Treatment of older patients with acute lymphoblastic leukemia

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The treatment of older patients with acute lymphoblastic leukemia (ALL) is an unmet medical need. With increasing age, ALL patients have a significantly lower clinical remission rate, higher early mortality, higher relapse rate, and poorer survival compared with younger patients. This is only partly explained by a higher incidence of poor prognostic factors in the older age group. Most importantly, intensive chemotherapy with or without stem cell transplantation (SCT) is less well tolerated in older patients. Some progress has been made with delivering age-adapted, moderately intensive chemotherapy protocols for Ph/BCR–ABL-negative ALL and combinations of tyrosine kinase inhibitors with chemotherapy in Ph/BCR–ABL-positive ALL. For the future, optimizing supportive care, introducing targeted therapies, novel immunotherapies, moderately intensified consolidation strategies, and reduced intensity SCT are promising approaches. Prospective clinical trials for older patients are urgently needed to test these approaches.

Learning Objectives

- Understand the challenges in the management of older patients with ALL
- Get an overview on published treatment results
- Identify optimized treatment strategies for older ALL patients

Introduction

Acute lymphoblastic leukemia (ALL) is often perceived as a pediatric malignancy due to the peak incidence at the age of 1 to 4 years. However, the incidence of ALL also increases in the older population. Excellent cure rates are achieved with intensive chemotherapy in pediatric ALL patients and in younger adults up to the age of 40 to 55 years. However, it remains a considerable challenge to define adequate regimens for older adults with ALL. Therefore this article will focus on patients >55 to 65 years.

There is one fundamental problem: ALL can be cured with time and dose-intensive chemotherapy, yet the delivery of both is less feasible with increasing age. Although the incidence of biological features associated with poorer prognosis increases slightly with older age, the lower tolerability of treatment is probably the major reason for poorer outcomes in older ALL patients. Furthermore, there is a vicious cycle starting from poor results and ending with the lack of large randomized prospective trials from which outcomes can be reported (Table 1). Overcoming this challenge will only occur if physicians realize that there is an urgent need for standardized treatment schedules adapted to the feasibility of delivering them to older patients, including older patients in clinical trials or establishing prospective registries, and introducing new treatment regimens with the addition of targeted compounds to dose-reduced chemotherapy to improve antileukemic activity.[1]

Unique clinical and biological considerations in older ALL patients

Biological features

The proportion of B-lineage ALL is higher (75% to 89% vs 59% to 66%) in patients >60 years vs <60 years[1] and the incidence of t(9;22) (Ph+) or complex aberrations increases[2]; Ph+ ALL accounts for 24% to 36% vs 15% to 19% in younger patients.[1] Also, other poor biological factors increase with age. In a mixed cohort of ALL patients, a significantly higher incidence of *TP53* mutations was observed in patients older vs younger patients <60 years (25% vs 11%).[3] The incidence of Ph-like ALL appears to be higher in adolescents and young adults.[4] In a cohort of 95 patients with B-precursor ALL, negative for *BCR-ABL1* and mixed lineage leukemia (MLL) rearrangements, and a median age of 42 years, the incidence of Ph-like ALL was 27%.[5] There was no linear increase of incidence with increasing age.[6] In another cohort of 132 adult precursor B-cell ALL patients (excluding *BCR-ABL1*, *MLL-AF4*, and *E2A-PBX1)* with a median age of 54 years, the overall incidence of Ph-like ALL was 10% and the incidence in patients >40 years was 8%.[7] In a large cohort of 692 patients with B-precursor ALL (including *BCR-ABL1* and MLL-rearranged cases), the incidence of Ph-like ALL was 24% with no increase in patients >40 years (20%) compared with younger ones (26%).[8] Prospective identification of Ph-like ALL is not part of the standard care of adult ALL so far. However, specific tests may be helpful to identify targetable lesions such as Jak2-mutations in patients with poor response or recurrence.

