

Management of older adults with acute lymphoblastic leukemia: challenges & current approaches

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Practice points

- The outcomes of older patients with acute lymphoblastic leukemia (ALL) remain poor. Enrollment of these patients on appropriate clinical trials should always be encouraged.
- Treatment with intensive chemotherapy is associated with high morbidity and mortality in older patients. Nonetheless, patients able to receive chemotherapy benefit from it.
- The use of tyrosine kinase inhibitors has dramatically improved the outcomes of Philadelphia-positive ALL. Achievement of molecular remission should be the goal as it results in improved survival.
- There are limited data on the role of allogeneic stem cell transplantation (SCT) in first remission in older patients with ALL, and its use remains controversial. Minimal residual disease assessment may become a useful tool to guide this decision.
- For patients with Philadelphia-positive ALL, the use of autologous SCT in first remission might be associated with outcomes comparable to those achieved with allogeneic SCT.
- The anti-CD19 bispecific T-cell engager antibody, blinatumomab, and the anti-CD22 antibody–drug conjugate, inotuzumab, are now approved for the treatment of patients with relapsed disease.

The management of acute lymphoblastic leukemia (ALL) in older patients is challenging. Older patients often have multiple comorbidities and poor performance status, and disease factors associated with poor prognosis are more common in this age group. Patient and disease-related factors should be taken into account to determine whether intensive therapy is appropriate. The use of comorbidity indices and comprehensive geriatric assessment tools can be valuable in this setting. Fit patients should be considered for aggressive therapies including allogeneic hematopoietic stem cell transplantation, whereas low intensity options may be more suitable for the frail. The Philadelphia (Ph) chromosome is present in up to half of the cases of ALL in older patients. The incorporation of TK inhibitors into the treatment plans of older patients with Ph-positive ALL has improved the outcomes significantly. For less fit patients with Ph-positive ALL, the use of TK inhibitors with reduced-intensity chemotherapy or steroids alone results in high rates of remission, but, without further consolidation, relapses are inevitable. Many novel targeted and immunotherapeutic agents are being developed, offering more effective and tolerable treatment options.

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Approximately 20–30% of all acute lymphoblastic leukemia (ALL) cases occur in patients older than 55–60 years [1–4]. While the long term outcomes of ALL have improved significantly in the pediatric population and to a lesser extent in young adults, elderly patients still have a very poor prognosis [2,3,5]. Half of the deaths from ALL occur in patients older than 55 years and their 5-year overall survival (OS) rate is at or below 10–20% [1,2,5,6]. The age cutoff to define elderly may vary, but as adopted in most clinical trials, 55–60 years will be used here in this review. The relatively low-age cutoff reflects the substantial challenges in treating this patient population. This review article focuses mainly on studies related to older patients with ALL. If not available, studies that included both younger

and older patients were included, with points/outcomes related to older patients highlighted. Randomized clinical trials and studies published in the last 5 years, whenever available, were emphasized.

Older patients with ALL commonly have multiple comorbidities and poor performance status and less often participate in clinical trials or receive intensive therapy [2,3,6]. As discussed later in this review, the inability to deliver optimal therapy to older patients and the higher induction death rate are important factors that contribute to the poor outcomes seen in older patients with ALL. However, even in studies looking at 'fit' patients treated with intensive chemotherapy, older age was associated with worse outcomes highlighting different disease biology in this group [2,7]. Factors associated with poor outcomes are more common in elderly patients, and include poor-risk cytogenetics such as the Philadelphia (Ph) chromosome, B-cell immunophenotype and secondary ALL [2].

