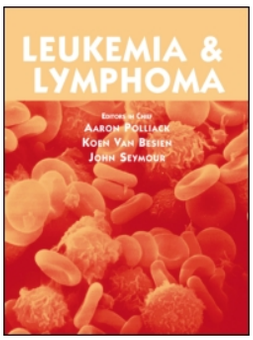

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REVIEW

Advances in adult acute lymphoblastic leukemia therapy

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ABSTRACT

Progress in adult acute lymphoblastic leukemia (ALL) treatment has been met with challenge until recently. A steady improvement in outcomes is being witnessed among adults with ALL, and it will be enhanced further with early referral of newly diagnosed ALL patients to specialized centers, enrolling more ALL adults in clinical trials, adopting pediatric-inspired ALL regimens in younger adults, tailoring treatments according to minimal residual disease response and disease genetics, incorporating novel therapies and tyrosine kinase inhibitors in frontline regimens, early referral to transplant when indicated, expanding the donor pool, and developing more effective salvage therapies for relapsed/refractory ALL. In this review, we will discuss the most significant advances in treating adult ALL observed in the last five years that have the potential to enhance adult ALL treatment and outcome.

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Introduction

The treatment of pediatric acute lymphoblastic leukemia (ALL) has become one of the most successful tales in cancer therapy, with cure rate nowadays approaching 90% [1]. In contrast, progress in treating adult ALL has been more challenging, until recently [2,3]. Some of the elements that were reasons for the observed inferior outcome for adults with ALL include higher-risk leukemia genetics, treatments yielding lower rates of long-term survival, noncompliance with treatment, intolerability to chemotherapy, and the lack of adult oncologists experienced in treating ALL. Another deficiency in adult ALL therapy, commonly observed in the United States, is the lack of a standardized regimen and the paucity of prospective data. This trend is the result of the enrollment of only a minority of newly diagnosed adult ALL patients on clinical studies, compared to the enrollment of the vast majority of pediatric ALL patients, which has led to accumulating valuable data that has contributed to the progressive improvement in the treatment of childhood ALL. Nonetheless, an incremental steady progress has been observed lately in adult ALL as the result of adopting pediatric-inspired regimens, better selection of high risk cases and early referral to transplant, increased availability of donors, incorporating minimal residual disease (MRD) in ALL treatment decision, understanding ALL genetics, and notably, available salvage options for relapsed/refractory (r/r) disease [2,3].

In this review, we will discuss the most significant advances in treating adult ALL witnessed in the last five years that have the potential to improve outcomes of adult ALL.

Ph-like ALL

Our understanding of ALL genetics is evolving and will likely influence treatment decisions. We are realizing that ALL is a heterogeneous leukemia, and patients with a normal karyotype on conventional cytogenetics carry a spectrum of relevant mutations that define prognosis and potential treatment.

Ph-like is a newly described entity in ALL that shares a similar gene expression profile to Ph + ALL but lacks t(9;22). Ph-like incidence appears to increase with age in the first two decades [4], but the frequency remains high afterward, observed in at least 20% of young, middle-aged, and older adults with B-cell ALL [5], and it is more common among Hispanic patients [6]. Ph-like ALL is characterized by a high frequency of IKZF1 alterations as well as, in the majority of cases, activating kinase mutations that are potentially targetable with TKIs [4,5]. CRLF2 is the most common involved mutation in Ph-like ALL, and activating

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JAK2 rearrangements/mutations also occurs in subset of CRLF2 mutated cases [4–6]. On the other hand, the ABL-class rearrangement was observed at a higher frequency in children with Ph-like ALL, and those cases are sensitive to dasatinib therapy [4].

Ph-like ALL carries a poor prognosis similar to Ph + ALL [4–8], and in one study, a worse outcome was reported among patients with Ph-like ALL who carry the CRLF2 mutation when treated with adult regimens [6]. Furthermore, patients with Ph-like ALL more frequently have detectable MRD after induction which contributed to the overall poor prognosis of this entity [6–8].

Therefore, identification of the Ph-like genotype has important implications in ALL therapy, since it can render the patient as high risk, may influence future therapies such as early use of allogeneic hematopoietic cell transplantation (alloHCT), and possibly lead to the beneficial effect of combining TKIs as part of the ALL regimen in a subset of Ph-like genetics. However, the complexity and the unavailability of gene expression profile microarray precluded the prevalence in identifying Ph-like ALL; thus, Roberts et al. have proposed a more practical approach to identify Ph-like ALL cases using conventional molecular and cytogenetic methods. (refer to the Supplementary Appendix for the algorithm to identify Ph-like ALL) [4].

