. completion date	ALL subtype	Age range, y	Regimen
II	NCT02877303	Nov, 2016	Nov, 2020	CD19+ BCP-ALL	≥14	single-arm blinatumomab + hyper-CVAD
III (RCT)	NCT02003222	Dec, 2013	Jun, 2021	Ph-neg CD19+ B-ALL	30-70	combination chemotherapy +/− blinatumomab
II	NCT02744768	May, 2017	Jun, 2021	Ph-pos CD19+ B-ALL	≥18	single-arm dasatinib + steroids (induction) followed by blinatumomab
II	NCT04329325	Mar, 2020	Mar, 2023	Ph-pos B-ALL	≥18	blinatumomab + TKI as consolidation and maintenance
II	NCT03367299	Jun, 2018	Sep, 2023	Ph-neg CD19+ BCP-ALL	18-65	single-arm blinatumomab + chemotherapy
II	NCT03147612	Feb, 2018	Feb, 2024	Ph-pos/-like CD19+ B-ALL	≥18	single-arm low intensity chemotherapy + ponatinib followed by ponatinib + blinatumomab
II	NCT03541083	Jun, 2018	Dec, 2026	Ph-neg/-pos CD19+ BCP-ALL	18-70	single-arm blinatumomab addition to prephase + consolidation chemotherapy
III (RCT)	NCT03914625	Jun, 2019	Jun, 2027	Standard risk CD19+ B-ALL	1-31	combination chemotherapy +/− blinatumomab
III	NCT03643276	Jul, 2018	Jul, 2028	Ph-neg CD19+ B-/T-ALL	≤17	blinatumomab + bortezomib + chemotherapy backbone[†]
II	NCT03709719	Oct, 2018	Oct, 2028	High risk CD19+ BCP-ALL in CR1[*]	18-59	single-arm blinatumomab-based consolidation and maintenance
St. Jude Total 17 protocol	NCT03117751	Apr, 2017	–	B-ALL MRD+	1-18	chemotherapy + blinatumomab/bortezomib/nelarabine/dasatinib/ruxolitinib
I/II	NCT02311998	Apr, 2015	Apr, 2020	Ph-pos CD22+ B-ALL	≥18	single-arm bosutinib + inotuzumab
IIa	NCT03610438	Dec, 2018	Nov, 2022	Ph-neg/-pos CD22+ BCP-ALL MRD+	≥18	single-arm inotuzumab
II	NCT03441061	Feb, 2018	Feb, 2023	CD22+ B-ALL MRD+	≥18	single-arm inotuzumab
III (RCT)	NCT03150693	Jun, 2017	Aug, 2024	Ph-neg CD22+ BCP-ALL	18-39	C10403 chemotherapy backbone +/− inotuzumab
III (RCT)	NCT03959085	Oct, 2019	May, 2027	High risk CD22+ B-ALL	1-24	post-induction chemotherapy +/− inotuzumab
II	NCT03913559	Apr, 2019	-	CD22+ BCP-ALL MRD+	≤21	single-arm inotuzumab
II/III	NCT03027739	Nov, 2016	Dec, 2020	CD19+ B-ALL MRD+	1-60	single-arm CD19 CAR-T
I	NCT03685786	Jun, 2018	Sep, 2021	CD19+ B-ALL, 0.01%≤MRD<10%	14-75	single-arm autologous CD19 CAR-T + autologous HSCT
I	NCT02529813	Dec, 2015	Dec, 2021	CD19+ B-ALL	1-80	single-arm CD19 CAR-T
II	NCT04225676	Feb, 2020	Feb, 2022	CD19+ B-ALL with B-cell recovery[‡]	≤25	single-arm tisagenlecleucel re-infusion
I/II	NCT04033302	Sep, 2019	Dec, 2023	T-ALL	6mo-75	single-arm allogeneic/autologous gene-edited CD7-specific CAR-T
II	NCT03876769	Jun, 2019	Aug, 2027	Ph-neg high risk CD19+ B-ALL MRD+	1-25	single-arm tisagenlecleucel
II	NCT01319981	Mar, 2013	Dec, 2020	B-ALL	≥18	hyper-CVAD + liposomal vincristine (hyperCMAD)
Ib	NCT02569476	Jan, 2016	Mar, 2020	B-cell lymphoid malignancies	≥18	single-arm obinotuzumab + zanubrutinib
III (RCT)	NCT01085617	Dec, 2010	Jul, 2023	Ph-neg/-pos ALL	25-65	UKALL14 chemotherapy backbone + rituximab (B-ALL) or nelarabine (T-ALL)
II	NCT00501826	Jul, 2007	Oct, 2020	T-ALL	>1	single-arm nelarabine + hyper-CVAD
III (RCT)	NCT02112916	Sep, 2014	Mar, 2020	T-ALL	2-30	modified aBFM backbone +/− bortezomib
ALL-MB 2015 protocol	NCT03390387	Nov, 2015	Nov, 2025	BCP-ALL with initial WBC≥100,000/μL	1-50	bortezomib + chemotherapy
II/III	NCT03564470	Feb, 2016	Aug, 2020	Ph-like B-ALL	14-55	single-arm dasatinib + chidamide + pediatric-inspired chemotherapy
III (RCT)	NCT02883049	Feb, 2012	Jun, 2021	Ph-like (TKI-sensitive mutations) high risk B-ALL	1-30	dasatinib + combined chemotherapy
II	NCT02723994	Aug, 2016	May, 2024	Ph-like (CRLF2-rearranged and/or JAK pathway mutant) high risk B-ALL[§]	≤21	ruxolitinib + combined chemotherapy
I	NCT03571321	Sep, 2019	Sep, 2024	Ph-like (CRLF2-rearranged and/or JAK2/EPOR fusions and/or other JAK pathway alterations) BCP-ALL	18-39	ruxolitinib + pediatric chemotherapy backbone
III (RCT)	NCT03589326	Aug, 2018	Sep, 2025	Ph-pos B-ALL	≥18	ponatinib / imatinib + reduced-intensity chemotherapy

AEIOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; B-ALL, B-cell acute lymphoblastic leukemia; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; aBFM, augmented Berlin-Frankfurt-Münster; CAR-T; chimeric antigen receptor T-cells; COG, Children's Oncology Group; CR1, first complete remission; CT-identifier, ClinicalTrials.gov identifier; ECOG, Eastern Cooperative Oncology Group; Est., estimated; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; HOVON, Hemato-Oncologie voor Volwassenen Nederland; HSCT, hematopoietic stem cell transplantation; hyper-CVAD, hyperfractionated cyclophosphamide + vincristine + adriamycin + dexamethasone; mo, months; MRD, minimal residual disease; Ph, Philadelphia chromosome; RCT, randomized-controlled trial; T-ALL, T-cell acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor; UKALL, United Kingdom Acute Lymphoblastic Leukemia; WBC, white blood cell count; y, years.
Clinical trials arranged according to the main agent of interest and in accordance with estimated completion date in increasing order.