Approach to treatment of elderly patients with ALL

The first step in treating older patients with ALL is to assess their ability to undergo aggressive therapy. Chronological age alone does not necessarily provide enough information regarding an individual's fitness or frailty, and other important determinants have to be considered. These include the presence of medical comorbidities, cognitive decline, polypharmacy, poor functional status, malnutrition, depression, and lack of social support [8]. Comorbidity burden can be measured by standardized indices such as the Charlson comorbidity index and the hematopoietic cell transplantation comorbidity index. In addition, there are various geriatric assessment tools that incorporate assessment of multiple other domains including cognitive and social function [9]. These have shown to provide valuable information in predicting treatment-related toxicities when applied in older patients with acute myeloid leukemia treated with intensive chemotherapy regimens [10–12]. Patients deemed unfit for intensive chemotherapy can be considered for less intensive approaches or supportive care only. Enrollment on appropriate clinical trials should always be encouraged, especially for this age group, given the paucity of data and the very poor outcomes achieved with current therapies.

Induction

Most ALL induction regimens include vincristine, a corticosteroid, and an anthracycline as a backbone, with other agents such as methotrexate, cytarabine, and cyclophosphamide often added. Asparaginase is also used in many regimens after it demonstrated efficacy in the pediatric population. Pegylated-asparaginase has replaced native *Escherichia coli* asparaginase as it offers a longer half-life and a lower risk of anti-asparaginase antibody formation [13]. Asparaginase is typically given at lower doses in older patients, given its considerable toxicity, especially hepatotoxicity, pancreatitis, and thrombosis [14–16].

Data have demonstrated that elderly patients may derive a benefit from intensive chemotherapy, although less than half of them are able to receive it [2,3,6]. In an analysis of 100 patients with ALL between the ages of 55 and 65 years treated with intensive chemotherapy, drug-dose reductions, omissions or delays occurred in approximately 50% of patients [14]. Intensive multiagent chemotherapy regimens in older populations achieve complete response (CR) rates of around 50–70%, with treatment-related mortality rates approaching 20–40% (Table 1) [1,2,6,17,18].

The GMALL group conducted the largest prospective trial in 268 older patients with newly-diagnosed Ph-negative ALL, using a dose-reduced pediatric-based (Berlin–Frankfurt–Munster) induction regimen [18]. The median age was 68 years, with 51% of patients aged between 66 and 75 years and 10% above 75 years. The induction regimen was divided into two phases (idarubicin, vincristine, and dexamethasone in Phase I, and cyclophosphamide and cytarabine in Phase II), followed by six alternating consolidation courses of intermediate-dose methotrexate and asparaginase with high-dose cytarabine for 1 year, and maintenance therapy up to 2 years. Eight treatments with rituximab were added for patients with CD20⁺ disease. The overall CR and early death rates were 76 and 14%, respectively (the CR and early death rates for the different age groups were: 84 and 7% in patients aged 55–65 years, 74 and 14% in patients aged 66–75 years, and 52 and 37% in patients older than 75 years). The 5-year OS rate was 23%. In a large single-center retrospective study, MD Anderson reported their experience with 122 older (≥60 years) patients with ALL treated with eight alternating courses of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone) with high doses of methotrexate and cytarabine followed by maintenance with 6-mercaptopurine, vincristine, methotrexate, and prednisone (POMP), and compared their outcomes with 34 older patients who received less intensive regimens and 409 younger patients treated with hyper-CVAD [19]. The CR rate was 84% for older patients treated with hyper-CVAD, 59% for older patients treated with less intensive regimens, and 92% for younger patients treated with hyper-CVAD, with treatment related mortality rates of 10, 12 and 2%, respectively. Infections were the major cause of death. In patients

Table 1. Selected studies of induction chemotherapy regimens in older patients with acute lymphoblastic leukemia.