It still needs to be explored whether alloHCT can potentially overcome the poor prognostic feature of Ph-like ALL and whether it should be routinely recommended. Furthermore, the high incidence of activating kinase mutations among Ph-like ALL has triggered combining a TKI, such as dasatinib and ruxolitinib, with upfront therapy for ALL (#NCT02883049, #NCT02420717); however, preclinical data indicated modest potential activity of JAK 1/2 inhibitors in JAK2 mutated Ph-like ALL [9].

Genetic polymorphism in ALL

The influence of inherited genetic variation (polymorphism) on treatment response and toxicity is an active area of research in ALL, and acquired information can lead to individualized therapy for treated patients and decrease excessive toxicity. Genome-wide association studies (GWAS) have identified correlations between inherited genetic variations for certain genes critical to anti-leukemic agents' metabolism and long-term outcomes [10,11]. The variation of thiopurine methyltransferase (TPMT) gene activity is one of the prototypical examples of utilizing genetic polymorphisms in ALL. Testing of TPMT genotype and phenotype has been introduced to guide mercaptopurine (MP) dosing during ALL therapy, as the TMPT enzyme affects the metabolism of MP and the level of active metabolites. Studies have shown correlations between loss-of-function variants in the TMPT gene and reduction in ALL relapse [12,13], but also at the cost of increasing MP toxicity [14]. On the other hand, germline variations in certain genes can influence other key ALL drug toxicities, such as asparaginase allergy and pancreatitis (GRIA1, HLA-DRB1, and ASNS) [15–17], steroid-induced osteonecrosis (ACP1) [18], anthracycline-induced cardiotoxicity (CBR3, HAS3) [19,20], vincristine-induced neuropathy (CEP72) [21], and methotrexate clearance and toxicity (SLCO1B1) [22].

However, many of the previously mentioned polymorphism studies are not in a commercially available format and are not examined routinely during ALL therapy, with the exception of the TMPT gene polymorphism. TPMT testing can be helpful in guiding 6-MP dose, but it can also be tested when unexplained cytopenia is encountered with standard doses of 6-MP. Most of the polymorphism studies were conducted in children, and future studies should address the influence of these variations in adult ALL to allow tailoring and personalized treatment and reducing overall treatment toxicity.

Incorporation of MRD in adult ALL management

Rates of morphologic complete remission after frontline induction therapy are high in newly diagnosed adults with ALL, and this finding is irrespective of the administered regimen. However, relapse remains the leading cause of treatment failure in adults with ALL, and almost half of adults who achieved remission eventually relapse. Thus, it was recognized early that CR is not a perfect surrogate for long-term outcomes in ALL. The ability to detect small residual clones of leukemic cells after induction that is not detected by morphology or routine flow cytometry has generated a powerful surrogate marker for leukemia sensitivity to chemotherapy and long-term outcomes. The prognostic ability of MRD represents an addition to the other conventional prognostic features in ALL, and it assists in guiding subsequent therapy, such as alloHCT. MRD can be measured by PCR-based, multicolor flow cytometric, or next generation sequencing methods [23–25], and current techniques can detect as low as 10^4–10^5 leukemic cells.

The timing of MRD assessment to determine patient prognosis and subsequent treatment choice varied by different regimens, and it remains a matter of debate in the adult ALL community. Early persistent MRD after

induction cycle 1 in the PALG 4-2002 (≥0.1%) and Intergroup C10403 (detectable) studies emerged as a poor prognostic factor [8,25], whereas the GMALL study showed that persistent MRD (≥0.01%) before and after consolidation 1 (between weeks 10 and 16) was associated with inferior OS, especially for those who did not undergo alloHCT [26]. Similarly, the PETHEMA ALL-AR-03 study showed inferior OS and DFS among adults with poor MRD clearance after induction (≥0.1%) and persistent MRD after early consolidation (≥5 × 0.01%) [27]. On the other hand, the GRAALL study demonstrated that the combination of early MRD response failure after induction (≥0.01%) and high-risk genetics can predict inferior long-term outcomes in adults with B and T cell ALL [28]. The adverse influence of positive MRD continues even after alloHCT (MRD was evaluated within 50 days before HCT in this study) [29]; however, most experts still recommend to transplant those patients whenever possible since it is a sign of chemoresistance that is unlikely to be overcome by additional chemotherapy [26,30]. However, this practice may change with the introduction of immunotherapy such as blinatumomab, where activity is observed irrespective of prior chemosensitivity and where encouraging results have been noted among patients with persistent MRD disease. On the other hand, studies have shown excellent long-term outcomes in adults with ALL who achieved and maintained an early MRD response in the context of pediatric inspired regimens, without the use of allogeneic HCT [31]. This pattern would allow sparing a subset of adults with ALL from the need of allogeneic HCT in first CR.

