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Review

New approaches to the treatment of older adults with acute lymphoblastic leukemia ☆

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ABSTRACT

Outcomes for older adults (defined here as ≥55-65 years old) with acute lymphoblastic leukemia (ALL) are poor, with long-term survival less than 20%. Pediatric chemotherapy regimens produce long-term cure rates of 80% to 90% in children and 60% to 70% in adolescents and young adults with Ph-negative ALL, however, tolerability of intensive chemotherapy becomes problematic with advanced age due to comorbidities and reduced tolerability of chemotherapy leading to high rates of treatment-related mortality. For older adults with Ph-positive ALL, BCR-ABL1-directed tyrosine kinase inhibitors in combination with corticosteroids or chemotherapy produce deep remissions with low treatment-related toxicity but optimal postremission therapy is not known. New therapeutic approaches for older adults with ALL involve integration of the novel targeted agents including monoclonal antibody-based therapy with blinatumomab and inotuzumab ozogamicin in the frontline. Ongoing studies will ideally define optimal combinations and sequencing of novel agents with or without chemotherapy, tyrosine kinase inhibitors, and/or corticosteroids to maximize efficacy while avoiding treatment-related death. Anti-CD19 chimeric antigen receptor modified T cells are a promising modality, with high rates of remission and minimal residual disease negativity achieved in early phase trials for adults with relapsed/refractory B-cell ALL but the tolerability of chimeric antigen receptor modified T cell therapies in older adults is yet to be well defined. Advances in minimal residual disease detection have helped to effectively stratify adults in complete response in terms of relapse risk and predicted relative benefit for allogeneic hematopoietic cell transplant. For older adults with ALL in complete response at high risk for relapse for whom myeloablative conditioning is predicted to result in excessive transplant-related mortality, reduced-intensity conditioning allogeneic hematopoietic cell transplant is a less toxic approach for providing a graft-versus-leukemia effect and long-term disease control.

Introduction

Acute lymphoblastic leukemia (ALL) is a rare malignancy with peak incidence in children 1 to 4 years of age. After a declining incidence into mid-adulthood, the incidence of ALL rises again with age such that approximately 20% to 30% of all ALL cases occur in adults 55 years of age and older. Older adults with ALL have dismal outcomes with long-term cure rates that have only modestly improved over the last several decades remaining less than 20% [1-5]. The poor outcomes of older adults are in sharp contrast to those of children and adolescents/young adults with ALL who now have cure rates of about 80% to 90% and 50% to 70%, respectively. Improved outcomes in younger patients can be attributed to high rates of participation in large cooperative group clinical trials and possibly adoption of pediatric-style chemotherapy regimens in adolescents/young adults [6,7]. While the incidence of some poor prognostic cytogenetic and molecular aberrations increases in the older age group, a major reason for inferior outcomes in older adults with ALL is limited tolerability of and high treatment-related mortality (TRM) with dose-intensive, prolonged chemotherapy regimens that achieve high cure rates in younger patients [8]. Additionally, TRM with myeloablative allogeneic hematopoietic cell transplant (alloHCT) increases with age. As such, older adults have not benefited from myeloablative alloHCT, a therapy has been shown to prolong survival among younger adults in first complete response (CR1), especially those with MRD-positivity after initial

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therapy. For Philadelphia chromosome (Ph) positive ALL, which increases in incidence with age and comprises the largest ALL subgroup among older adults, outcomes have improved due to the introduction of highly effective BCR-ABL1-targeted tyrosine kinase inhibitors (TKIs). While Ph-positive ALL was previously associated with a poor prognosis prior to the introduction of TKIs, outcomes now may be better than Ph-negative ALL in older adults [9,10].

Treatment of older adults with ALL may now be changing for the better due to the development of novel antibody-based therapies such as blinatumomab and inotuzumab ozogamicin (InO) now approved for relapsed/refractory (R/R) B-cell ALL and blinatumomab for minimal residual disease (MRD) positive ALL. Novel approaches using these and other agents in the front-line may increase the efficacy of treatment for older ALL while decreasing TRM. Here we review current treatment for older adults with ALL, novel frontline approaches in older adults incorporating blinatumomab and/or InO, the role of reduced intensity conditioning HCT for older adults with ALL, and potential future role of anti-CD19 chimeric antigen receptor modified T cells (CAR-T) in older adults.