Year [†]	Group/study	Age	No. of patients	CR rate %	Induction/early death rate %	OS rate %		
						1 year	3 years	5 years
2000	MD Anderson [69]	>60	44	79	16			17
2001	SWOG 8419 [70]	50–84	85	41	37			<10
2002	GIMEMA 0208 [71]	50–60	121	68	–			15
2005	CALGB [72]	>60	129	57	–		12	
2007	PETHEMA ALL96 [‡] [17]	56–67	33	58	36			39
2008	SWOG 9400 [73]	50–65	43	63	–			23
2008	EWALL [74]	56–73	40	85	0	61		
2012	MRC UKALL XII/ECOG2993 [14]	55–64	100	70	18			21
2012	GMALL [‡] [18]	55–85	268	76	14			23
2016	Multicenter [39]	51–72	30	67	3	63		
2016	PETHEMA, ALLOLD07 [‡] [75]	56–79	54	74	13	50		

[†] Year of study publication.
[‡] Included patients with Ph-negative ALL only.
 ALL: Acute lymphoblastic leukemia; CR: Complete response; OS: Overall survival; Ph: Philadelphia.

treated with hyper-CVAD, death in CR occurred in 34% of older patients and 7% of younger patients. The 5-year OS rates were 20, 9, and 48%, respectively [19].

Given the pronounced myelosuppression from both ALL and disease-directed therapy, particularly in older patients, supportive therapy with blood product transfusions, granulocyte colony-stimulating factor (CSF) and prophylactic antibiotics is a crucial component of ALL induction therapies. The use of granulocyte-CSF is associated with a shorter duration of neutropenia, a lower rate of neutropenic fever and a higher CR rate, but with no significant effect on survival [20].

CNS prophylaxis

As the CNS is a sanctuary site for ALL, prophylaxis with intrathecal chemotherapy given at intervals throughout induction and postremission therapy is an essential part of ALL treatment protocols. Methotrexate, cytarabine and steroids are the most commonly used intrathecal agents for CNS prophylaxis. In contrast to other TKI inhibitors (TKIs), dasatinib crosses the blood–brain barrier; however, it results in low CSF levels, and prophylaxis with intrathecal chemotherapy is still recommended [21–23].

Ph-positive ALL

Approximately half of the elderly patients with ALL have the Ph chromosome, making it the most common cytogenetic abnormality in this age group [24,25]. While the Ph chromosome has historically been associated with worse outcomes, this has improved with the introduction of the TKIs [25,26]. For example, a Swedish population-based study of 155 older patients with ALL showed no evidence of worse outcomes for those with Ph-positive ALL [26]. Further, in a multicenter, retrospective study of 98 elderly patients, those with Ph-positive ALL (n = 47) treated with induction chemotherapy and TKI (87% with imatinib) had superior OS compared with patients with Ph-negative ALL treated with similar chemotherapy alone (median 12 vs 8 months; p = 0.037) [25].

For patients unfit for intensive chemotherapy, TKIs can be combined with steroids alone or with low-intensity chemotherapy regimens. Most patients achieve complete hematologic responses with such an approach but remissions are usually short-lived (Table 2) [27,28]. TKIs also provide deeper responses and better outcomes when combined with intensive chemotherapy regimens [29]. In a study by the GMALL group of 55 elderly patients with Ph-positive ALL, induction with imatinib was associated with significantly higher CR rates than with multiagent chemotherapy (96 vs 50%) and had lower toxicity [30]. In the LAL0201 trial, 30 newly diagnosed elderly patients with Ph-positive ALL (median age 69 years, range 61–83) received induction with imatinib plus prednisone for 45 days. Imatinib was then continued in responding patients. All evaluable patients achieved complete hematologic responses. The 1-year OS and disease-free survival (DFS) rates were 74 and 48%, respectively. Treatment was well tolerated with no major toxicities [27]. The GRAAPH-2005 study randomized 268 patients younger than 60 years with Ph-positive ALL to receive imatinib combined with hyper-CVAD or imatinib combined with dexamethasone

Table 2. Selected studies in older patients with Ph-positive acute lymphoblastic leukemia.