Clinical features

Features associated with a large tumor mass or rapid progression such as high white blood cell count, mediastinal tumors, or other organ involvement appear to be less common in older patients.[1] Performance status frequently deteriorates in older patients with the onset of disease. In 2 studies, 30% to 43% of older patients compared

Conflict-of-interest disclosure: N.G. has received research funding and honoraria for consultancy or speaker activities from Amgen, Pfizer, Jazz, Gilead Sciences, Sigma Tau, Baxalta, and Novartis.

Off-label drug use: None disclosed.

Table 1. Issues with the management of older ALL patients

Issues
Poorer results in older ALL patients
Negative perception of cure rates by physicians
Less recruitment into clinical trials
Limited biological studies
Lack of prospective clinical trials
Heterogeneity of patient characteristics
Increase of poor prognostic features
Higher mortality and morbidity from chemotherapy
Variety of dose reductions and low time/dose intensity

with 18% to 22% of those <60 years had a performance status of 2 or more at diagnosis.[1]

Secondary ALL

Although rare, secondary ALL may become increasingly important, particularly in older patients. The most frequent primary malignancies are breast cancer, non-Hodgkin lymphoma, and Hodgkin lymphoma with a latency period of median 60 months.[9] Patients with secondary ALL are generally older (median age at onset: 62 years) compared with patients with de novo ALL (44 years) and have a significantly poorer survival.[9]

Comorbidity scoring and complete geriatric assessment

Sixty to 84% of older ALL patients suffer from comorbidities.[1] Diabetes (46%), vascular disease (18%), heart failure (15%), and chronic lung disease (12%) are frequently observed.[10] Renal insufficiency, cardiac or vascular diseases, osteoporosis, dementia, and depression are also relevant for potential adjustment of treatment. It is essential for treatment scheduling to gain a complete and structured overview on comorbidities, including current medications.

Prognostic factors in older ALL patients

Increasing age at presentation is one of the most relevant prognostic factors for outcome of ALL and this correlation is evident within pediatric ALL populations.[11] Because older patients experience higher mortality and relapse rates, prognostic factors for both of these types of events have to be analyzed. Prognostic factors for relapse risk in younger ALL patients[11] are probably also valid in older patients, such as early T-cell ALL, pro–B-cell ALL, elevated white blood cell count, and Ph+ ALL. Individual response to therapy measured by minimal residual disease (MRD) is the most significant prognostic factor in ALL, independent of age group.[12] Persistence of MRD in older adults is associated with a relapse rate above 90% despite continued intensive chemotherapy.[11,13] In older patients with less intensive therapy, a higher rate of MRD persistence and an even poorer outcome can be expected. Therefore, prospective evaluation of MRD is essential to identify those who could benefit from alternative, experimental treatments.

In older patients, potential prognostic factors for early death risk are relevant as well. In the German Multicenter Study Group for Adult ALL (GMALL) study comorbidity score, age and performance status before onset of leukemia were identified as significant.[14] What are the benefits from identifying predictors for early mortality? Patients at high risk of early death may be identified for intensive supportive care during a prephase therapy (see section to follow). Of not-large registry data have shown that early mortality is similar with so called "palliative" approaches.[15]

General issues in the management of older ALL patients

Co-medications and the risk of adverse events

Older patients usually take a number of medications, including alternative therapies and dietary supplements. Relevant interactions with medications such as tyrosine kinase inhibitors (TKIs) and other toxicity risks have to be considered. In older patients, physiologic changes may also have an impact on pharmacokinetics and pharmacodynamics of cytostatic drugs. Common problems include, for example polyneuropathies and constipation with vincristine, diabetes and hyperglycemia with steroids, the known cardiac toxicities of anthracyclines and liver toxicities induced by asparaginase, and methotrexate or purine analogs.