Therefore, MRD status in adults with ALL predicts outcomes similar to those in children, and MRD status can be incorporated into decision-making with respect to subsequent approaches such as immunotherapy and/or proceeding to alloHCT in the attempt to prevent frank leukemia relapse and spare patients from intensified therapy. However, given the conflicting timing of MRD assessments in adults that influence prognosis, such approaches are recommended to be regimen-dependent and applied at the specific times as dictated by each unique regimen.

Adopting pediatric regimens in adults

Although ALL is typically considered as a pediatric leukemia, 40% of affected patients are diagnosed after age 20 [32], and thus, a large percentage of ALL patients are expected to be treated by adult oncologists. However, the proportion of ALL in regular adult oncologist practice is much smaller than in pediatric oncologist practice, where ALL represents the most common childhood cancer. In fact, large numbers of adult community oncologists rarely diagnose ALL and initiate therapy, and therefore, among the majority of adult oncologists in the community, there is naturally less familiarity with complex ALL regimens and their potential unique toxicities. Thus, it becomes crucial to refer ALL adult patients to specialized centers early after diagnosis to accommodate complicated treatment courses and to avoid serious treatment consequences as well as inadequate therapy.

Historically, adult oncologists have perceived that pediatric ALL regimens are too toxic in the adult population, especially the frequent application of asparaginase. Multiple retrospective analyzes comparing outcomes of adolescent and young adults (AYA) with ALL treated on either adult or pediatric prospective clinical studies have demonstrated the superiority of pediatric regimens among the AYA group over adult regimens [33–36]. For instance, a retrospective analysis compared outcomes of 321 AYA (16–20 years) patients treated either on the Children's Cancer Group (CCG) pediatric prospective trials or the Cancer and Leukemia Group B (CALGB) adult prospective trials during the same period. The analysis has shown inferior 7-year event-free survival (EFS) (34% vs. 63%, $p < .001$) and overall survival (OS) (46% vs. 67%, $p < .001$) among AYA patients treated on the CALGB trials [36]. Meanwhile, a series of prospective studies have made it apparent that pediatric-inspired ALL regimens are feasible in younger adults, with manageable toxicities and potentially more encouraging results [8,37–41]. Today, modern ALL regimens in adults derive their principles from pediatric regimens, where asparaginase is given frequently with a goal of maintaining asparagine depletion for prolonged periods during therapy, and with a focus on frequent delivery of non-myelosuppressive drugs such as steroids and vincristine, escalating methotrexate doses, early and frequent administration of intrathecal chemotherapy, and avoiding myeloablative therapy used in adult regimens. Table 1 summarizes reported pediatric inspired regimens in adult ALL.

The upper age of pediatric-inspired regimens remains a matter of debate. Oncologists are more hesitant to administer such regimens as age increases, primarily because of the concern of increased asparaginase related toxicities [42,43]. Therefore, studies employing pediatric-inspired ALL regimens restricted enrollment to younger adults, but the definition of younger adults was inconsistent among different groups, and while some limited upper age to 30–40 years [8,39,41,44,45], others extended

Table 1. Pediatrics inspired regimens.

Study	Number	Median age	CR%	Induction death (%)	OS	DFS/EFS
C10403 [47]	296	24 (17–39)	NR	4 (1)	2-yr = 78%	2-yr EFS = 66%
DFCI [38]	92	28 (18–50)	85	1 (1)	4-yr = 67%	4-yr DFS = 69%
USC [37]	51	32 (18–57)	96	0 (0)	7-yr = 51%	7-yr DFS = 58%
PETHEMA [39]	81	20 (15–30)	98	1 (1)	6-yr= 69%	6-yr EFS = 61%
GRAAL-2003 [40]	225	31 (15–60)	94	14 (6)	3.5-yr = 60%	3.5-yr EFS = 55%
HOVON [41]	54	26 (17–39)	91	2 (4)	2-yr = 72%	2-yr EFS= 66%
FRALLE 2000 [45]	89	19 (15–29)	99	NR	5-yr= 66%	5-yr EFS = 61%
MDACC [44]	85	21 (12–39)	94	1 (1)	3-yr = 74%	3-yr CRD = 70%
GMALL 07/03 [149]	1226	35 (15–55)	91%	4–5%	3-yr = 60–67%	NR

CR: complete remission; OS: overall survival; DFS: disease free survival; EFS: event free survival; NR: not reported.

enrollment to patients up to age 50 years [38], and even 60 years [37,40,46].