Year [†]	Group/study	Treatment		Age	No. of patients	CR rate %	OS rate %
		Induction	Postinduction				
2006	GRAALL AFR09 [76]	CTX	Imatinib + CTX	58–78	30	72	66 (1 year)
2007	GIMEMA LAL0201-B [27]	Imatinib + pred	Imatinib + PC	61–83	30	100	74 (1 year)
2007	GMALL [30]	Imatinib	Imatinib + CTX	54–79	28	96	57 (1.5 years)
		CTX	Imatinib + CTX	58–78	27	50	41 (1.5 years)
2011	GIMEMA LAL1205 [28]	Dasatinib + pred	Dasatinib + PC	24–77 [‡]	54	100	69 (1.5 years)
2015	MD Anderson [22]	Dasatinib + CTX	Dasatinib + CTX	21–80 [§]	72	96	46 (5 years)
2015	MD Anderson [33,34]	Ponatinib + CTX	Ponatinib + CTX	21–80	64	98	76 (3 years)
2016	EWALL-PH-01 [32]	Dasatinib + CTX	Dasatinib + CTX	59–83	71	96	36 (5 years)

[†] Year of study publication.
[‡] 12 patients >60 years.
[§] 46 patients >50 years.
 ALL: Acute lymphoblastic leukemia; CR: Complete response; CTX: Chemotherapy; OS: Overall survival; PC: Physician choice; Pred: Prednisone.

and vincristine, with both groups receiving high-dose methotrexate and cytarabine in combination with imatinib as a second cycle. Higher CR rates were achieved with imatinib in combination with low-intensity chemotherapy (98 vs 91%), with no significant difference in event-free survival (EFS) and OS at 3 years between the two groups [31].

Clinical trials using the second-generation TKI, dasatinib, in patients with newly diagnosed Ph-positive ALL followed. In the LAL1205 study, 53 patients were treated with dasatinib for 12 weeks plus prednisone (12 patients were older than 60 years). All patients achieved complete hematologic response with more than half of them achieving major molecular response (MMR) by the end of the treatment. The treatment was well tolerated but more than half of the patients relapsed by 2 years [28]. Subsequently, the EWALL-PH-01 study combined dasatinib with low-intensity chemotherapy (induction with vincristine and dexamethasone and consolidation with methotrexate, asparaginase and 6-mercaptopurine) in 71 patients (median age 69 years, range 59–83) [32]. Dasatinib was continued until relapse or death. The CR rate was 96% with 65% of the patients achieving MMR. The treatment-related mortality rate was 4%, while the 1-year relapse-free survival (RFS) was 58% and 5-year OS was 36% [32].

A single-institution study evaluated the combination of dasatinib with hyper-CVAD in 72 patients with a median age of 55 years (64% of patients were older than 50 years). Patients who achieved CR were started on maintenance therapy with dasatinib, vincristine, and prednisone. The combination was highly effective with a CR rate of 96% and a complete molecular response rate of 65%. The median DFS and OS were 31 and 47 months, respectively. However, more than half of the patients could not receive the eight planned induction chemotherapy cycles due to poor tolerance (43%) or early death (13%). Serious infections occurred in more than 60% of the patients during induction and in more than 90% during consolidation [22].

Ponatinib is a potent third generation TKI that has activity in patients harboring the T315I BCR-ABL mutation which has been implicated in the development of resistance to other TKIs at the time of relapse [22,32]. A single-center Phase II trial evaluated ponatinib in combination with hyper-CVAD in 64 patients (the median age was 48 years, range 21–80). The CR rate was 98% with remarkably high MMR and complete molecular response rates of 97 and 77%, respectively. The 3-year OS rate was 76%. Ponatinib dose had to be reduced due to serious vascular events (three cases of myocardial infarction with two deaths). Other serious toxicities included pancreatitis in 19% and other thrombotic events in 6% [33,34]. In a propensity score analysis of patients treated on the previously mentioned Phase II trials of hyper-CVAD with either dasatinib or ponatinib, the 3-year EFS and OS rates were significantly higher in patients treated with ponatinib (for EFS: 69 vs 46% and for OS: 83 vs 56%). Ponatinib achieved deeper molecular responses and higher minimal residual disease (MRD) negativity [35].