Prephase therapy

The question whether intensive induction therapy has to be started immediately is important for practical management. Overall, it appears prudent to start a prephase treatment with, at a minimum, steroids, in order to limit disease progression and gain time to initiate supportive care measures, collect relevant diagnostic tests including an assessment of potential treatment targets, check for clinical trial options, and give the patient some time to accommodate the situation.

Supportive care

The application of granulocyte colony-stimulating factor during chemotherapy may attenuate neutropenia and influence infection-related mortality. Antibiotic prophylaxis is given in most centers, but the benefit of antifungal prophylaxis, particularly the use of azoles, has not been proven for ALL induction and may contribute to additional toxicities, particularly those related to vincristine. Instead strict surveillance, standardized diagnostic procedures, and early onset of antifungal therapy may be reasonable approaches.

Induction therapy

Achievement of clinical remission (CR) is the pre-requisite for long-term survival in ALL. Therefore induction therapy is the most critical phase for management. In older patients, induction mortality has a wide range (0% to 42%) (Table 2),[14,16-25] and early death occurs also before the onset of chemotherapy. The most frequent cause of death in induction is infection.

Treatment results in older ALL patients

Population-based studies

Registries give an impression on the overall outcome of unselected older ALL patients.[2,15,26,27] Survival rates in patients >60 years were 12% at 5 years in Northern England.[2] For those aged between 65 to 74 years, survival was 25% in Sweden where outcome further decreased to 10% in patients >74 years.[15] Five-year OS in patients aged 60 to 69 years increased from 8% in the years 1992 to 2001 to 20% in the years 2002 to 2011, whereas only marginal improvements from 5% to 10% were observed for patients >70 years.[28]

Palliative treatment

Some 30% to 70% of the older patients are allocated to palliative therapy mainly due to poor performance status at diagnosis.[2,29-31] Most studies have shown an advantage of more intensive therapy such as higher CR rate, lower early death, better remission duration, and median survival (Table 2) compared with palliative care.

Table 2. Outcome from prospective trials designed for older ALL patients

Reference	Year	Age (y)	Ph+	Patients (N)	CR rate (%)	Early death	Failure	CCR*	DFS*	OS†
16	1996	60-73 (64)	Yes	22	59	18%	14%	12	9	20% (2 y)
23	1997	55-86 (67)	Yes	40	85	n.r.	n.r.	n.r.	14	16% (2 y)
24	2002	65 (55-81)	Yes	58	43	10%	47%	5	10	n.r.
17	2004	69 (61-79)	Yes	17	76	17%	6%	20	21	38% (2 y)
19	2007	65 (56-77)	No	33	58	36%	6%	46% (2 y)	7	39% (1 y)
20	2008	66 (60-78)	Yes	17	71	29%	0%	82% (1 y)	n.r.	71% (1 y)
25	2008	66 (56-73)	No	54	85	0%	15%	9	n.r.	61% (1 y)
18	2011		No						n.r.	
	Arm 1	68 (55-77)		31	90	7%	3%	32% (2 y)		35% (2 y)
	Arm 2	66 (60-80)		29	72	10%	17%	52% (2 y)		24% (2 y)
14	2012	57 (55-85)	No	268	76	14%	10%	32% (5 y)	n.r.	23% (5 y)
21	2016	58 (51-72)	Yes	30	67	3%	30%	n.r.	52% (2 y)	52% (2 y)
22	2016	66 (56-79)	No	54	74	14%	14%	n.r.	8; 24% (2 y)‡	12; 30% (2 y)‡

Arm 1, continuous infusion doxorubicin; Arm 2, pegylated doxorubicin; CCR, continuous complete remission; DFS, disease-free survival; n.r., not reported; OS, overall survival; Ph+, Ph/BCR–ABL1-positive ALL included yes or no.
*Median months or probability.
†Probability.
‡Estimated from Kaplan-Meier curve.