[*] High risk defined as presence of KMT2A gene rearrangement and/or IKZF1 (Ikaros) intragenic deletion and/or high postinduction Ig-TCR MRD ≥0.01%.

[†] Blinatumomab for intermediate risk patients; bortezomib for patients with slow response to induction chemotherapy.

[‡] B-cell recovery defined as peripheral blood absolute B-lymphocyte count ≥50/μL or peripheral blood B-lymphocyte ≥10% of the total lymphocytes or peripheral blood absolute B-lymphocyte count ≥200/μL.

[§] High risk defined as age ≥10 years, WBC ≥50×10^3/μL, CNS3 leukemia at diagnosis, systemic steroid pretreatment without presteroid WBC documentation.

strating CR rates of 88% to 96%, CMR rate of 65%, 3-year OS and DFS of 69% and 62%, respectively, for dasatinib (72-97 patients, median age 44-55 years) [99-101]. Not to mention 2-year OS of 72% for nilotinib (90 patients, median age 47 years) [102]. Most recently, frontline addition of the third-generation TKI, ponatinib, to a hyper-CVAD backbone showed a CR rate of 100% including CMR rate of 74% at 3 months and 84% overall. The estimated 5-year continuous CR, EFS, and OS rates were 84%, 68%, and 73%, respectively (86 patients, median age 46 years) [103-105]. Two ponatinib-related deaths from myocardial infarction raised concerns and re-

sulted in an amendment with ponatinib dose reduction. Yet, a great benefit of ponatinib involves the activity against common resistance mutations to earlier generation TKIs such as T315I. Forty-seven percent of heavily pretreated Ph-positive ALL patients with resistance/unacceptable side effects from dasatinib/nilotinib achieved major molecular response with ponatinib [106]. However, no direct head-to-head comparisons of the different TKIs in Ph-positive ALL have been done, although ponatinib-based regimens seem superior over regimens based on earlier generation TKIs both in propensity-matched score and meta-analyses [107,108].

In contrast to the use of an intensive backbone with TKIs, combination with lower intensity regimens has proven feasible with just as excellent outcomes but less toxicity. In the GRAAPH-2005 phase III trial randomizing Ph-positive ALL patients to imatinib combined with higher or lower intensity regimens, no difference in 5-year EFS (42 vs 32%, $P = .13$) and OS (48 vs 43%, $P = .37$) was found (268 patients, median age 47 years) [109]. Even chemotherapy-free regimens may be associated with favorable outcomes in a selected group of Ph-positive patients with early, deep response. The GIMEMA LAL1509 trial evaluated dasatinib and steroids in induction combined with a risk-adapted approach, in which 18% of patients achieved early CMR (on day 85) and continued with dasatinib alone—resulting in a 2.5-year DFS of 75%. The remaining patients who did not achieve CMR on day 85 continued with subsequent chemotherapy with/without HSCT. The overall 3-year OS and 2.5-year DFS were 58% and 49%, respectively (60 patients, median age 42 years) [110]. Thus, trials based on low intensity or chemotherapy-free regimens with TKIs in combination with novel agents are ongoing (Tables 2 and 3) such as the frontline phase II GIMEMA LAL2116 D-ALBA trial (NCT02744768). This trial is including dasatinib induction followed by dasatinib in combination with blinatumomab postinduction for patients achieving complete hematologic response. Preliminary results demonstrated molecular response rates of 26% at the end of induction and of 54%, 68%, and 80% after 2, 3, and 4 cycles of blinatumomab, respectively. One-year DFS and OS were 92% and 96% (63 patients, median age 55 years) [111].

The role of HSCT

Advances in our understanding of ALL disease biology (cytogenetics, genomics, and MRD) along with refinement of risk-adapted frontline approaches have allowed for reservation of HSCT for a select group of patients with high-risk ALL in CR1 (eg, MRD persistence, KMT2A rearrangement, early T-cell precursor (ETP-), Ph-like or Ph-positive ALL) [112-114]. Yet, the role of HSCT in CR1 in general is being questioned with the unprecedented results of novel agents—but still remains routine practice in CR2 or later [115,116].

Excellent long-term OS rates (5-year OS up to 83%) have been demonstrated in adults with Ph-positive ALL (median age 46 years) who achieve early deep molecular remissions following TKI (ponatinib) plus an intensive regimen without HSCT in CR1 [55,97,105]. Accordingly, the benefit in DFS of HSCT in the GRAAPH-2005 randomized trial of imatinib combined with higher or lower intensity regimens was restricted to patients (median age 47 years) with persistent MRD after 2 cycles [109]. In contrast, Ph-positive patients (median age 44 years) significantly benefitted in DFS and OS from HSCT in CR1 following dasatinib plus hyper-CVAD in a landmark analysis from the SWOG study [101]. Noteworthy is that MRD data were not available. Another important point is the complete absence of trials evaluating the role of HSCT in AYAs with Ph-positive ALL, thus limiting extrapolation of existing data to this distinct subgroup of patients associated with a highly different treatment response as well as toxicity profile [117].

In AYAs with Ph-negative ALL, significant survival benefit with allogeneic HSCT in CR1 over conventional adult ALL regimens was established in the pre-MRD era [118,119]. Yet, recent retrospective studies have evaluated the optimal postremission treatment in AYAs, comparing allogeneic HSCT with contemporary pediatric-inspired non-HSCT regimens (DFCI/CALGB 10403) in age-matched comparative analyses. These findings clearly favor pediatric-inspired regimens over HSCT in CR1 with superior OS (73 vs 45%, $P < .0001$) and DFS (71 vs 40%, $P < .0001$) as well as lower nonrelapse mortality (6% vs 37%, $P < .0001$) [120,121]. Accordingly, allogeneic HSCT has been associated with inferior OS (HR 2.0, $P < .001$), inferior DFS (HR 1.5, $P = .002$), and increased nonrelapse mortality (HR 3.9, $P < .001$) in multivariate analyses [120,121]. Interestingly, relapse was more likely with HSCT within 15 months from the time of CR1, whereas relapse became more likely with chemotherapy beyond 15 months [121]. Yet, neither MRD data nor high-risk genetics such as Ph-like aberrations were included in the analyses. Importantly, allogeneic HSCT has been associated with significant longer DFS in a subgroup of AYAs with persistent MRD postinduction of pediatric-inspired protocol treatment (GMALL 06/99 / 07/03 and GRAALL-2003/5) as well as with presence of focal *IKZF1* gene deletion in BCP-ALL patients [122], when compared with no HSCT [122,123]. However, MRD eradication at the time of remission did not change the inferior outcome of the Ph-like ALL subset in adults in a small study by Jain et al. [112,124]. It is currently unclear whether allogeneic HSCT in CR1 is superior to pediatric-based regimens in Ph-like ALL and whether these patients should be treated with allogeneic HSCT irrespective of the MRD status.