Postremission therapy

The optimal postremission treatment strategy for older patients with ALL is not well established. Options include consolidation/intensification plus maintenance chemotherapy, autologous hematopoietic stem cell transplantation (SCT) or allogeneic SCT. Toxicity and poor tolerance often preclude the use of intensive and prolonged postremission chemotherapy in older patients. Different protocols incorporate different chemotherapeutic agents but they

are, in general, similar to those used for induction albeit given at lesser intensities. For patients with Ph-positive ALL, TKIs are typically continued indefinitely, particularly for those who do not proceed to allogeneic SCT.

Autologous SCT

For patients with Ph-negative ALL, autologous SCT is not recommended as postremission therapy as it has not been shown to be associated with better outcomes compared with chemotherapy alone or allogeneic SCT [36]. However, for Ph-positive ALL, incorporating TKIs with autologous SCT seems to be an effective treatment strategy and may achieve outcomes comparable to those achieved with allogeneic SCT. This was shown in a study of 59 patients with Ph-positive ALL with an upper age limit of 66 years who were treated with imatinib plus chemotherapy. Patients in CR were eligible to receive allogeneic SCT or autologous SCT followed by maintenance with imatinib. The 5-year OS was similar between the allogeneic SCT (n = 45) and autologous SCT plus maintenance (n = 9) groups [37]. Similarly, the GRAAPH-2005 study of patients younger than 60 years with Ph-positive ALL showed no significant difference in RFS and OS in patients who received autologous (n = 35) or allogeneic (n = 161) SCT [31]. A smaller study by the CALGB group demonstrated similar findings (19 patients received autologous and 15 allogeneic SCT) [38]. Treatment using a TKI in combination with low-intensity chemotherapy initially, then more intensified chemotherapy in subsequent cycles followed by consolidation with autologous SCT is emerging as a promising approach, but more data are still needed given the relatively small numbers of patients treated in clinical trials so far [31,38].

Allogeneic SCT

Few studies have looked at the role of consolidative allogeneic SCT in older patients with ALL. A small Phase II study of 30 patients with a median age of 58 years (range 51–72) showed no survival advantage for the 12 patients who received allogeneic SCT over consolidation with chemotherapy [39]. A retrospective study of 80 patients older than 40 years with Ph-negative ALL showed no difference in the 3-year DFS and OS between patients who received chemotherapy only or allogeneic SCT in first remission. While allogeneic SCT was associated with a lower risk of disease relapse, the benefit was abrogated by the higher nonrelapse mortality rate [40]. Similarly, a meta-analysis that included more than 2900 patients with Ph-negative ALL showed a survival benefit with matched sibling donor myeloablative allogeneic SCT only in patients younger than 35 years. The lack of benefit in the older patients was due to the associated high nonrelapse mortality rates [41]. The GRAAPH-2005 study previously mentioned showed a significant survival benefit with the use of allogeneic SCT versus chemotherapy alone in patients with Ph-positive ALL in first CR (hazard ratio = 0.64; p = 0.02); however, only patients younger than 60 years were included [31]. Similar studies in older patients with Ph-positive ALL are lacking.