The use of asparaginase in adults has exhibited a similar toxicity profile to what is observed in children, but with higher rates of liver toxicity and thrombosis among adults [42,43,47]. On the other hand, the risk of allergic reactions has been noted to be lower in adults compared to the risk in children [43], but this finding could be related to the prevalent use of pre-asparaginase medications in adults but not children. Nonetheless, masking the clinical manifestation of asparaginase-induced allergic reactions may result in silent hypersensitivity, resulting in compromising asparaginase activity. Currently, Erwinia L-asparaginase is available for patients who develop an allergic reaction to *Escherichia coli*-derived asparaginase, motivating recommendations to monitor asparaginase activity to ensure adequate inhibition of asparagine, and for those with inadequate activity, a consideration to switch to Erwinia should be taken [48]. However, Erwinia L-asparaginase is dosed more frequent compared to PEG-asparaginase (six doses of the former are equivalent to one of the latter), which may create an inconvenience for patients. Nonetheless, a recent multicenter retrospective study of Erwinia asparaginase has highlighted its overall safety and low toxicity when used after prior allergic reaction to *E. coli*-derived asparaginase, including in adult patients [49], leading to testing Erwinia as part of the ALL regimen for older patients (>60 years) (NCT#02647190). On the other hand, the interest in prolonging asparagine depletion prompted developing a long-acting form of asparaginase, 'Calaspargase Pegol (SC-PEG)', and in a randomized pediatric study using the Dana-Farber Cancer Institute (DFCI) ALL regimen comparing PEG-asparaginase to SC-PEG, a single dose of SC-PEG resulted in more sustained serum asparaginase activity (SAA), and led to less frequent dosing of asparaginase beyond induction with a comparable SAA and toxicity profile [50]. Asparaginase toxicity in adults is summarized in Table 2.

Table 2. Asparaginase toxicities and management [42,43].

Toxicity	Grade III–V	Notes
Hyperbilirubinemia	14–24%	Reversible. Not an indication to hold subsequent asparaginase therapy
Transaminases	36–54%	Reversible. Not an indication to hold subsequent asparaginase therapy
Thrombosis	8–11%	Start anticoagulation. Asparaginase can be resumed while the patient remains on anticoagulation for non-life-threatening thrombosis cases
Bleeding	<1%	Rare
Hypertriglyceridemia	51%	Reversible. No relation to clinical pancreatitis
Pancreatitis	5–13%	Permanent discontinuation of asparaginase due to high risk of recurrent pancreatitis if rechallenged. Chemical pancreatitis is not an indication to hold subsequent doses of asparaginase
Allergy	1–7%	Replace with *Erwinia* asparaginase
Hypofibrinogenemia (<100)	16–48%	Avoid replacement with cryoprecipitate due to high risk of thrombosis

When upfront pediatric inspired ALL regimens are used in adults, allogeneic hematopoietic cell transplantation (alloHCT) consolidation should not be recommended routinely in Ph − ALL, especially for those who achieve early MRD negative status, as a high proportion of those patients are expected to be cured with chemotherapy alone. In a recent retrospective analysis comparing 422 patients (18–50 years) having Ph-negative ALL who underwent alloHCT in first complete remission (CR) (as reported to the Center for International Blood and Marrow Transplantation Research [CIBMTR]) with 108 age-matched patients treated with the DFCI pediatric-inspired regimen, overall survival (OS) was better among patients who were treated with chemotherapy [51].

However, ALL regimens require a strict adherence with the administering treatments on time without delays or missing doses, and this fact usually represents a difficulty in adults who have other daily responsibilities related to family and work.

One example of the detrimental effect of noncompliance with ALL therapy is the lower adherence with oral MP during maintenance therapy and the increased risk of relapse [52]. Although the study was conducted in children, the same will likely apply to adults with ALL.

Progress in Philadelphia chromosome positive ALL

Philadelphia chromosome positive (Ph+) ALL is a leukemia predominantly encountered in adults, and the incidence tends to increase with age [53]. Ph + ALL treatment and prognosis have evolved over the last decade, and the disease has transformed from a leukemia with a lower CR rate and higher relapse postremission when compared to Ph − ALL into one where remission is easily achieved in the majority of treated patients, and remission is usually maintained until the time of consolidation with transplant. This advancement was mainly attained by the introduction of tyrosine-kinase inhibitors (TKIs), which have become the backbone of Ph + ALL regimens [54–57].

With the introduction of effective TKIs that have a high single agent activity, the intensity of the accompanied chemotherapy regimen was questioned and challenged. The randomized GRAAPH-2005 study demonstrated a higher CR rate and lower induction related mortality with imatinib combined with weekly vincristine and intermittent dexamethasone, as compared to imatinib combined with part A hyperCVAD, in newly diagnosed Ph + ALL patients, with comparable molecular response and long-term outcomes [58]. Likewise, other studies combining TKIs (imatinib or dasatinib) with mild therapy including a steroid with or without vincristine reported complete hematological remissions in the vast majority of treated patients [59–61].