Ph-negative ALL – frontline therapy in older adults

Regimens used in older adults with Ph-negative ALL have historically been derived from adult ALL protocols that include dose-intensive multi-agent chemotherapy and intrathecal chemotherapy with or without asparaginase (see Table 1). These regimens are associated with higher rates of treatment TRM and inferior survival in older adults compared to younger adults [11-14]. Lower intensity protocols that employ lower cumulative doses of chemotherapy and omit asparaginase in induction are comparatively better-tolerated in older adults, however long-term survival is limited due to high rates of relapse [15-18].

Pediatric ALL regimens contain high cumulative doses of non-myelosuppressive agents, such as asparaginase, glucocorticoids, and vincristine, that produce long-term cure rates in the majority of patients [6,7]. A major limiting factor of pediatric-inspired regimens in older adults is the inclusion of asparaginase during induction which is associated with major hepatic, thromboembolic, pancreatic, and metabolic toxicities. The upper age limit for tolerability of pediatric-inspired regimens in adults is a matter of debate, though several prospective trials have identified increased treatment-related mortality and asparaginase-related toxicity in adults ≥40- to 55-year old [18-22]. Other groups have shown, however, that modified pediatric regimens may be utilized safely and effectively in fit older adults. In a phase II study of a modified pediatric regimen in adults aged >50-year old with Ph-negative or Ph-positive disease, pegylated asparaginase during induction was associated with severe hepatic toxicity at doses of 2000 U/m^2 or 1500 U/m^2, however liver toxicity was minimal when the dose was reduced to 500 U/m^2 and limited only to Ph-negative patients [23]. The PETHEMA group compared outcomes of adults aged 55 to 65 years enrolled on 1 of 2 pediatric-inspired protocols versus a semi-intensive adult protocol and found that patients treated intensively had higher CR rate (85% vs 64%), lower incidence of relapse (39% vs 60%), and similar, although high, incidence of TRM (28% vs 21%) which translated to superior event-free survival (EFS) at 2 years (37% vs 21%, P= .002) [24]. Other groups have shown safety and feasibility of pediatric-inspired consolidation after semi-intensive induction in older adults [25].

Ph-positive ALL – frontline therapy in older adults

Prior to the advent of BCR-ABL1-targeted TKIs, older adults with Ph-positive ALL had 5-year survival rates of approximately 10%. This was attributable to intrinsic chemotherapy resistance of most Ph-positive ALL, high induction death rates in older adults, and ineligibility for myeloablative allogeneic HCT [26]. With marked single-agent activity and excellent safety profile, TKIs such as imatinib, dasatinib, and ponatinib have changed management of all patients with Ph-positive disease. The addition of imatinib to standard intensive chemotherapy in adults up to age 65 with Ph-positive ALL demonstrated improved survival compared to chemotherapy alone, in large part by facilitating allogeneic HCT in CR1 [27]. Other trials of imatinib added to intensive chemotherapy demonstrated significantly worse outcomes in older compared to younger adults [28].

Frontline therapy for older adults with Ph-positive ALL has evolved toward the use of lower-intensity induction (low-intensity chemotherapy or corticosteroids alone) in combination with second- or third-generation TKIs [29-31]. Induction with a TKI and corticosteroids achieves CR rates of 95% to 100% with rare early deaths although optimal consolidation after CR is not known in older adults and relapse is common with TKI alone, principally due to outgrowth of clones with resistance mutations in the BCR-ABL1 kinase domain [29,32-34]. The second-generation TKIs dasatinib and nilotinib may be superior to imatinib due to activity against a wider spectrum of BCR-ABL1 kinase domain mutations and some penetration into the CNS in the case of dasatinib [35-38]. Ponatinib, a third-generation TKI, may have an advantage over imatinib and second-generation TKIs due to activity against the BCR-ABL1 T315I mutation which is present in approximately 75% of Ph-positive ALL relapsed after complete remission to dasatinib containing therapy [32-34]. Notably, BCR-ABL1 T315I mutant clones can be detected at diagnosis or early in treatment prior to TKI administration providing further support for early administration of ponatinib to potentially improve outcomes in Ph-positive ALL [39,40]. The optimal TKI for Ph-positive ALL is not yet established, but there is evidence that ponatinib containing regimens result in higher rates of CMR, defined as absence of the BCR-ABL1 transcript by quantitative PCR testing with sensitivity of 0.001% to 0.01% [41,42]. Three-month CMR has been shown to be a predictor of overall survival and may also predict which patients can be spared from allogeneic HCT in CR1 [43]. Caution should be emphasized with ponatinib in older adults with respect to cardiovascular toxicity including myocardial infarction and stroke, although this may be mitigated with dose reduction and patient selection [42]. Another open question is whether more intensive chemotherapy provides an advantage over lower intensity approaches in combination with a TKI for fit older adults with Ph-positive ALL, although at least 1 study showed no difference in outcomes between a low- versus high-intensity combination with imatinib for adults up to age 60 [30]. See Table 2 for regimen overview.