Using MRD-based guidance as the only risk factor for stratification of postremission therapy (maintenance or HSCT in CR1) in adults with ALL, impressive survival rates for nontransplanted/MRD-negative compared with transplanted/MRD-positive patients have been demonstrated (ie, 5-year OS and DFS of 75 vs 33% and 72 vs 14%, respectively) [125]. Generally, MRD guides contemporary postinduction treatment given its powerful ability to predict relapse, and persistent MRD is regarded as an indication for HSCT in CR1 [56,112,114,116,126,127]. However, even after HSCT outcomes still remain poor in this subset of patients [92,128]. Recently published Northern American expert guidelines recommend blinatumomab prior to HSCT in patients with detectable MRD, given the impressive efficacy for MRD eradication [114]. To this add that clinical trials evaluating the efficacy of inotuzumab for MRD-positive B-ALL are ongoing (Table 3). However, we do not know from existing evidence whether patients, in whom novel agents eradicate MRD, will benefit from subsequent consolidative HSCT. Although the data should be interpreted with caution, no difference between patients in CR1 with HSCT after blinatumomab and patients without HSCT was found in an underpowered ad hoc Mantel-Byar analysis of OS (110 patients; odds ratio 1.8, $P = .2$) from the phase II BLAST trial for MRD-positive Ph-negative or -positive B-ALL in CR1/2 [78]. Interestingly, for patients treated in CR2 in the BLAST trial, the outcome of patients without HSCT after blinatumomab was inferior (odds ratio 0.3, $P = .02$) [78]. In contrast, no survival benefit was found between those who received consolidative HSCT and those who did not among responders to single-arm blinatumomab in the TOWER trial [129] and among patients achieving MRD eradication following CD19-CAR-T-cells [47] in an R/R B-ALL setting. However, none of these trials were sufficiently powered to conclude on post-HSCT outcomes.

Treatment-related toxicities of the pediatric-based approach

Aside from the common myelotoxicity-associated burden of chemotherapy as well as the toxicity characteristics of TKIs and novel agents addressed in the previous sections, young adults display a unique toxicity profile related to the pediatric-based ap-

proach. However, it is a myth that the pediatric-based approach characterized by the intensive asparaginase use is too toxic for young adults [10-12,130]. In general, young adults tolerate the pediatric regimens as well as children, given the almost identical tolerated intervals between treatment phases across age groups when adjusting for the assigned treatment intensity [131]. Yet, the overall toxicity burden will increase with older age as a result of more frequent stratification to higher risk arms for older patients, given the more frequent presence of T-lineage ALL and high-risk karyotypes as well as poorer responses to induction therapy [131]. To this adds the higher burden of a few serious asparaginase- and/or steroid-related toxicities in young adults when compared with the toxicity profile in children with ALL—irrespective of the assigned risk group [10]. These include venous thromboembolism (VTE), asparaginase-associated pancreatitis (AAP), and osteonecrosis (ON) with cumulative incidences ranging 15% to 18%, 10% to 11%, and 15% to 20%, respectively [10,15-17,132]. In addition, hepatotoxicity with hyperbilirubinemia and/or transaminitis is one of the commonest toxicities to pegylated asparaginase therapy in adults being reported in 25% to 50% of patients, not least in the older and obese patients [133-135]. Generally, hepatotoxicity is transient and without hepatic failure [135]. Asparaginase high-grade hyperbilirubinemia mostly occurs during the early part of induction therapy, that is, when patients have leukemic liver infiltration [136,137], and case reports indicate that L-carnitine may reduce pegylated asparaginase-induced hyperbilirubinemia [138-142].

Preventive strategies to reduce asparaginase-associated toxicities include use of lower asparaginase doses [143-145], intermittent rather than continuous asparaginase [146], and novel asparaginase formulations. L-asparaginase loaded red blood cells (GRASPA) is a new asparaginase formulation with the ability to protect the drug against proteolytic enzymes and neutralizing antibodies, enhancing its half-life, and reducing the frequency of adverse events [147]. The GRASPALL 2005-01 phase I/II randomized trial of GRASPA vs *Escherichia coli*-derived L-asparaginase in relapsed ALL patients aged 1 to 55 years demonstrated the efficacy of GRASPA and a reduction in hypersensitivity reactions [148]. There is a paucity of evidence regarding more toxicity-specific approaches, for example, thromboprophylaxis of VTE in adult ALL patients. The recent randomized THROMBOTECT trial included 949 children with ALL and demonstrated a significantly lower risk of thromboembolism during induction therapy with prophylactic antithrombin or low molecular weight heparin (enoxaparin) compared with low-dose unfractionated heparin (1.9% and 3.5% vs 4.4%, both $P \leq .01$) without any difference in bleeding events [149]. Of note, the study was open-label, 33% declined treatment of the subcutaneously injected enoxaparin, and cross-over between the treatment arms was allowed. Yet, the results were confirmed in an as-treated analysis. Additionally, the ongoing PREVAPIX-ALL study is randomizing ALL patients aged 1 to 17 years to the direct oral anticoagulant apixaban vs standard of care for VTE prevention (NCT02369653). An ongoing Cochrane systematic review explores the efficacy and safety of thromboprophylaxis in adults with ALL undergoing asparaginase-based therapy [150]. Further, the synthetic somatostatin analogue, octreotide, has proven safe and effective as prophylactic treatment preventing AAP recurrence in smaller ALL patient cohorts [151-154]. Other suggested preemptive strategies involve alcohol avoidance and statins/gemfibrozil for serum triglyceride >1000 mg/dL to obviate AAP [144], although evidence of steroid- and asparaginase-induced hypertriglyceridemia as a harbinger for AAP is conflicting [135,155-162]. As are data regarding hypertriglyceridemia and ON [161,163]. Given that steroids are considered the primary risk factor for ON, preemptive approaches have involved new dosage strategies. Split vs continuous dexamethasone dosage significantly reduced ON incidence in the COG-1961 randomized trial of high-risk ALL patients aged 1 to 21 years, being most pronounced in patients aged ≥16 years (11.3 vs 37.5%, $P = .0003$) [132].