Compared to imatinib, second-generation TKIs are more potent and active against more frequently encountered resistant mutations in Ph + ALL. Both dasatinib and nilotinib were introduced into upfront therapy in Ph + ALL [59,62,63], and although results were encouraging, no head-to-head comparisons were directly made. However, the T315I mutation is observed among ∼75% of relapsed Ph + ALL cases [59], and it is universally resistant to all first- and second-generation TKIs. On the other hand, ponatinib is a third-generation TKI that has documented activity against the T315I mutation, and as single agent, ponatinib produced a major cytogenetic response in 47% of refractory Ph + ALL patients, irrespective of the T315I mutation [64]. This finding encouraged the introduction of ponatinib in upfront therapy in Ph + ALL in combination with hyperCVAD. The combination was very active and yielded complete cytogenetic remission in all patients, as well as a complete molecular remission approaching 80%. Cardiac toxicity and thrombosis were raised as concerns during the study, but reducing the ponatinib dose among molecular responders appears to overcome this issue [65]. Comparing two consecutive prospective studies in Ph + ALL patients treated with hyperCVAD and either dasatinib or ponatinib using a propensity score analysis, authors reported favorable OS and EFS in the ponatinib arm [66]. A randomized controlled phase 3 trial is warranted.

Allogeneic HCT remains the standard consolidation for adults with Ph + ALL whenever feasible nowadays. Allogeneic HCT improved survival of adults with Ph + ALL treated with imatinib- and dasatinib-based regimens when was performed in CR1 [58,67,68]. The US intergroup study treated Ph + ALL adults with hyperCVAD and dasatinib, and for patients with available HLA matched related or unrelated donors, alloHCT was recommended in CR1 which was followed by maintenance dasatinib. The study reported superior RFS ($p = .038$) and OS ($p = .037$) among transplanted patients compared to those treated with chemotherapy and dasatinib only [68]. Figure 1 illustrates the results of the US Intergroup study in Ph + ALL and the benefit of allogeneic HCT in this setting. However, this notion may change when a more potent TKI such as ponatinib is used as part of frontline therapy, as the phase II study did not show an advantage of alloHCT consolidation for Ph + ALL patients treated with hyperCVAD and ponatinib. However, the study was not primarily intended to assess the benefits of consolidative allogeneic HCT consolidation in this setting, and therefore the data are hypothesis-generating [65].

Advances in transplantation in ALL

Allogeneic HCT remains a crucial element in adult ALL therapy, and it is indicated as part of frontline therapy for adults with high risk ALL. However, the definition of high risk ALL that necessitates early HCT has evolved from traditional clinical factors such as patient age and initial white blood cell counts to factors dependent on molecular/genetic features and MRD dynamics after initiating therapy, especially when pediatric-inspired regimens are used. Most experts agree that alloHCT is indicated in adults treated with adequate therapy in the presence of high risk cytogenetics (Ph+, MLL gene rearrangement, complex karyotype, hypodiploidy (especially those with low hypodiploidy and near-haploidy)), persistent MRD, and