Monoclonal antibody-based therapies in older adults with relapsed/refractory ALL

Blinatumomab

Blinatumomab is a bispecific T-cell engaging antibody construct that is designed to direct cytotoxic T-cells to CD19-expressing lymphoblasts, resulting in T-cell activation and lysis of B-cell ALL cells as well as normal B-cells. For adults with R/R Ph-negative ALL randomized to receive blinatumomab or standard chemotherapy in the phase III TOWER trial, patients treated with blinatumomab had higher CR rate (33.6% vs 15.7%, P< .001), better EFS (HR 0.55, P< .001) and better OS (median 7.7 vs 4.0 mo; HR 0.71, P= .01) [44]. Notably, response rate was lower with high bone marrow ALL burden. Patients with less than 50% marrow lymphoblasts at screening had a CR/CRi rate of 66% versus a CR/CRi of 34% for those with 50% or more lymphoblasts in the marrow. Blinatumomab also has activity in R/R Ph-positive ALL, as demonstrated by a 36% CR/CRh rate (including 4 of 10 patients with the T315I mutation) in a phase II

Table 1
Selected regimens for older adults with Ph-negative ALL.

Study	Ph	Induction	Postremission	N	Age, y (range)	CR, %	IM, %	OS
MDACC [11]	±	CPM, VCR, DOX, DEX	HDMTX + araC x4 alternating with CPM, VCR, DOX, DEX x3	122 (≥60y)		84 (≥60y)	10 (≥60y)	20% (5 y, ≥60y)
				409 (<60y)		92 (<60y)	2 (<60y)	48% (5 y, <60y)
UKALL12/E2993[14]	±	Phase 1: DNR, VCR, L-ASP, PDN	INT: HDMTX + ASP x3	100 (55-65y)		73 (≥55y)	18 (≥55y)	21% (5 y, ≥55y)
		Phase 2: CPM, araC, 6MP	CONS: alloHCT, autoHCT, or chemo	1814 (14-54y)		93 (<55y)	4 (<55y)	41% (5 y, all ages)
GRAALL-SA1 [17]	-	C1: DOX (Arm A) or PEG-DOX (Arm B), VCR,DEX	VCR + DOX (Arm A) or PEG-DOX (Arm B) x2 alternating with CPM, araC, 6MP x2	60	55-80	82 (overall)	7 (Arm A)	10 mo (median, both arms)
		C2: DOX (Arm A) or PEG-DOX (Arm B), VCR, DEX, CPM				90 (Arm A)	10 (Arm B)	35% (2 y, Arm A)
						72 (Arm B)		24% (2 y, Arm B)
GMALL [16]	-	Ph1: DEX, VCR, IDA	IDMTX + L-ASP x3 alternating with araC x2, then re-induction with CPM, VCR, IDA, araC	268	67 (55-85)	76	14	23% (5 y)
		Ph2: CPM, araC						
ALLOLD07 [15]	-	Ph1: DEX, VCR, IDA	IDMTX + L-ASP x3 alternating with araC x3	56	66 (56-79)	74	13	12.4 mo (median)
		Ph2: CPM, araC						
DFCI [23]	±	DOX, VCR, PDN, PEG-ASP	CONS1: clofarabine, PDN, PEG-ASP	30	58 (51-72)	67	3	52% (2 y, CR1)
			CNS: DOX, VCR, DEX, 6MP, PEG-ASP					
			CONS2: DOX, VCR, DEX, 6MP, PEG-ASP x 8 cycles					
GRAALL-2005 [22]	±	VCR, DNR, L-ASP, CPM	CONS1: araC, DEX, L-ASP (block I); VCR, MTX, L-ASP, 6MP (block II); MTX, CPM, VP16 (block III)	93 (55-60y)	36	80 (≥55y)	18 (≥55y)	27.4% (5 y, ≥55yo)
		Salvage: IDA, araC	CONS2: same as CONS1	787 (18-60y)		92 (all ages)	6 (all ages)	58.5% (5 y, all ages)
			LI: PDN, VCR, L-ASP, CPM (early CR) or IDA, araC (late CR)					