Importantly, evidence-based primary as well as secondary preventive strategies are warranted in dealing with treatment-related toxicities, as the greatest threat to the patient is not the toxicity itself but rather the consequence on ALL treatment. Serious treatment-related toxicities often cause delay or premature discontinuation of key antileukemic agents, for example, asparaginase, translating into an increased risk of relapse [164-169]. Pre-emptive tactics along with the use of novel agents may allow downscaling of the toxic chemotherapy backbone and in turn reduce the burden of toxicities, as we know it today.

Adherence

Studies of childhood ALL have associated nonadherence to oral treatment with increased risk of relapse; a challenge that increases with age [170,171]. So far, the data for adolescents are very limited [172] and nonexisting for young adults, but application of MEMS TrackCap technology to assess adherence in young adults with ALL is ongoing (NCT03150693). Adherence in young adults involves complex psychosocial challenges that stress the need for a multidisciplinary care team to handle this age group [26,27,173].

Conclusion

The optimal treatment approach to young adults with ALL in 2020 inevitably involves immunotherapy and molecularly targeted therapy, but the role remains to be defined. Replacing toxic chemotherapy with these novel agents has the potential not only to improve the cure rate and deepen the responses but also reduce the burden of therapy. The markedly improved survival emphasizes that most patients are chemo-sensitive. Yet, collaborative strategies are needed to address all causes of treatment failure including cytogenetic profiling, sensitive MRD monitoring, drug exposure optimization and adherence as well as recruitment of a higher proportion of AYA patients into clinical trials.

Author contributions

C.U.R. conceptualized the review and wrote the original draft of the review. K.S. conceptualized the review, critically reviewed and edited the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminhematol.2020.08.001.

References

[1] US Department of Health and Human Services: Closing the gap: research and care imperatives for adolescents and young adults with cancer. Available at: https://www.cancer.gov/types/aya/research/ayao-august-2006.pdf/. Accessed February 4, 2020

[2] Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol 2003;21(5):774–80.
[3] Testi AM, Valsecchi MG, Conter V, et al. Difference in outcome of adolescents with acute lymphoblastic leukemia (ALL) enrolled in pediatric (AIEOP) and adult (GIMEMA) protocols. Blood 2004;104(11):1954-.
[4] de Bont JM, Holt B, Dekker AW, et al. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. Leukemia 2004;18(12):2032–5.
[5] Hallbook H, Gustafsson G, Smedmyr B, Soderhall S, Heyman M. Treatment outcome in young adults and children >10 years of age with acute lymphoblastic leukemia in Sweden: a comparison between a pediatric protocol and an adult protocol. Cancer 2006;107(7):1551–61.
[6] Ramanujachar R, Richards S, Hann I, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer 2007;48(3):254–61.
[7] Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood 2008;112(5):1646–54.
[8] Usvasalo A, Räty R, Knuutila S, et al. Acute lymphoblastic leukemia in adolescents and young adults in Finland. Haematologica 2008;93(8):1161–8.
[9] Ram R, Wolach O, Vidal L, Gafter-Gvili A, Shpilberg O, Raanani P. Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: systematic review and meta–analysis. Am J Hematol 2012;87(5):472–8.
[10] Toft N, Birgens H, Abrahamsson J, et al. Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. Leukemia 2018;32(3):606–15.
[11] Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood 2019;133(14):1548–59.
[12] DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. Leukemia 2015;29(3):526–34.
[13] Huguet F, Chevret S, Leguay T, et al. Intensified therapy of acute lymphoblastic leukemia in adults: report of the randomized GRAALL-2005 clinical trial. J Clin Oncol 2018;36(24):2514–23.
[14] Gökbuget N, Beck J, Brandt K, et al. Significant improvement of outcome in adolescents and young adults (AYAs) aged 15-35 years with acute lymphoblastic leukemia (ALL) with a pediatric derived adult ALL protocol; results of 1529 AYAs in 2 consecutive trials of the German Multicenter Study Group For Adult ALL (GMALL). Blood 2013;122(21):839.
[15] Rank CU, Toft N, Tuckuviene R, et al. Thromboembolism in acute lymphoblastic leukemia: results of NOPHO ALL2008 protocol treatment in patients aged 1 to 45 years. Blood 2018;131(22):2475–84.
[16] Rank CU, Wolthers BO, Grell K, et al. Asparaginase-associated pancreatitis in acute lymphoblastic leukemia: results from the NOPHO ALL2008 treatment of patients 1-45 years of age. J Clin Oncol 2020;38(2):145–54.
[17] Mogensen SS, Harila-Saari A, Mäkitie O, et al. Comparing osteonecrosis clinical phenotype, timing, and risk factors in children and young adults treated for acute lymphoblastic leukemia. Pediatr Blood Cancer 2018;65(10):e27300.
[18] Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. J Clin Oncol 2017;35(9):975–83.
[19] Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014;371(11):1005–15.
[20] Tasian SK, Loh ML, Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. Blood 2017;130(19):2064–72.