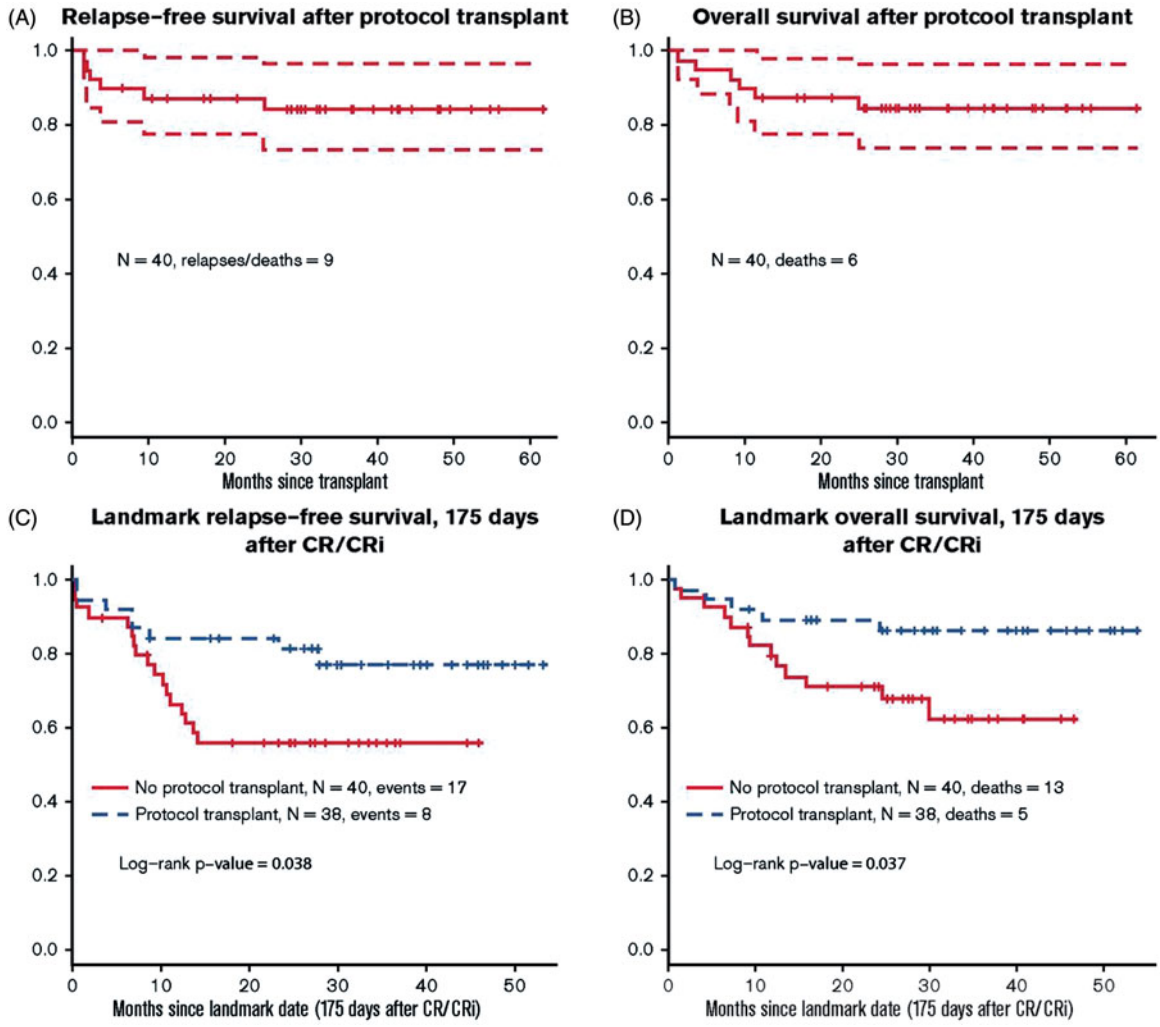

Figure 1. Outcomes after dasatinib and allogeneic stem cell transplantation from the US intergroup study. Reprinted from Ref. [68] with permission from the American Society of Hematology.

possibly high-risk molecular features, such as Ph-like ALL. On the other hand, allogeneic HCT is the only curative therapy for advanced ALL, including relapsed and refractory (r/r) disease. Therefore, transplantation in ALL has evolved in parallel with chemotherapy, and new modalities of transplantation have been developed to address some of the previous challenges related to the following: transplantation in the elderly, identifying a suitable donor, and transplantation for chemo-refractory ALL.

As increased age limits the ability to deliver adequate effective ALL therapy, such as asparaginase and repeated doses of vincristine, transplantation has emerged as a method to reduce relapse risk in older patients. Historically, the intensity of myeloablative conditioning (MAC) has precluded older patients from receiving alloHCT when indicated. This perception has changed with the introduction of reduced intensity conditioning (RIC) transplantation, which has overcome this obstacle through reducing conditioning intensity to improve toxicity profiles and rely more on the graft versus leukemia effect to prevent relapse. RIC-based allogeneic HCT provided a feasible option for older patients and for younger ones with co-morbidities. The procedure has proved to be tolerable and potentially curative for 30% to 60% of high-risk patients with ALL [69,70], comparing favorably to chemotherapy treatment in older patients [71], and possibly resulted in improving ALL outcomes among older adults [2]. When compared retrospectively to MAC, alloHCT using RIC in ALL was associated with a higher relapse rate but lower non-relapse mortality, and resulted in similar leukemia free survival (LFS) and OS overall [72].

Identifying a suitable donor was one of the leading limitations for using alloHCT in ALL when indicated. The recent innovation in T cell replete HLA-haploidentical HCT using post-transplant cyclophosphamide allowed more patients to have a donor choice to proceed with transplantation when needed. As similarly

found in other hematological malignancies, haploidentical HCT was feasible in ALL and produced encouraging results [73,74]. In a multicenter retrospective analysis of 109 patients with high-risk ALL, 1-year non-relapse mortality (NRM), relapse rate (RR), and disease-free survival (DFS) for all patients were 21%, 27%, and 51%, respectively, and 3-year DFS for those in first CR was 52% [73]. As relapse remains the leading cause of treatment failure after haploidentical HCT, novel modalities are being developed to overcome this hurdle, including escalating the dose of targeted radiation-based condition regimens (NCT#02446964) and post-transplant preemptive chimeric-antigen receptor (CAR) T cell therapy [75].