araC = cytarabine; CPM = cyclophosphamide; CR = complete response; DEX = dexamethasone; DNR = daunorubicin; DOX = doxorubicin; HDMTX = high-dose methotrexate; IDA = idarubicin; IDMTX = intermediate-dose methotrexate; IM = induction mortality; L-ASP = L-asparaginase; N = number of patients; OS = overall survival; PEG-asp = pegylated asparaginase; PEG-DOX = pegylated doxorubicin; PDN = prednisone; Ph = Philadelphia chromosome; VCR = vincristine; y = years; mo, months; 6MP = 6-mercaptopurine.

Table 2
Selected regimens for older adults with Ph-positive ALL.

Study	Regimen	N	Median age, y (range)	CR, %	IM, %	OS
LAL0201-B [28]	Imatinib + prednisone	29	69 (61-83)	100	0	20 mo (median)
MDACC [29]	Imatinib + hyperCVAD	54 (all)	51 (17-84)	93	2	43% (5y, all pts)
		16 (>60y)				14% (5 y, age >60)
LAL1205 [32]	Dasatinib + prednisone	53	54 (24-77)	100	0	69.2 (20 mo)
MDACC [33]	Dasatinib + HyperCVAD	72	55 (21-80)	96	4	52% (5 y)
EWALL-Ph01 [31]	Dasatinib, vincristine, dexamethasone	91	69	96	4	36% (5 y)
CALGB 10701[34]	Dasatinib + dexamethasone induction followed by alloHCT, autoHCT, or chemo	64	60 (22-87)	97	0	55% (3 y)
Korean [36]	Nilotinib + multi-agent chemotherapy	90	47 (17-77)	91	9	72% (2 y)
EWALL-Ph02 [35]	Nilotinib, vincristine, dexamethasone	72	65.5	94	1.3	47 (4 y)
LAL 1811[37]	Ponatinib + prednisone	42	68 (27-85)	95	2.3	87.5% (1 y)
MDACC [39]	Ponatinib + hyperCVAD	86	46 (21-80)	100	0	78% (3 y)

CR = complete response; HyperCVAD = hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone; IM = induction mortality; mo = months; N = number of patients; OS =overall survival; y = years.

Table 3
Novel therapies for adults with relapsed/refractory ALL.

Study	Agent	Eligibility	N	Age, y (range)	Response rate	MRD negative	alloHCT rate	OS, median, months
TOWER [40]	Blinatumomab	R/R Ph- ALL	271	41 (18-80)	34% (CR) 44% (CR/CRh/CRi)	76%	24%	7.7
ALCANTARA [41]	Blinatumomab	R/R Ph+ ALL	45	55 (23-78)	36% (CR/CRh)	88%	25%	7.1
INO-VATE [46]	Inotuzumab ozogamicin	R/R B-ALL	164	47 (18-78)	74% (CR/CRi)	71%	48%	7.7
MSKCC [52]	19-28z CAR T cells	R/R B-ALL	53	44 (23-74)	83% (CR)	47%	39%	12.9
KTE-X19 [53]	CAR T	R/R B-ALL	45	46 (18-77)	68% (CR/CRi)	73%	NR	NR
U Wash [54]	CAR T	R/R B-ALL	53	39 (20-76)	85% (CR)	85%	40%	20 mo (MRD-neg CR) 5 mo (no response)

alloHCT = allogeneic hematopoietic cell transplantation; CRh = complete response with partial hematologic recovery; Cri = complete response with incomplete count recovery; CR = complete response; mo = months; MRD = minimal residual disease; N = number of patients; OS = overall survival; y = years.

trial of adults who were refractory to or intolerant of at least one second- or third-generation TKI [45]. In a phase II single-arm trial of 116 adults with MRD positivity ($\geq 10^{-3}$) in CR after induction, treatment with up to 4 cycles of blinatumomab converted 88% of patients to MRD negativity, which was associated with higher RFS and OS compared to persistently MRD positive patients (38.8 vs 12.5 months) [46].