Treatment according to protocols for adult ALL patients

The majority of published data are based on results reported for the subgroup of older patients treated within protocols designed for adult ALL in general (Table 2), including US cooperative group trials. One large data set confirmed considerable mortality of 18%.[32] The authors concluded that induction therapy designed for younger patients may be too intensive for older patients.[32] Patients may acquire severe infections, nonpredefined treatment modifications occur frequently, and treatments may be interrupted or even stopped due to severe complications. Overall, potential conclusions from these studies are very limited.

Prospective studies for older ALL patients

Protocols specifically designed for older ALL patients have the theoretical aim to provide a chance of cure on the one hand and to limit toxicity, early mortality, and hospitalization duration on the other, and thereby maintain as much quality of life as possible (Table 3).[2,15,17,26,27,29-43]

One central question is whether and/or which anthracycline has to be included in induction regimens for older patients, because these drugs contribute considerably to bone marrow toxicity. One approach is the use of idarubicin in induction, based on a potentially lower cardiac and hepatic toxicity.[16] The results of liposomal anthracyclines in elderly ALL are not convincing so far.[17,18]

Asparaginase is an essential compound in the treatment of ALL. The PETHEMA group reported the results of an intensive induction regimen, including asparaginase for older ALL patients. The early death rate, mainly due to infection, was rather high (36%) and was reduced after omission of asparaginase and cyclophosphamide.[19] A high early mortality rate (29%) and a number of complications including infections (71%), cardiac toxicity (18%), and hyperglycemia (24%) were also observed in another trial utilizing asparaginase during induction therapy.[20] Furthermore a pediatric-based regimen using pegylated asparaginase during induction in older patients revealed grade 3-4 bilirubin increases in 33% of the patients.[21] Thrombosis and pancreatitis are other relevant toxicities of asparaginase. Altogether, there is some evidence that the use of asparaginase during induction therapy may be associated with increased risks in older patients. Therefore, it would be advisable to start asparaginase in older patients later during consolidation.

The majority of complications in older ALL patients is observed during induction, thus there is still space for intensification of consolidation therapy. Based on this assumption, a consensus treatment protocol for older patients with ALL was defined by the European Working Group for Adult ALL (EWALL). The 4-week, pediatric-based induction comprises dexamethasone, vincristine, and idarubicin in phase 1 and cyclophosphamide and cytarabine in phase 2. Consolidation consists of 6 alternating cycles with

Table 3. Outcome with different treatment approaches in older patients with ALL

Approach	Reference (s)	Age range (y)	Studies (N)	Patients (N)	CR*	Early death*	Survival†
Population-based studies	2, 15, 26, 27	>65	4	n.r.	40%‡	n.r.	6%-30%
Palliative treatment	29-31, 33	60-91	4	94	43% (34%-53%)	24% (18%-42%)	7 (3-10) mo
Intensive chemotherapy designed for adult ALL without focus on older patients	17, 32, 34-43	60-92	12	519	56% (40%-81%)	23% (6%-42%)	14% (3%-29%)

Adapted from Gökbuget.[1]
n.r., not reported.
*Weighted means and range from cited studies for CR rates, early death rates, and survival.
†Weighted means and ranges for survival probability at 2 or more years as reported in the cited studies or median survival time and ranges, respectively.
‡From Toft et al.[27]

intermediate-dose methotrexate combined with asparaginase and high-dose cytarabine, followed by maintenance. The median age at enrollment was 66 (56-73) years with 22% >70 years. The incidence of grade 3-4 cytopenias was 90%, and infections during phase 1 and 2 of induction occurred in 16% and 25% of the patients, respectively. Toxicities were less pronounced during consolidation and asparaginase was well tolerated. CR, survival, and continuous CR rates after 1 year were 85%, 61%, and 49%, respectively.[10] Another report based on the same backbone, showed CR rates of 74% and an OS of 30% at 2 years. The authors also observed grade 3-4 infections in 62% of the patients during induction therapy with a median duration of neutropenia of 24 days, whereas consolidation was far better tolerated even when including the use of asparaginase.[22]