[21] Pui C-H, Roberts KG, Yang JJ, Mullighan CG. Philadelphia chromosome-like acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2017;17(8):464–70.
[22] Harvey RC, Tasian SK. Clinical diagnostics and treatment strategies for Philadelphia chromosome-like acute lymphoblastic leukemia. Blood Adv 2020;4(1):218–28.
[23] Roberts KG, Gu Z, Payne-Turner D, et al. High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. J Clin Oncol 2017;35(4):394–401.
[24] Chiaretti S, Messina M, Della Starza I, et al. Philadelphia-like acute lymphoblastic leukemia is associated with minimal residual disease persistence and poor outcome. First report of the minimal residual disease-oriented GIMEMA LAL1913. Haematologica 2020. Online ahead of print.
[25] Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology–drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349(12):1157–67.
[26] Zebrack B, Bleyer A, Albritton K, Medearis S, Tang J. Assessing the health care needs of adolescent and young adult cancer patients and survivors. Cancer 2006;107(12):2915–23.
[27] Lang MJ, David V, Giese-Davis J. The age conundrum: a scoping review of younger age or adolescent and young adult as a risk factor for clinical distress, depression, or anxiety in cancer. J Adolesc Young Adult Oncol 2015;4(4):157–73.
[28] Raponi S, De Propris MS, Intoppa S, et al. Flow cytometric study of potential target antigens (CD19, CD20, CD22, CD33) for antibody-based immunotherapy in acute lymphoblastic leukemia: analysis of 552 cases. Leuk Lymphoma 2011;52(6):1098–107.
[29] Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16(1):57–66.
[30] Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. J Clin Oncol 2017;35(16):1795–802.
[31] Rambaldi A, Ribera JM, Kantarjian HM, et al. Blinatumomab compared with standard of care for the treatment of adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia. Cancer 2020;126(2):304–10.
[32] Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376(9):836–47.
[33] Rambaldi A, Huguet F, Zak P, et al. Blinatumomab consolidation and maintenance therapy in adults with relapsed/refractory B-precursor acute lymphoblastic leukemia. Blood Adv 2020;4(7):1518–25.
[34] von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016;34(36):4381–9.
[35] Duell J, Dittrich M, Bedke T, et al. Frequency of regulatory T cells determines the outcome of the T-cell-engaging antibody blinatumomab in patients with B-precursor ALL. Leukemia 2017;31(10):2181–90.
[36] Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375(8):740–53.
[37] Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer 2019;125(14):2474–87.
[38] Jabbour E, Gökbuget N, Advani A, et al. Impact of minimal residual disease status in patients with relapsed/refractory acute lymphoblastic leukemia treated with inotuzumab ozogamicin in the phase III INO-VATE trial. Leuk Res 2020;88:106283.
[39] Jabbour E, Sasaki K, Ravandi F, et al. Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. Cancer 2018;124(20):4044–55.
[40] Sasaki K, Kantarjian HM, Ravandi F, et al. Sequential combination of inotuzumab ozogamicin (InO) with low-intensity chemotherapy (mini-hyper--CVD) with or without blinatumomab is highly effective in patients (pts) with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) in first relapse. Blood 2019;134(suppl_1):3806-.
[41] Jain N, Klisovic RB, Stock W, et al. Interim data from a phase 1 study evaluating pyrrolobenzodiazepine-based antibody drug conjugate ADCT-402 (loncastuximab tesirine) targeting CD19 for relapsed or refractory B-cell acute lymphoblastic leukemia. Blood 2017;130(suppl 1):1321-.
[42] Buechner J, Grupp SA, Maude SL, et al. Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): update to the interim analysis. Clin Lymphoma Myeloma Leuk 2017;17:S263–4. https://doi.org/10.1016/j.clml.2017.07.030.
[43] Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378(5):439–48.
[44] Grupp SA, Maude SL, Rives S, et al. Updated analysis of the efficacy and safety of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia. Blood 2018;132(suppl 1):895-.
[45] Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371(16):1507–17.
[46] Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet (London, England) 2015;385(9967):517–28.
[47] Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med 2018;378(5):449–59.
[48] Dai H, Wu Z, Jia H, et al. Bispecific CAR-T cells targeting both CD19 and CD22 for therapy of adults with relapsed or refractory B cell acute lymphoblastic leukemia. J Hematol Oncol 2020;13(1):30.
[49] Advani AS, McDonough S, Coutre S, et al. SWOG S0910: a phase 2 trial of clofarabine/cytarabine/epratuzumab for relapsed/refractory acute lymphocytic leukaemia. Br J Haematol 2014;165(4):504–9.
[50] Gorin N-C, Isnard F, Garderet L, et al. Administration of alemtuzumab and G-CSF to adults with relapsed or refractory acute lymphoblastic leukemia: results of a phase II study. Eur J Haematol 2013;91(4):315–21.
[51] Messinger YH, Gaynon PS, Sposto R, et al. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. Blood 2012;120(2):285–90.
[52] Alford SE, Kothari A, Loeff FC, et al. BH3 inhibitor sensitivity and Bcl-2 dependence in primary acute lymphoblastic leukemia cells. Cancer Res 2015;75(7):1366–75.