Two important toxicities observed with blinatumomab are cytokine release syndrome (CRS) and neurotoxicity. High tumor burden was recognized in phase II studies of blinatumomab as a risk factor for CRS, which is mediated by increased levels of inflammatory cytokines related to activated cytotoxic T cells. In later trials, CRS was mitigated by administration of a dexamethasone prephase for patients with a high tumor burden before starting therapy, a step-wise dose escalation during the first cycle, and dexamethasone premedication. The precise mechanism of neurotoxicity with blinatumomab is not known, however prior neurologic events are a risk factor [47,48]. Neurologic events and cytokine release syndrome of grade 3 or higher occurred in 9.4% and 4.9% of patients respectively in the blinatumomab arm on the phase III TOWER trial [44]. In a comparison of older (≥65 years old) to younger adults enrolled on 2 blinatumomab phase II studies, the incidence of grade 3 and higher adverse events was similar between age groups (86% vs 80%) except for grade 3 and higher neurologic adverse events which occurred with greater frequency in older adults (28% vs 13%) [47].

Inotuzumab ozogamicin

Inotuzumab ozogamicin (InO) is an antibody-drug conjugate consisting of an anti-CD22 humanized monoclonal antibody bound to the alkylating agent calicheamicin. In the latest follow-up of a randomized phase III INO-VATE trial of InO versus standard chemotherapy for adults aged ≥18yo with R/R B-cell ALL, patients who received InO had better CR/CRi (73.8% vs 30.9%, $P< .0001$) and longer 2-year OS (22.8% vs 10%; HR 0.75, $P= .0105$) [49]. Hepatic toxicity including veno-occlusive disease/sinusoidal obstruction syndrome (VOD) has been observed with InO, and the risk for developing VOD is increased when allogeneic HCT is performed after InO-based therapy. The frequency of VOD was higher in initial trials where InO was given at a single dose of 1.8 mg/m^2 every 3 to 4 weeks, and lower in subsequent trials where InO was given in weekly fractionated doses [49,50]. In the phase III INO-VATE study, VOD occurred in 14.0% of patients in the InO arm. In a subgroup analysis of INO-VATE that compared older (≥55yo) versus younger (<55yo) adults, older patients who proceeded to alloHCT after InO had higher rate of VOD (41% vs 17%) [51]. See Table 3 for summary.

Investigational regimens – frontline therapy for older adults

Given the marked single-agent activity of blinatumomab and InO in R/R B-cell ALL and the tolerable safety profile of these agents in older adults relative to traditional chemotherapy, several active clinical trials are evaluating these agents in the frontline setting in older adults with B-cell ALL either as monotherapy, given in sequence, or given in combination with chemotherapy or TKIs.

Ph-negative B-cell ALL

For older adults with Ph-negative B-cell ALL, SWOG 1318 (NCT02143414) is evaluating blinatumomab administered for 1 to 2 cycles until CR/CRi, then 3 cycles of blinatumomab as postremission therapy followed by POMP maintenance for 18 months in adults age 65 years or older with newly-diagnosed B-cell ALL. In a preliminary report of 29 patients with median age 75 years (range 66-84 years), 66% achieved CR/CRi with 1-year estimated OS and DFS of 65% and 56% respectively. Among patients in CR/CRi with MRD data, 12 of 13 (92%) achieved MRD negativity [52].