The role of allogeneic SCT in patients with ALL in first remission remains a topic of debate. With the better outcomes achieved with current induction strategies, especially the use of TKIs in Ph-positive ALL, more patients are able to achieve remission and with less toxicity [31]. In addition, the use of reduced intensity conditioning regimens and the improvement in supportive care have extended the base of eligibility for transplantation [31]. On the other hand, the limited data available do not show a survival advantage with the use of allogeneic SCT for older patients [39–41]. MRD assessment is emerging as an important tool for risk stratification and determining the need for allogeneic SCT. Two studies of younger patients (less than 55–60 years of age) with high risk, Ph-negative ALL in first CR have indicated that allogeneic SCT might not be needed in patients with negative MRD [42,43]. Such studies are lacking in patients with Ph-positive ALL, but the deep remissions reported with the combination of chemotherapy and TKIs suggest the same [35], though this is yet to be confirmed. However, it is important to keep in mind that the definition of negative MRD and when to test for it are not yet standardized, and that older patients were not included in these studies. MRD assessment has become a key element in ALL clinical trials, and its role in treatment selection remains an area of active research.

Treatment of relapsed disease

The relapse rate for patients with ALL remains high and achieving a second remission is difficult [44]. This is even more challenging for elderly patients where the treatment options with conventional chemotherapy are very limited by the poor outcomes and excessive toxicities [44]. Novel immune-based therapies targeting various surface antigens expressed on ALL cells have demonstrated very encouraging results in this setting and have changed the treatment paradigm of ALL.

Anti-CD19 bispecific t-cell engager: blinatumomab

Blinatumomab is a bispecific T-cell engager antibody against CD3 and CD19 that is designed to direct cytotoxic T cells to CD19-expressing B cells [45]. Blinatumomab is currently approved by the US FDA for relapsed/refractory Ph-negative and Ph-positive ALL, and the EMA for relapsed/refractory Ph-negative ALL. The large Phase III multicenter TOWER study compared blinatumomab with standard-of-care chemotherapy in patients with relapsed/refractory Ph-negative B cell ALL. The mean age was 41 years (range 18–80). Blinatumomab resulted in significantly higher remission rates (44 vs 25%) and improvement in 6-month EFS (31 vs 12%) and OS (7.7 vs 4 months) [46]. The single-arm, multicenter ALCANTARA trial evaluated the role of blinatumomab in 45 patients with Ph-positive ALL who had relapsed or were refractory to TKIs. Half of the patients were older than 55 years. The CR rate was 36% with 88% of responders achieving MRD negativity. The median duration of response was 6.7 months [47].

Notably, blinatumomab seems to have similar clinical efficacy irrespective of age. In a pooled analysis from two Phase II studies of patients with relapsed/refractory B cell ALL treated with blinatumomab, older patients had CR/CR with incomplete hematologic recovery (CRh) and MRD negativity rates similar to younger patients [48]. Cytokine release syndrome and neurological toxicities including encephalopathy and seizures are the main serious toxicities of blinatumomab, and are more common in older patients [47,48].

With these very promising results in patients with relapsed/refractory B-cell ALL, blinatumomab is currently being studied in the upfront setting. An ongoing Phase III randomized trial (ECOG E1910, NCT02003222) is evaluating the role of consolidation with blinatumomab following induction with intensive chemotherapy in patients between the ages of 30 and 70 years with newly diagnosed Ph-negative ALL. A Phase II trial (SWOG S1318, NCT02143414) is currently evaluating the role of frontline therapy with blinatumomab in patients 65 years or older who are not candidates for intensive chemotherapy. In this trial, patients with Ph-negative ALL receive induction and postremission therapy with blinatumomab followed by maintenance with POMP, while those with Ph-positive ALL receive induction with dasatinib and prednisone, postremission therapy with blinatumomab followed by maintenance with dasatinib and prednisone.