The GMALL has conducted thus far the largest prospective trial specifically designed for older patients with Ph/BCR–ABL-negative ALL. Pediatric (Berlin-Frankfurt Munster)-based, dose-reduced induction therapy with idarubicin, dexamethasone, vincristine, cyclophosphamide, and cytarabine was followed by alternating consolidation cycles for 1 year and maintenance. Patients with $CD20^+$ ALL received rituximab in combination with chemotherapy. The median age of this cohort was 67 (55-85) years. In 268 patients the CR rate was 76%, early death rate 14%, mortality in CR 6%, continuous remission 32%, and survival 23% at 5 years.[14] Patients <75 years with an Eastern Cooperative Oncology Group performance status below 2 had an 86% CR rate, 10% early death, and 36% survival at 3 years. Interestingly, the replacement of triple intrathecal therapy during induction resulted in a reduced early mortality. Moderate intensification of consolidation as in the EWALL regimen, with inclusion of high-dose cytarabine and intermediate-dose methotrexate and native *Escherichia coli* asparaginase was tolerated. Overall, mortality in CR was 6% only.[14]

Overall, pediatric-based regimens in ALL are undoubtedly successful and should be scheduled with prospectively defined adaptations with respect to tolerability in older patients. The most important modification of induction therapy in older patients is probably the omission of asparaginase, and the flexible, reduced dose of anthracyclines. In consolidation, intensified treatment should be attempted, and during this treatment phase even asparaginase may be surprisingly well tolerated at moderate doses. Thus, patients aged 55 to 70 years and 70 to 75 years tolerated pegylated asparaginase at dose levels of 1000 U/m^2 and 500 U/m^2, respectively, as single-drug interim therapy during consolidation. Combination with high-dose methotrexate will be further explored and careful use is recommended in patients with preexisting liver disease, including steatosis or relevant obesity (body mass index >30) (Nicola Gökbuget, personal communication).

Treatment of older patients with Ph/BCR–ABL-positive ALL

The use of TKIs is a very promising approach for the large proportion of older patients with Ph+ ALL (Table 4).[22,44-51] Nowadays, older patients with Ph+ ALL may have a better chance to achieve a CR than patients with Ph^- ALL. The use of TKIs upfront is most promising. The GMALL conducted a first randomized study to evaluate the efficacy of imatinib single-drug induction compared with chemotherapy. The remission rates were 96% and 50%, respectively.[46] Only 11% of the patients achieved a molecular remission. A follow up including nonrandomized data yielded a CR rate of 88% in 121 patients, together with a 22% 5-year survival rate.[49]

The Gruppo Italiano Malattie Ematologiche dell'Adulto trial used imatinib (800 mg) with prednisone for induction, followed by imatinib single-drug treatment. The CR rate, survival, and disease-free survival were 100%, 74%, and 48% after 1 year.[45] A subsequent trial with dasatinib (140 mg) and prednisone, followed by dasatinib single-drug treatment was not specifically designed for older patients (range, 24-76 years). The CR rate was 92% and survival was 69% at 20 months. Post-remission therapy was at the discretion of the treating physician and 14 of 19 patients with TKI monotherapy relapsed with a high frequency of T315I mutations.[47] Another trial was based on a rotating schedule with 6 weeks of nilotinib treatment alternating with imatinib treatment. In 39 patients, the CR rate was 94% and the OS at 1 year was 79%. Nearly all relapsed patients in this trial showed mutations associated with TKI resistance.[48]