[53] Frismantas V, Dobay MP, Rinaldi A, et al. Ex vivo drug response profiling detects recurrent sensitivity patterns in drug-resistant acute lymphoblastic leukemia. Blood 2017;129(11):e26–37.
[54] Lacayo NJ, Pullarkat VA, Stock W, et al. Safety and efficacy of venetoclax in combination with navitoclax in adult and pediatric relapsed/refractory acute lymphoblastic leukemia and lymphoblastic lymphoma. Blood 2019;134(suppl_1):285.
[55] Samra B, Jabbour E, Ravandi F, Kantarjian H, Short NJ. Evolving therapy of adult acute lymphoblastic leukemia: state-of-the-art treatment and future directions. J Hematol Oncol 2020;13(1):70.
[56] DeAngelo DJ, Jabbour E, Advani A. Recent advances in managing acute lymphoblastic leukemia. Am Soc Clin Oncol Educ Book 2020;40:330–42.
[57] Shiraz P, Payne KJ, Muffly L. The current genomic and molecular landscape of Philadelphia-like acute lymphoblastic leukemia. Int J Mol Sci 2020;21(6).
[58] Kim SK, Knight DA, Jones LR, et al. JAK2 is dispensable for maintenance of JAK2 mutant B-cell acute lymphoblastic leukemias. Genes Dev 2018;32(11-12):849–64.
[59] Weston BW, Hayden MA, Roberts KG, et al. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. J Clin Oncol 2013;31(25):e413–e4e6.
[60] Lengline E, Beldjord K, Dombret H, Soulier J, Boissel N, Clappier E. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with EBF1-PDGFRB fusion. Haematologica 2013;98(11):e146–e1e8.
[61] DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood 2007;109(12):5136–42.
[62] Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2019.
[63] Chonghaile TN, Roderick JE, Glenfield C, et al. Maturation stage of T-cell acute lymphoblastic leukemia determines BCL-2 versus BCL-XL dependence and sensitivity to ABT-199. Cancer Discov 2014;4(9):1074–87.
[64] Li Z, He S, Look AT. The MCL1-specific inhibitor S63845 acts synergistically with venetoclax/ABT-199 to induce apoptosis in T-cell acute lymphoblastic leukemia cells. Leukemia 2019;33(1):262–6.
[65] Bride KL, Vincent TL, Im SY, et al. Preclinical efficacy of daratumumab in T–cell acute lymphoblastic leukemia. Blood 2018;131(9):995–9.
[66] Moradi Manesh D, El-Hoss J, Evans K, et al. AKR1C3 is a biomarker of sensitivity to PR-104 in preclinical models of T-cell acute lymphoblastic leukemia. Blood 2015;126(10):1193–202.
[67] Evans K, Duan J, Pritchard T, et al. OBI-3424, a novel AKR1C3-activated prodrug, exhibits potent efficacy against preclinical models of T-ALL. Clin Cancer Res 2019;25(14):4493–503.
[68] Rao SS, O'Neil J, Liberator CD, et al. Inhibition of NOTCH signaling by gamma secretase inhibitor engages the RB pathway and elicits cell cycle exit in T-cell acute lymphoblastic leukemia cells. Cancer Res 2009;69(7):3060–8.
[69] Gao J, Van Meter M, Hernandez Lopez S, et al. Therapeutic targeting of notch signaling and immune checkpoint blockade in a spontaneous, genetically heterogeneous mouse model of T-cell acute lymphoblastic leukemia. Dis Models Mech 2019;12(9) dmm040931.
[70] Zweidler-McKay PA, DeAngelo DJ, Douer D, et al. The safety and activity of BMS-906024, a gamma secretase inhibitor (GSI) with anti-notch activity, in patients with relapsed T-cell acute lymphoblastic leukemia (T-ALL): initial results of a phase 1 trial. Blood 2014;124(21):968-.
[71] Rodriguez S, Abundis C, Boccalatte F, et al. Therapeutic targeting of the E3 ubiquitin ligase SKP2 in T-ALL. Leukemia 2020;34(5):1241–52.
[72] Okada Y, Jiang Q, Lemieux M, Jeannotte L, Su L, Zhang Y. Leukaemic transformation by CALM-AF10 involves upregulation of Hoxa5 by hDOT1L. Nat Cell Biol 2006;8(9):1017–24.
[73] Stein EM, Garcia-Manero G, Rizzieri DA, et al. The DOT1L inhibitor pinometostat reduces H3K79 methylation and has modest clinical activity in adult acute leukemia. Blood 2018;131(24):2661–9.
[74] Irving J, Matheson E, Minto L, et al. Ras pathway mutations are prevalent in relapsed childhood acute lymphoblastic leukemia and confer sensitivity to MEK inhibition. Blood 2014;124(23):3420–30.
[75] Cooper ML, Choi J, Staser K, et al. An "off-the-shelf" fratricide-resistant CAR-T for the treatment of T cell hematologic malignancies. Leukemia 2018;32(9):1970–83.
[76] Wang SLX, Gao L, Yuan Z, et al. Clinical safety and efficacy study of TruUCAR™ GC027: the first-in-human, universal CAR-T therapy for adult relapsed/refractory T-cell acute lymphoblastic leukemia (r/r T-ALL). In: American Association for Cancer Research (AACR) Virtual Annual Meeting I; 2020.
[77] Ravandi F, Jorgensen JL, O'Brien SM, et al. Minimal residual disease assessed by multi-parameter flow cytometry is highly prognostic in adult patients with acute lymphoblastic leukaemia. Br J Haematol 2016;172(3):392–400.
[78] Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131(14):1522–31.
[79] Richard-Carpentier G, Kantarjian HM, Short NJ, et al. Updated results from the phase II study of hyper-CVAD in sequential combination with blinatumomab in newly diagnosed adults with B-cell acute lymphoblastic leukemia (B-ALL). Blood 2019;134(suppl_1):3807-.
[80] Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. N Engl J Med 2016;375(11):1044–53.
[81] Guerra VA, Jabbour EJ, Ravandi F, Kantarjian H, Short NJ. Novel monoclonal antibody-based treatment strategies in adults with acute lymphoblastic leukemia. Ther Adv Hematol 2019;10:2040620719849496.
[82] Bazarbachi AH, Yilmaz M, Ravandi F, et al. A phase 2 study of hyper-C-VAD plus ofatumumab as frontline therapy in CD20+ acute lymphoblastic leukemia (ALL): updated results. J Clin Oncol 2018;36(15_suppl):7041-.
[83] Zhou H, Gao Y, Wang Q, et al. A novel oral histone deacetylase inhibitor chidamide is highly effective and well-tolerated in adult early T-cell precursor and Ph-like acute lymphoblastic leukemia. Blood 2018;132(suppl 1):4011-.
[84] Kannan S, Aitken MJL, Herbrich SM, et al. Antileukemia effects of notch-mediated inhibition of oncogenic PLK1 in B-cell acute lymphoblastic leukemia. Mol Cancer Ther 2019;18(9):1615–27.
[85] Dunsmore KP, Winter S, Devidas M, et al. COG AALL0434: a randomized trial testing nelarabine in newly diagnosed t-cell malignancy. J Clin Oncol 2018;36(15_suppl):10500.
[86] Dunsmore K, Winter S, Devidas M, et al. COG AALL0434: randomized trial of escalating dose versus high dose methotrexate and nelarabine for adolescents and young adults with newly diagnosed T-cell acute lymphoblastic leukemia. Pediatr Blood Cancer 2019;66(S4):e27989.
[87] Kadia TM, Gandhi V. Nelarabine in the treatment of pediatric and adult patients with T-cell acute lymphoblastic leukemia and lymphoma. Expert Rev Hematol 2017;10(1):1–8.
[88] Schrappe M, Bleckmann K, Zimmermann M, et al. Reduced-intensity delayed intensification in standard-risk pediatric acute lymphoblastic leukemia defined by undetectable minimal residual disease: results of an international randomized trial (AIEOP-BFM ALL 2000). J Clin Oncol 2018;36(3):244–53.
[89] Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol 2013;14(3):199–209.
[90] Ribera J-M, Oriol A, Morgades M, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. J Clin Oncol 2014;32(15):1595–604.
[91] Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood 2015;126(8):964–71.
[92] Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. JAMA Oncol 2017;3(7):e170580.
[93] Bassan R, Intermesoli T, Scattolin A, et al. Minimal residual disease assessment and risk-based therapy in acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2017;17S:S2–9.
[94] Scherer F, Kurtz DM, Diehn M, Alizadeh AA. High-throughput sequencing for noninvasive disease detection in hematologic malignancies. Blood 2017;130(4):440–52.
[95] Kotrova M, Muzikova K, Mejstrikova E, et al. The predictive strength of next-generation sequencing MRD detection for relapse compared with current methods in childhood ALL. Blood 2015;126(8):1045–7.
[96] Wood B, Wu D, Crossley B, et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. Blood 2018;131(12):1350–9.
[97] Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2016;128(4):504–7.
[98] Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 2014;123(6):843–50.
[99] Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood 2010;116(12):2070–7.
[100] Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer 2015;121(23):4158–64.
[101] Ravandi F, Othus M, O'Brien SM, et al. US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. Blood Adv 2016;1(3):250–9.
[102] Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood 2015;126(6):746–56.
[103] Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome–positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol 2015;16(15):1547–55.
[104] Short NJ, Kantarjian HM, Ravandi F, et al. Frontline hyper-CVAD plus ponatinib for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: updated results of a phase II study. J Clin Oncol 2017;35(15_suppl):7013-.
[105] Short NJ, Kantarjian HM, Ravandi F, et al. Long-term safety and efficacy of hyper-CVAD plus ponatinib as frontline therapy for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2019;134(suppl_1):283-.