Given the higher response rates seen when blinatumomab is given in setting of low marrow blast percentage, strategies to reduce bone marrow blast percentage prior to blinatumomab are being studied. A single arm, phase II study at MD Anderson is evaluating InO in combination with mini-hyper-CVD (a lower intensity version of the conventional hyper-CVAD regimen) in adults aged 60 years or older with newly-diagnosed Ph-negative B-cell ALL. In the initial version of the protocol, InO was given as a single dose during cycles 1 to 4 of mini-hyperfractionated cyclophosphamide, vincristine, dexamethasone . The protocol was amended after early observation of VOD, and the most recent protocol version involves an InO dosing schema of 0.6 mg/m^2 on day 2 and 0.3 mg/m^2 on day 8 of cycle 1 and then 0.3 mg/m^2 on days 2 and 8 of cycles 2 to 4. Additionally, after completion of the 4 cycles of mini-hCVD plus InO, patients now receive 4 cycles of blinatumomab before proceeding to maintenance. In the latest follow-up, a response rate (CR/CRp/CRi) of 98% with MRD-negativity of 94% was reported in 64 patients (median age 68) treated with the regimen. The overall rate of VOD was 9% and 21 patients (33%) died in CR/CRp, with death in CR/CRp being more common in patients ≥70 years old than in patients 60 to 69 years old (50% vs 22%). The 3-year continuous remission and OS rates in the entire group were 76% and 54% respectively [53]. Randomized study is needed to evaluate this regimen compared to traditional elderly regimens. Given the continued high rates of nonrelapse mortality with chemotherapy in older adults, Alliance 041703 (NCT03739814) is studying lower intensity induction with the highly active agent InO at full dose for 1 to 2 cycles to reduce or eliminate marrow lymphoblasts prior to blinatumomab for 4 to 5 cycles is being investigated in adults 60 years of age or older unfit for allogeneic HCT with newly-diagnosed CD22+ B-cell ALL.

Other strategies being evaluated for fit older adults with Ph-negative B-cell ALL are blinatumomab cycles in consolidation as an addition to intensive chemotherapy (NCT02003222, ECOG 1910), blinatumomab prior to and after standard induction chemotherapy (NCT03541083, HOVON146ALL) and InO in combination with other

Table 4
Investigational studies of novel agents for older adults with newly-diagnosed ALL.

Study	CT Identifier	Phase	Ph	Age, y	Treatment
SWOG 1318	NCT02143414	II	-	≥65	Blinatumomab followed by POMP maintenance
HOVON146ALL	NCT03541083	II	-	18-70	Chemotherapy with 3 cycles of blinatumomab given during prephase, consolidation, and prior to alloHCT or maintenance
ECOG 1910	NCT02003222	III	-	30-70	Chemotherapy → 2 cycles blinatumomab after induction. MRD- after induction randomized to blina versus no blina before consolidation/maintenance.
Alliance 041703	NCT03739814	II	-	≥60	InO followed by blinatumomab
MDACC	NCT01371630	II	-	≥65	InO + low intensity chemo ± blinatumomab, followed by POMP maintenance
EWALL INO	NCT03249870	II	-	≥55	InO + low intensity chemo
GIMEMA D-Alba	NCT02744768	II	+	≥18	Dasatinib + prednisone followed by blinatumomab
MDACC	NCT03263572	II	+	≥60	Blinatumomab + ponatinib
SWOG 1318	NCT02143414	II	+	≥65	Dasatinib + prednisone followed by blinatumomab

alloHCT = allogeneic hematopoietic cell transplantation; CT = clinicaltrials.gov; InO = inotuzumab ozogamicin; MRD = minimal residual disease; Ph = Philadelphia chromosome; POMP = mercaptopurine, vincristine, methotrexate, prednisone; y = years.

low-intensity chemotherapy regimens (NCT03249870, EWALL INO). See Table 4 for summary of regimens.