The largest prospective study so far in older patients with Ph+ ALL used an EWALL chemotherapy backbone with vincristine, dexamethasone, and dasatinib (140 mg) for induction. Consolidation and maintenance according to the EWALL backbone was combined with intermittent dasatinib applications. In 71 patients the CR rate was 96%. The regimen was feasible and the survival after 5 years of follow up was 36%, which is promising. Persistent MRD above 0.1% after induction and consolidation was associated with poorer remission duration of only 5 months.[51] A subsequent EWALL trial with a similar backbone but with nilotinib (400 mg twice daily) instead of dasatinib was started subsequently. Again, a high CR rate of 97% was reported. Thirty percent of patients achieved a complete molecular remission after induction.[50] Overall, there is increasing evidence that second-generation TKIs in combination with dose-reduced chemotherapy can induce very high CR rates with low mortality in older patients. The rate of molecular remissions appears to be higher compared with imatinib-based regimens. Moderate intensive consolidation therapies in combination with TKIs are tolerated well. Long-term results have to be assessed after 5 or more years and show a still high rate of relapses. New approaches may include reduced intensity stem cell transplantation (SCT), MRD-based change of TKIs, or use of new immunotherapies.

SCT in older patients with ALL

For patients >55 to 65 years of age, the indication for SCT is rarely made due to the expected high transplant-related mortality, although reduced-intensity conditioning (RIC) might be promising. In selected older patient populations with a median age of 38 to 56 years, RIC yielded survival rates between 18% to 48%, relapse incidence rates of 36% to 50%, and transplant-related mortality rates between 21% to 41%.[1]

Prospective trials with SCT indication in older patients are rare. One study used SCT as postremission therapy in all older patients (dose reduced over the age of 60 years). Twelve out of 20 CR patients actually received SCT with no apparent survival advantage for transplanted patients.[21] A retrospective analysis of patients >40 years showed no survival advantage of SCT compared with chemotherapy (40% vs 46%); whereas SCT was associated with a lower relapse rate, but this advantage was offset by the higher mortality experienced by participants.[52]

Indication for SCT and the optimal conditioning regimen in older patients need to be defined. Furthermore, there is a dilemma because MRD is the most relevant prognostic factor for relapse risk in older patients but outcome of SCT is poorer in MRD-positive ALL. RIC-SCT could be considered in older patients with persistent MRD,

Table 4. Prospective trials in older patients with Ph/BCR–ABL-positive ALL

Reference	Year	Median age (y)	Patients (N)	Induction	Post-induction	CR rate (%)	Survival rate (%)
44	2006	66	30	CH	IM + CH	72	66% (1 y)
45	2007	69	29	IM + PRED	IM + PC	100	74% (1 y)
46	2007	68	R: 28	IM	IM + CH	96	57% (1.5 y)
			27	CH	IM + CH	50	41% (1.5 y)
47*	2011	54	53	DASA + PRED	DASA + PC	100	69% (1.5 y)
48	2012	66	39	NILO + IM	NILO + IM	94	64% (2 y)
49	2012	66	121	IM ± CH	IM + CH	88	22% (5 y)
50	2014	66	47	NILO + CH	NILO + CH	97	n.r.
22	2016	66	53	IM + CH	IM + CH	87	57% (2 y)†
51	2016	69	71	DASA + CH	DASA + CH	96	36% (5 y)

CH, chemotherapy; DASA, dasatinib; IM, imatinib; NILO, nilotinib; PC, physicians choice; PRED, prednisone; R, randomization; y, years of follow up.
*Not specifically designed for older patients.
†Estimated from Kaplan-Meier curves.

combined with the attempt to reduce MRD by targeted therapies if available, and to measure MRD after SCT in order to administer either maintenance or immunologic therapies in case of MRD positivity.