[106] Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013;369(19):1783–96.
[107] Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. Cancer 2016;122(23):3650–6.
[108] Jabbour E, DerSarkissian M, Duh MS, et al. Efficacy of ponatinib versus earlier generation tyrosine kinase inhibitors for front-line treatment of newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2018;18(4):257–65.
[109] Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood 2015;125(24):3711–19.
[110] Chiaretti S, Vitale A, Elia L, et al. Multicenter total therapy GIMEMA LAL 1509 protocol for de novo adult Ph+ acute lymphoblastic leukemia (ALL) patients. Updated results and refined genetic-based prognostic stratification. Blood 2015;126(23):81.
[111] Chiaretti S, Bassan R, Vitale A, et al. A dasatinib-blinatumomab combination for the front-line treatment of adult PH+ ALL patients. Preliminary results of the GIMEMA LAL2116 D-ALBA trial; on behalf of GIMEMA acute leukemia working party. In: Presented at the 24th European Hematology Association Annual Congress, Amsterdam, the Netherlands; 2019.
[112] Giebel S, Marks DI, Boissel N, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 2019;54(6):798–809.
[113] Issa GC, Kantarjian HM, Yin CC, et al. Prognostic impact of pretreatment cytogenetics in adult Philadelphia chromosome-negative acute lymphoblastic leukemia in the era of minimal residual disease. Cancer 2017;123(3):459–67.
[114] Short NJ, Jabbour E, Albitar M, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: a consensus of North American experts. Am J Hematol 2019;94(2):257–65.
[115] Hoelzer D, Bassan R, Dombret H, et al. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27(suppl 5):v69–82.
[116] Carobolante F, Chiaretti S, Skert C, Bassan R. Practical guidance for the management of acute lymphoblastic leukemia in the adolescent and young adult population. Ther Adv Hematol 2020;11:2040620720903531.
[117] Soverini S, Bassan R, Lion T. Treatment and monitoring of Philadelphia chromosome-positive leukemia patients: recent advances and remaining challenges. J Hematol Oncol 2019;12(1):39.
[118] Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard--risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2008;111(4):1827–33.
[119] Gupta V, Richards S, Rowe J. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta–analysis. Blood 2013;121(2):339–50.
[120] Seftel MD, Neuberg D, Zhang M-J, et al. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. Am J Hematol 2016;91(3):322–9.
[121] Wieduwilt MJ, Stock W, Advani AS, et al. Superior survival with post-remission pediatric-inspired chemotherapy compared to myeloablative allogeneic hematopoietic cell transplantation in adolescents and young adults with Ph-negative acute lymphoblastic leukemia in first complete remission: comparison of CALGB 10403 to patients reported to the CIBMTR. Blood 2019;134(suppl_1):261-.
[122] Dhédin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood 2015;125(16):2486–586.
[123] Gökbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood 2012;120(9):1868–76.
[124] Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood 2017;129(5):572–81.
[125] Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). Blood 2009;113(18):4153–62.
[126] Bassan R, Brüggemann M, Radcliffe HS, Hartfield E, Kreuzbauer G, Wetten S. A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. Haematologica 2019;104(10):2028–39.
[127] Gökbuget N, Dombret H, Giebel S, et al. Minimal residual disease level predicts outcome in adults with Ph-negative B-precursor acute lymphoblastic leukemia. Hematology 2019;24(1):337–48.
[128] Pavlů J, Labopin M, Niittyvuopio R, et al. Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia: a retrospective registry study on 2780 patients from the acute leukemia working party of the EBMT. J Hematol Oncol 2019;12(1):108.
[129] Jabbour EJ, Gökbuget N, Kantarjian HM, et al. Transplantation in adults with relapsed/refractory acute lymphoblastic leukemia who are treated with blinatumomab from a phase 3 study. Cancer 2019;125(23):4181–92.
[130] Boissel N, Sender LS. Best practices in adolescent and young adult patients with acute lymphoblastic leukemia: a focus on asparaginase. J Adolesc Young Adult Oncol 2015;4(3):118–28.
[131] Toft N, Birgens H, Abrahamsson J, et al. Risk group assignment differs for children and adults 1-45 years with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol. Eur J Haematol 2013;90(5):404–12.
[132] Mattano LA Jr, Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. Lancet Oncol 2012;13(9):906–15.
[133] Christ TN, Stock W, Knoebel RW. Incidence of asparaginase-related hepatotoxicity, pancreatitis, and thrombotic events in adults with acute lymphoblastic leukemia treated with a pediatric-inspired regimen. J Oncol Pharm Pract 2018;24(4):299–308.
[134] Denton CC, Rawlins YA, Oberley MJ, Bhojwani D, Orgel E. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens. Pediatr Blood Cancer 2018;65(3). doi:10.1002/pbc.26891.
[135] Aldoss I, Douer D, Behrendt CE, et al. Toxicity profile of repeated doses of PEG-asparaginase incorporated into a pediatric-type regimen for adult acute lymphoblastic leukemia. Eur J Haematol 2016;96(4):375–80.
[136] Walz-Mattmüller R, Horny HP, Ruck P, Kaiserling E. Incidence and pattern of liver involvement in haematological malignancies. Pathol Res Pract 1998;194(11):781–9.
[137] Siegel SE, Stock W, Johnson RH, et al. Pediatric-inspired treatment regimens for adolescents and young adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: a review. JAMA Oncol 2018;4(5):725–34.
[138] Alshiekh-Nasany R, Douer D. L-carnitine for treatment of pegasparaginase-induced hepatotoxicity. Acta Haematol 2016;135(4):208–10.
[139] Rausch CR, Paul S, Marx KR, et al. L-carnitine and vitamin B complex for the treatment of pegasparaginase-induced hyperbilirubinemia. Clin Lymphoma Myeloma Leuk 2018;18(5):e191–e1e5.
[140] Schulte RR, Madiwale MV, Flower A, et al. Levocarnitine for asparaginase-induced hepatic injury: a multi-institutional case series and review of the literature. Leuk Lymphoma 2018;59(10):2360–8.
[141] Arora S, Klair J, Bellizzi AM, Tanaka T. L-carnitine and vitamin B complex for PEG-L-asparaginase-induced hepatotoxicity. ACG Case Rep J 2019;6(8):e00194.
[142] Blackman A, Boutin A, Shimanovsky A, Baker WJ, Forcello N. Levocarnitine and vitamin B complex for the treatment of pegaspargase-induced hepatotoxicity: a case report and review of the literature. J Oncol Pharm Pract 2018;24(5):393–7.
[143] Derman BA, Streck M, Wynne J, et al. Efficacy and toxicity of reduced vs. standard dose pegylated asparaginase in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia. Leuk Lymphoma 2020;61(3):614–22.
[144] Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma 2011;52(12):2237–53.
[145] Douer D, Aldoss I, Lunning MA, et al. Pharmacokinetics-based integration of multiple doses of intravenous pegaspargase in a pediatric regimen for adults with newly diagnosed acute lymphoblastic leukemia. J Clin Oncol 2014;32(9):905–11.
[146] Albertsen BK, Grell K, Abrahamsson J, et al. Intermittent versus continuous PEG-asparaginase to reduce asparaginase-associated toxicities: a NOPHO ALL2008 randomized study. J Clin Oncol 2019;37:1638–46.
[147] Thomas X, Le Jeune C. Erythrocyte encapsulated l-asparaginase (GRASPA) in acute leukemia. Int J Hematol Oncol 2016;5(1):11–25.
[148] Domenech C, Thomas X, Chabaud S, et al. l-asparaginase loaded red blood cells in refractory or relapsing acute lymphoblastic leukaemia in children and adults: results of the GRASPALL 2005-01 randomized trial. Br J Haematol 2011;153(1):58–65.
[149] Greiner J, Schrappe M, Claviez A, et al. THROMBOTECT—a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. Haematologica 2019;104(4):756–65.
[150] Utke Rank C, Lynggaard LS, Toft N, et al. Prophylaxis of thromboembolism during therapy with asparaginase in adults with acute lymphoblastic leukaemia. Cochrane Database Syst Rev 2019(9).
[151] Suzuki M, Takata O, Sakaguchi S, Fujimura J, Saito M, Shimizu T. Retherapy using L-asparaginase with octreotide in a patient recovering from L-asparaginase-induced pancreatitis. Exp Hematol 2008;36(3):253–4.
[152] Tokimasa S, Yamato K. Does octreotide prevent L-asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia? Br J Haematol 2012;157(3):381–2.
[153] Buie LW, Moore J, van Deventer H. Successful use of octreotide as a chemoprotectant for prevention of PEG-asparaginase-induced pancreatitis. Pharmacotherapy 2014;34(8):e149–51.