Anti-CD22 antibody–drug conjugate: inotuzumab

CD22 is expressed in more than 90% of patients with B-cell ALL making it an attractive therapeutic target [49]. Inotuzumab ozogamicin is an anti-CD22 monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic. It is currently approved for the treatment of relapsed/refractory B cell ALL by the EMA and the FDA. The INO-VATE ALL trial was a large Phase III study that randomized patients with relapsed/refractory B-cell ALL to receive either inotuzumab or standard intensive chemotherapy [50]. Inotuzumab was shown to be associated with significantly higher CR rates (81 vs 29%), higher MRD negativity (for patients in CR: 78 vs 28%) and longer PFS (5 vs 2 months). Importantly, more than a third of the patients were older than 55 years, and in those treated with inotuzumab, the CR and MRD negativity rates were similar to those in younger patients [50]. In two single-center Phase II trials of patients with Ph-negative, CD22-positive ALL, inotuzumab was combined with lower-intensity or ‘mini’ hyper-CVAD with or without rituximab in the frontline and salvage settings [51,52]. In newly diagnosed patients who were 60 years or older (n = 43), the combination resulted in CR/CR with incomplete platelet recovery rate of 95% and MRD negativity in 96%. The 3-year OS was 54%, which compared favorably with historical controls treated with hyper-CVAD alone (3-year OS of 31%) [51]. In the salvage setting (n = 59, median age of 35 years, range 18–87), the overall response rate was 78% with 59% of the patients achieving CR. For patients in CR, the rate of MRD negativity was 82%. The median RFS and OS were 8 and 11 months, respectively. Using a propensity score analysis to compare the results with historical controls treated with inotuzumab monotherapy, the combination resulted in significantly higher overall response rate (75 vs 63%) and 1-year OS (43 vs 27%) [52]. Venous-occlusive liver disease has been reported in 10–15% of patients treated with inotuzumab, with higher risk in patients undergoing allogeneic SCT [50–52].

Other therapies

Vincristine sulfate liposome injection

Vincristine sulfate liposome injection (VSLI) is a modified formulation of vincristine with enhanced stability and better tissue penetration compared with the standard formulation [53,54]. Despite being given at a higher dose (2.25 mg/ml [2]) and without dose capping, its toxicities, mainly peripheral neuropathy and constipation, do not occur at a frequency higher than with the standard formulation. Further, it does not typically cause bone marrow

suppression and is given on a once-per-week basis. In a Phase II trial of 65 patients with ALL with second or greater relapse, who were previously treated with standard vincristine, the CR/CRh rate with VSLI was 20%, with an overall response rate of 35% [55]. VSLI is used off label as monotherapy in the frontline setting for unfit patients.

Nelarabine

Nelarabine, a purine nucleoside analog, has single agent activity in both adults and children with T-cell ALL, and is currently approved in the USA for the treatment of patients with relapsed/refractory T cell ALL. In two Phase II trials of adult patients with relapsed/refractory T-cell ALL or lymphoblastic lymphoma treated with nelarabine monotherapy, the overall response rate was 41–46%, with a 1-year OS rate of 24–28% [56,57]. Neurotoxicity, including neuropathy, mental status change, and seizures, has been reported in up to 16% of patients, but is usually mild and reversible (grades 3 and 4 in less than 5%) [56,57]. In a Phase II trial of 40 adult patients with T-cell ALL or lymphoblastic lymphoma (median age of 38 years, range 19–78), the combination of nelarabine and hyper-CVAD as frontline therapy resulted in a CR rate of 91% with a 3-year DFS of 63% [58].

Anti-CD20 monoclonal antibodies: rituximab & ofatumumab

CD20 expression of more than 20% is found in approximately 30–40% of patients with B-ALL and is associated with a poor prognosis [49,59]. The anti-CD20 monoclonal antibody, rituximab, has shown clinical benefit when combined with intensive induction chemotherapy regimens in patients younger than 60 years with newly diagnosed, CD20 positive, Ph-negative ALL (4-year EFS of 55% with the combination vs 43% with chemotherapy alone) [60]. However, similar clinical trials are lacking in elderly patients. In fact, a single-center study of patients with CD20 positive ALL showed no benefit from adding rituximab to modified hyper-CVAD in patients older than 60 years when compared with historical controls treated with the standard hyper-CVAD regimen alone [61]. Rituximab is therefore not recommended as part of induction or maintenance therapy for elderly patients. Ofatumumab is a second generation anti-CD20 that binds with greater avidity than rituximab. A single-center Phase II study combined ofatumumab with hyper-CVAD in 55 patients with newly diagnosed CD20 positive ALL (median age 41 years, range 18–71). Interim analysis showed an MRD negativity in 93% of the patients and 3-year CR and OS rates of 78 and 68%, respectively [62]. These results compare favorably with those achieved historically with rituximab, and suggest a potential role for ofatumumab and other next generation anti-CD20 antibodies in the treatment of ALL.