Historically, autologous HCT was attempted as a consolidation in ALL, but results were disappointing and the procedure was abandoned [76–78]. However, autologous HCT consolidation is reemerging recently as a potentially satisfactory treatment for Ph + ALL in the TKI era, where molecular remissions can be achieved frequently. In the GRAAPH-2005 study, Ph + ALL patients who achieved a major molecular response after cycle 2 had comparable relapse-free survival (RFS) ($p = .82$) and OS ($p = .86$) if they received MAC-based autologous or allogeneic HCT [58]. Consistent with the GRAAPH study, the CALGB-10001 study also showed no difference in DFS ($p = .99$) and OS ($p = .95$) for Ph + ALL patients in first CR who were treated with a pre-HCT TKI-based regimen and underwent autologous or allogeneic HCT [79], but the small number of patients in the study requires confirmation in a larger study.

As ALL therapy advances, a subset of ALL patients will continue to be refractory to available conventional and novel therapies, and this will limit the curative potential of alloHCT in younger patients with available donors. ALL with active disease at the time of HCT carries dismal outcomes, with a 3-year OS of 16%, mainly because of leukemia relapse post HCT [80]. Increasing the radiation dose during conditioning has the potential to prevent leukemia relapse but results in higher NRM [81]. The advancement of intensity-modulated radiation therapy (IMRT) allows escalating radiation doses during conditioning and selectively targeting involved tissues while sparing healthy vital tissues, with the goal of improving disease control and reducing excessive toxicity. We conducted a phase I study at City of Hope using total marrow and lymphoid irradiation (TMLI) at doses of 1200–2000 cGy in combination with high dose cyclophosphamide and etoposide in 51 patients with refractory acute leukemia and active disease at the time of HCT. The study included 16 patients with active ALL, and the TMLI dose was escalated safely to 2000 cGy. The study showed encouraging results, with 1-year NRM and OS of 8% and 55%, respectively [82].

Radiation-based conditioning has been the standard MAC regimen in ALL whenever possible. However, because of long-term radiation-related toxicities, novel radiation-free conditionings have been explored. Clofarabine is a purine nucleoside that has activity in advanced ALL [83]. Investigators at MD Anderson Cancer Center have reported outcomes of i.v. pharmacokinetically (PK) dosed busulfan in combination with clofarabine as a conditioning regimen for 107 adults (median age of 38 years) with ALL. The combination regimen was safe and yielded 2-year PFS and OS rates of 62% and 70%, 34% and 57%, and 35% and 35% for patients in first CR, second CR, and more advanced ALL, respectively. The 2-year NRM was 31% [84]. In another phase II study for ALL patients in first CR, the combination of fludarabine with PK-directed i.v. busulfan yielded 2-year RFS and OS rates of 61% and 65%, respectively, in 65 ALL patients (median age of 42 years) in first CR [85].

Other studies are incorporating maintenance therapy post alloHCT, such as blinatumomab (NCT#02807883) and TKIs in high-risk ALL, in attempts to reduce post-HCT relapse [86].

ALL in older adults

Older adults (usually defined as ≥60 years) with ALL continue to perform poorly overall [71,87], with only modest progress observed lately (3 year OS =11% vs. 16%, $p < .001$, for patients treated in 1990–1999 and 2000–2011, respectively) [3]. However, a subset of older adults can be cured with therapy, but treatments need to be tailored according to patient chronological and physical ages.

Advancements in treating older adults with Ph + ALL and the utilization of RIC allogeneic HCT in older adults were discussed earlier; here we note that subtype-oriented therapy is feasible in elderly patients with ALL and resulted in improving outcomes among those with Ph + ALL compared to those with Ph − ALL [88], mainly because of the introduction of TKIs. Studies have shown that older adults do not tolerate intensive conventional ALL regimens well, with high risk of treatment-related mortality (TRM) [89,90]. For example, the PETHEMA ALL-96 study showed improved OS and reduced TRM when cyclophosphamide and asparaginase were eliminated from induction in older patients with ALL (>55 years) [89], while a recent analysis from GRAAL-2005 has shown that older adults (55–59 years) with ALL were less able to

tolerate commonly drugs routinely used in ALL, including asparaginase, cytarabine, methotrexate, vincristine, steroids, and anthracycline, and overall, those older patients had improved tolerability to adult-type regimens such as those based on hyper-fractionated cyclophosphamide [90].

However, administering age-directed drug dosing and formulation may need to be included when we treat older adults with ALL. For example, the use of modified reduced doses of pegasparaginase (500 IU/m^2) was reported safe in older adults with ALL [91], and the use of short-acting Erwinia asparaginase in older adults regimen is actively being tested (>60 years), which has the benefit of shortening the duration of toxicity if it occurs once the drug is held. Other considerations when treating older adults with ALL include close monitoring of vincristine neurotoxicity and anthracycline cardiotoxicity, and the careful administration of high dose methotrexate with adequate hydration. The use of granulocyte-stimulating agents to avoid neutropenia is encouraged as well as prophylactic antimicrobial therapy [92].