[154] Sakaguchi S, Higa T, Suzuki M, Fujimura J, Shimizu T. Prophylactic use of octreotide for asparaginase-induced acute pancreatitis. Int J Hematol 2017;106(2):266–8.
[155] Parsons SK, Skapek SX, Neufeld EJ, et al. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Blood 1997;89(6):1886–95.
[156] Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. J Clin Gastroenterol 2003;36(1):54–62.
[157] Cohen H, Bielorai B, Harats D, Toren A, Pinhas-Hamiel O. Conservative treatment of L-asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2010;54(5):703–6.
[158] Persson L, Harila-Saari A, Hed Myrberg I, Heyman M, Nilsson A, Ranta S. Hypertriglyceridemia during asparaginase treatment in children with acute lymphoblastic leukemia correlates with antithrombin activity in adolescents. Pediatr Blood Cancer 2017;64(10) e26559.
[159] Mogensen PR, Grell K, Schmiegelow K, et al. Dyslipidemia at diagnosis of childhood acute lymphoblastic leukemia. PloS One 2020;15(4):e0231209.
[160] Tong WH, Pieters R, de Groot-Kruseman HA, et al. The toxicity of very prolonged courses of PEGasparaginase or Erwinia asparaginase in relation to asparaginase activity, with a special focus on dyslipidemia. Haematologica 2014;99(11):1716–21.
[161] Bhojwani D, Darbandi R, Pei D, et al. Severe hypertriglyceridaemia during therapy for childhood acute lymphoblastic leukaemia. Eur J Cancer 2014;50(15):2685–94.
[162] Raja RA, Schmiegelow K, Sorensen DN, Frandsen TL. Asparaginase-associated pancreatitis is not predicted by hypertriglyceridemia or pancreatic enzyme levels in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2017;64(1):32–8.
[163] Mogensen SS, Schmiegelow K, Grell K, et al. Hyperlipidemia is a risk factor for osteonecrosis in children and young adults with acute lymphoblastic leukemia. Haematologica 2017;102(5):e175–e1e8.
[164] Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 2001;97(5):1211–18.
[165] Storring JM, Minden MD, Kao S, et al. Treatment of adults with BCR-ABL negative acute lymphoblastic leukaemia with a modified paediatric regimen. Br J Haematol 2009;146(1):76–85.
[166] Aldoss I, Pullarkat V, Martinez D, Ji L, Douer D. The number of peg-asparaginase doses administered is a determinant of relapse risk in adult ALL treated with a pediatric-like regimen. Blood 2013;122(21):3915-.
[167] Gupta S, Wang C, Raetz EA, et al. Impact of asparaginase discontinuation on outcome in childhood ALL: a report from the Children's Oncology Group (COG). J Clin Oncol 2019;37(15_suppl):10005-.
[168] Wetzler M, Sanford BL, Kurtzberg J, et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. Blood 2007;109(10):4164–7.
[169] Højfeldt SG, Grell K, Abrahamsson J, et al. Relapse following truncation of asparaginase in NOPHO ALL2008. In: Nordic Society of Paediatric Haematology and Oncology 37th Annual Meeting, Aalborg, Denmark; 2019. nopho.org2019.
[170] Bhatia S, Landier W, Shangguan M, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. J Clin Oncol 2012;30(17):2094–101.
[171] Bhatia S, Landier W, Hageman L, et al. Systemic exposure to thiopurines and risk of relapse in children with acute lymphoblastic leukemia: a Children's Oncology Group Study. JAMA Oncol 2015;1(3):287–95.
[172] Schmiegelow K, Heyman M, Gustafsson G, et al. The degree of myelosuppression during maintenance therapy of adolescents with B-lineage intermediate risk acute lymphoblastic leukemia predicts risk of relapse. Leukemia 2010;24(4):715–20.
[173] Husson O, Huijgens PC, van der Graaf WTA. Psychosocial challenges and health-related quality of life of adolescents and young adults with hematologic malignancies. Blood 2018;132(4):385–92.
[174] Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol 2005;23(15):3376–82.
[175] Gokbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131(14):1522–31.