Chimeric antigen receptor T cells

The chimeric antigen receptor (CAR) is composed primarily of a single-chain antibody specific to tumor antigen, fused to T-cell activation and co-stimulatory domains. The resulting receptor, when expressed on the surface of the T-cell, mediates binding to the target tumor antigen, independent of MHC recognition, and subsequently activates the T-cell and induces target cell lysis [63]. CAR T-cell therapy has been explored in multiple hematologic malignancies with the most mature data in ALL, where it has been approved by the FDA for the treatment of pediatric and young (<25 years) adult patients with relapsed/refractory B-cell ALL. The approval was based on the updated results of the Phase II clinical trial, ELIANA, of pediatric/young adult patients with relapsed/refractory B cell ALL treated with CTL019 (tisagenlecleucel) CAR T cells. Of the 75 evaluable patients, 81% achieved CR/CRh within 3 months of CAR T-cell infusion, with all patients achieving MRD negativity. The 1-year EFS and OS rates were 50 and 76%, respectively [64,65]. A Phase I trial in adult patients with heavily pretreated relapsed/refractory ALL treated with 19–28z CAR T cells has also shown very promising results, although the number of treated patients is relatively small and longer follow-up is needed [66]. Of the 53 patients treated with CAR T cells and evaluated for safety and efficacy (83 patients were enrolled onto the trial), 44 patients (83%) achieved CR, and 67% achieved MRD negativity (48 patients had sufficient bone marrow samples for evaluation of MRD status). With a median follow-up of 29 months, the median EFS and OS were 6 and 13 months, respectively. There was no significant difference in the rate of CR in the 8 patients older than 60 years compared with younger patients (the median age for treated patients was 44 years, range 23–74). Severe cytokine release syndrome and neurotoxic effects occurred in 26 and 42% of the patients, respectively, and were not more common in older patients [66].

Ph-like ALL

A subset of patients with Ph-negative ALL has a gene expression profile similar to those with Ph-positive ALL. This entity of Ph-like ALL is associated with poor outcomes [67,68]. The prevalence of Ph-like ALL in patients 60 years

or older is around 25%. Kinase-activating alterations are present in the majority of patients and include CRLF2 rearrangements, ABL class fusions, JAK2 or EPOR rearrangements and other JAK-STAT pathway mutations [67,68]. Importantly, the activation of the ABL1 and JAK/STAT pathway might be a therapeutic target for several ABL inhibitors, such as imatinib and dasatinib and JAK kinase inhibitors, such as ruxolitinib. Clinical trials in this area are ongoing.

Conclusion & future perspective

The introduction of several novel antibody-based, targeted, and cellular therapies has changed the treatment paradigm of ALL, with many more agents targeting the diverse molecular and genetic alterations in ALL in development. Elderly patients, in particular, are in dire need for novel therapies as treatment with conventional chemotherapy has been associated with poor outcomes and unacceptable toxicities. The high remission rates achieved with second and third generation TKIs cast doubt on the need to use intensive chemotherapy and transplant in Ph-positive ALL, particularly for older patients. Several challenges exist including finding the appropriate sequencing of different therapies, knowing how to incorporate MRD assessment in the decision making process, and management of a new set of toxicities that might be more common in elderly patients. For these reasons, the need to enroll older patients with ALL on appropriate and well-designed clinical trials cannot be overstressed enough.

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