New treatment options in older patients with ALL

ALL blasts express a number of antigens, such as CD33, CD22, CD19, or CD52, which could be a target for antibody therapy.[53] Approximately half of older patients who suffer from B-precursor ALL demonstrate CD20 positivity (>20%). In younger patients with $CD20^+$ ALL, there is promising data for the combination of chemotherapy and rituximab, and the positive effect of rituximab on outcome was recently confirmed in a randomized study.[54]

A new promising approach is the administration of a bi-specific T-cell–engaging antibody that recognizes CD19, blinatumomab, which has the potential to engage cytotoxic T cells in patients for lysis of $CD19^+$ leukemia cells. CR rates of ~45% have been observed for treatment of relapsed/refractory ALL with unfavorable features such as early or refractory relapse.[55] Importantly, there was no difference in terms of response rates or outcome between younger and older patients.[56] Very promising response rates of ~80% and median survival of 36 months were described for treatment of molecular-resistant or relapsed disease.[57]

The CD22-directed, calecheamicin-conjugated antibody inotuzumab induced CR rates above 80% in relapsed/refractory $CD22^+$ ALL and demonstrated a significant advantage compared with standard-of-care chemotherapy regimens.[58] Finally, genetically modified T cells directed to several surface antigens in ALL (eg, chimeric antigen receptor T cells) are being currently explored predominantly in children and younger adults with promising results. Further studies are needed to establish data on efficacy and tolerability in older patients. Several other new drugs are of interest for optimizing treatments in older ALL patients. The use of nelarabine for newly diagnosed T-cell patients is of interest after promising results and acceptable toxicity in the relapsed setting. New drugs with different mechanisms of action may be used in combination in the future with chemotherapy, such as proteasome inhibitors, histone-deacetylase inhibitors, hypomethylating agents, or targeted drugs such as Flt3-, ABL1-, or Jak2 inhibitors in defined subgroups of ALL.[59]

Summary and future prospects

- For the general management of older ALL patients, it is essential to distinguish between fit and unfit patients in whom an unacceptably high mortality of induction therapy has to be expected. A third group are patients in generally good condition before the onset of leukemia but in whom the risk of leukemia-associated complications may indicate a benefit from using an extended prephase treatment with intensive supportive care measures in order to improve the general condition and start intensive induction therapy afterward.
- The attempt to achieve a CR should be made whenever possible. The major risk for older ALL patients is death due to infections. It is therefore essential to provide intensive supportive care, including anti-infectious prophylaxis and the use of granulocyte colony-stimulating factor. On the other hand, any non-essential medications should be avoided to reduce the risk of cross-reactions and additional toxicities.
- All older ALL patients need a comprehensive diagnostic classification, including set-up of an MRD assay. The identification of Ph+ ALL is crucial because even in very old patients, TKI can induce a high CR rate with reasonable durability.
- In older as in younger patients, a pediatric-based induction strategy is endorsed in Ph^- ALL. Dose reductions for anthracyclines are essential and asparaginase during induction cannot be recommended outside of clinical trials. For fit older patients, consolidation chemotherapy may be intensified and maintenance treatment is essential. Whenever available, targeted drugs can be added to treatment strategies in older patients, such as rituximab or nelarabine.
- MRD evaluation is of utmost importance. MRD persistence or recurrence is the most relevant prognostic factor and indication for SCT. New compounds, depending on license label, can be successfully used to treat MRD with promising long-term results with or even without subsequent SCT.[57]
- Treatment options may change, as soon as new drugs or strategies become available. Future promising approaches may be based on dose-reduced chemotherapy in combination with targeted drugs as demonstrated in a recent study with inotuzumab in combination with reduced Hyper-CVAD,[60] or as tested in an ongoing study with blinatumomab in combination with chemotherapy maintenance in Ph^- ALL, or in combination with dasatinib in Ph^+ ALL (#NCT02143414). If such regimens prove efficacy, in larger or even randomized trials, this may change the overall treatment strategy in adult ALL.
- Prospective trials specifically designed for older ALL patients are needed and patients should, whenever possible, be entered in trials or registries. Since 2009, the GMALL study group has established a prospective national registry, which documents standard-of-care

results of newly diagnosed adult ALL patients in more than 100 centers in Germany. Furthermore, detailed treatment recommendations are provided. This system is also open for international collaborators.

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