Ph-positive ALL

In the phase II GIMEMA LAL2116 D-Alba study of adults ≥18 years old with newly diagnosed Ph-positive ALL, dasatinib plus corticosteroid induction is followed by consolidation with dasatinib and blinatumomab for minimum of 2 cycles (maximum of 5 cycles). In a preliminary report of 53 patients with a median age of 54.5 years (range 24-82 years), 56.3% achieved a molecular response after 2 cycles of blinatumomab defined as CMR or positive nonquantifiable response, and the likelihood of achieving a molecular response increased with additional cycles of blinatumomab beyond the first 2 (65.7% after 3rd cycle, 80% after 4th cycle). Twelve-month OS and DFS were 94.2% and 87.8% [54]. SWOG 1318 is evaluating the same combination, except that dasatinib/prednisone and blinatumomab are given sequentially during induction followed by postremission therapy with blinatumomab and dasatinib given in an alternating fashion for 3 cycles followed by maintenance dasatinib (NCT02143414). MD Anderson is evaluating daily ponatinib in combination with blinatumomab for 5 cycles in older or unfit adults with Ph-positive ALL (NCT03263572). See Table 4 for summary of regimens.

Anti-CD19 CAR T

CAR-T involves genetic modification of T cells to express a recombinant receptor directed against a tumor antigen, and currently there is 1 anti-CD19 CAR product that is approved for R/R B-ALL up to the age of 26. Major toxicities associated with anti-CD19 CAR-T are CRS and neurotoxicity both of which can be severe or fatal. Second generation CAR constructs contain either a CD28 or 4-1BB co-stimulatory domain, which enhance T cell toxicity and longevity [55]. In older adults, experience with anti-CD19 CAR T therapy is limited to a small number of patients included in early phase clinical trials. In a phase I trial at Memorial Sloan Kettering, 53 adults (8 over 60 years of age) with R/R B-ALL received lymphodepleting chemotherapy followed by 19-28z CAR-T cells producing a CR rate of 83% and MRD-negativity in 32/48 (67%) who were evaluable. With a median follow-up of 29 months, median RFS and OS were 6.1 months and 12.9 months respectively. Outcomes were correlated with disease burden, such that patients with low disease burden (<5% BM blasts) had a median RFS and OS of 10.6 months and 20.1 months, respectively. Among the 32 patients who achieved MRD-negative CR, 16 (50%) relapsed including 6 who had undergone allogeneic HCT after CAR-T. CRS was observed in 26% of patients with 1 death related to CRS [56] .KTE-X19 is another 19-28z CAR-T product that has been evaluated in adults with R/R B-ALL in a phase I trial. Among 41 adults treated with KTE-X19 who had at least 2 months follow-up, CR/CRi was achieved in 68% and MRD-negativity in 73%. Grade 3 or higher CRS and neurotoxicity occurred in 29% and 38% of patients, and there were 2 deaths related to CRS [57]. Another phase 1/2 trial at the University of Washington is evaluating an anti-CD19 CAR-T construct with a 4-1BB costimulatory domain. Among 59 adults (median age 39 years, range 20-76 years) with R/R B-ALL, 45/53 (85%) evaluable for response achieved MRD-negative CR, which was associated with better EFS (7.6 vs 0.8 months) and OS (20.0 vs 5.0 months). In multivariate analysis for patients who achieved MRD-negative CR, receipt of allogeneic HCT after CAR-T was associated with better EFS (HR 0.39). Two-year estimates of EFS and OS in patients who underwent allogeneic HCT after achieving MRD-negative CR with CAR-T were 61% and 72% respectively, with cumulative relapse incidence of 17% (all CD19+) and TRM of 23% [58]. See Table 3 for summary.

Allogeneic hematopoietic cell transplant

Allogeneic HCT for adults with ALL has been used to reduce the risk of relapse after achievement of CR. In several early donor versus no-donor comparisons of myeloablative conditioning (MAC) allogeneic HCT in adults with ALL in CR1, the benefit of HCT in CR1 was established in terms of increasing long-term leukemia-free survival rates to 45% to 75% versus 30% to 40% with chemotherapy alone [59,60]. A meta-analysis of donor versus no-donor comparison studies showed that the survival benefit for MAC HCT in CR1 was restricted to younger adults (less than 35 years old) [61]. In recent years, detection of residual disease below the minimal CR threshold (MRD) after induction has been recognized as the strongest independent risk factor for relapse regardless of specific MRD assay, timing of assessment, or level of detection [62]. Several groups have demonstrated a DFS benefit for HCT in CR1 for adults with Ph-negative ALL who have detectable MRD after induction, while in contrast those without detectable MRD did not

benefit from HCT [63,64]. For Ph-positive patients, HCT in CR1 has traditionally been recommended. There is emerging data however suggesting that Ph-positive patients treated with TKI-based regimens who achieve an early complete molecular response may have excellent long-term outcomes without allogeneic HCT [35,38].

Reduced intensity conditioning (RIC) allogeneic HCT allows for a graft-versus-leukemia effect with less toxicity in older adults and those with comorbidities or poor fitness. A CIBMTR analysis of 273 adults aged 55 years or older who underwent RIC allogeneic HCT for ALL between 2001 and 2012 reported 3-year NRM, CIR, and OS of 25%, 47%, and 38% respectively. Older age (66+ vs 55-60), disease status (CR1 vs ≥CR2), and lower performance status scores were associated with worse outcomes [63]. Retrospective comparisons of MAC versus RIC for adults undergoing HCT for ALL in CR1 have not demonstrated a survival benefit for one over the other, and the impact of pre-HCT MRD on outcomes according to conditioning intensity has yet to be identified [65-68].

Conclusions

Treatment of older adults with ALL is rapidly evolving now with the advent of novel targeted agents with high efficacy and reduced toxicity. While there is no established standard of care for older adults with newly diagnosed Ph-negative ALL, experience with protocols of standard adult-type or pediatric-based chemotherapy regimens suggest that these regimens result in excessive toxicity and poor outcomes in older adults. It may be possible that low doses of asparaginase during induction and/or intensified asparaginase in consolidation will be tolerated well in older adults, however these are questions that would be best addressed best in the context of a clinical trial. A promising approach for older adults with Ph-negative B-cell ALL is the use of blinatumomab and InO in the frontline setting. Preliminary results from early phase trials of blinatumomab monotherapy and InO in combination with low-intensity chemotherapy show high rates of MRD-negative complete responses, however it is unclear how these regimens compare to anthracycline-based chemotherapy in terms of long-term efficacy. Furthermore, the high rate of death in CR (33%) reported in older patients treated with the InO/mini-hyperfractionated cyclophosphamide, vincristine, dexamethasone regimen suggests potential safety concern of combining InO with chemotherapy in the older population. For older adults with Ph-positive ALL, frontline therapy with a TKI in combination with chemotherapy or corticosteroids is the current standard of care. Though data from head-to-head prospective comparisons of imatinib versus second- or third-generation TKIs are absent, dasatinib or ponatinib appear more effective for achieving an early CMR and reduce the likelihood of relapse with BCR-ABL1 kinase domain mutations. Blinatumomab in the frontline setting for Ph-positive B-cell ALL is also being explored in early phase trials, and preliminary results from the GIMEMA D-Alba study suggest that blinatumomab given after dasatinib/prednisone induction increases the likelihood of achieving a CMR compared to dasatinib/prednisone alone and may lead to durable remissions perhaps by eliminating BCR-ABL1 T315I mutation carrying clones. An unanswered question regarding blinatumomab in the frontline setting is whether the optimal use of this agent is with induction, as prophylactic therapy in case of MRD persistence after induction, or as a routine component of postremission therapy.

For older adults with R/R Ph-negative B-cell ALL, either blinatumomab or InO are appropriate options with the goal of achieving MRD-negative CR ideally followed by allogeneic HCT for those who are HCT candidates. Caution regarding HCT after InO must be emphasized given the risk for developing VOD of the liver. Anti-CD19 CAR-T is being compared to blinatumomab or InO for adults with R/R disease in a planned randomized phase III trial (NCT03628053). For older adults with Ph-negative ALL who have persistent MRD after initial therapy, blinatumomab ideally followed by RIC allogeneic HCT is appropriate. For Ph-positive patients, allogeneic HCT in CR1 remains the standard of care for adults who are HCT candidates. Adults with Ph-positive ALL who achieve an early CMR can have excellent long-term outcomes without allogeneic HCT, however, the ideal postremission therapy after CMR should be addressed in the context of a clinical trial when possible. Given the dismal outcomes of older patients with ALL treated with traditional cytotoxic chemotherapy, progress in treatment ultimately relies on rapid enrollment older adults on clinical trials developing novel approaches with highly active novel targeted agents.

Conflict of interest

The authors, Marc Schwartz, MD and Matthew Wieduwilt, MD, PhD, declare no conflicts of interest.

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