In contrast, immune-based and targeted therapies have shown encouraging leukemia responses irrespective of patient age, and generally, they were tolerated even in older adults. This finding motivated introducing these therapies during frontline treatment of older adults with ALL such as inotuzumab + mini-HyperCVD and blinatumomab in combination with TKI or low dose chemotherapy in older patients [93].

Adoptive cellular therapy (chimeric antigen receptor-modified T cells)

Chimeric antigen receptors (CAR) are synthetic receptors incorporated into T cells to target a molecule of interest on the surface of tumor cells. CAR T cells mediate direct killing of targeted cells, bypassing the normal T cell activation and antigen processing and presentation, and therefore, circumventing some of the tumor resistance mechanisms toward immunotherapy. CD19 has emerged as an ideal target for CAR T cell therapy toward B cell ALL, as the antigen is widely expressed in the majority of cases [94], and inducing hypogammaglobulinemia is generally manageable.

The introduction of second-generation CARs with a co-stimulatory domain has overcome the short persistence encountered in early first generation CARs studies, as these CAR T cells proved to be active with encouraging responses [95,96]. A series of single-center studies were conducted using different second-generation CD19CAR T cell platforms, and consistently, all have shown promising high response rates in r/r B-cell ALL, irrespective of co-stimulatory domain or transduction method [75,97–100].

The manufacturing of a CAR is individualized for each patient, and the process usually requires several weeks before the product is ready for infusion. The majority of enrolled patients will require salvage treatment while CAR T cells are being manufactured to keep leukemia under reasonable control. The majority of CAR T cells protocols include a lymphodepleting regimen before infusing CAR T cells to improve CAR T cell engraftment and persistence [101]. Studies have shown a correlation between higher disease burden before CAR T cells infusion and the severity of cytokine release syndrome (CRS) [98,100], and intensifying lymphodepleting regimen resulted in lessening CRS severity among those cases compared to a historical control in one study [102]. This finding has motivated several groups to incorporate risk-adapted optimization of lymphodepleting regimens based on disease burden [100,103,104]. After infusion, CAR T cells usually expand and persist, but this event varies on the basis of CAR T cell properties. However, associations between CAR T cell expansion and response as well as persistence and response duration were noted in some studies [99,105]. Studies have shown the ability of CAR T cells to traffic to the central nervous system (CNS) [97,99,100], a sanctuary site in ALL that has been a challenge for other therapies, and interest has emerged in utilizing CAR T cells therapy for CNS ALL since responses have been observed [99,106]. Refer to Table 3 for CAR T cell studies in ALL.

Furthermore, studies have shown the feasibility of transducing donor-derived T cells for prior allogeneic HCT recipients using T cells leukapheresed from the patient or taken directly from the donor [75,97,98,107], and the infusion of donor-derived CAR T cells was associated with comparable toxicities, while GVHD was only rarely encountered [75,100,107].

CAR T cell therapy is associated with unique toxicities, including CRS, neurotoxicity, and, as expected, hypogammaglobulinemia as the result of normal B cell depletion. CRS is the result of rising circulating cytokine levels in response to immunotherapy, and onset usually occurs early after initiating treatment. CRS most commonly presents with fevers, similar to infection, but other associated symptoms are encountered such as flu-like symptoms, hypoxemia, hypotension, transaminitis, and neurotoxicity. CRS is common following CAR T cell infusion; the majority of cases have been mild, but a subset of patients develop life-threatening manifestations that require intervention with tocilizumab and/or steroids [97,100]. CRS was correlated with disease burden [98,100], and stratifying

Table 3. CAR T cells studies.

Center	Age group	*N*	Prior alloHCT	CR/Cri % (MRD %)	LFS, RFS, DFS	OS
UPenn/CHOP [97]	Pediatrics/adults	30	15	90 (79)	EFS = 67% (at 6 months)	78% (at 6 months)
MSKCC [98]	Adults	16	4	88 (75)	NR	NR
NCI [99]	Pediatrics/adults	21	8	67 (86)	LFS = 79% (at 4.8 months)	52% (at 6 months)
MDACC [75]	Adults	17	17	–	PFS = 53% (at 1 year)	63% (at 1 year)
FHRCC [100]	Adults	29	11	93 (86)	NR	NR

alloHCT: allogeneic hematopoietic cell transplantation; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; MRD: minimal residual disease; LFS: leukemia free survival; RFS: relapse free survival; DFS: disease free survival; OS: overall survival; PFS: progression free survival; NR: not reported.

patients into higher or lower lymphodepleting regimens on the basis of disease burden before infusion was shown to lessen severe CRS [102]. Neurotoxicity is another common adverse event encountered during CAR T cell therapy, and sometimes it can overlap with and be part of CRS manifestations, but may occur independent of one another [97,99,100]. The majority of neurotoxicity cases were reversible, but the pathophysiology of CAR-induced neurotoxicity remains poorly understood.

The promise of CAR T cell therapy that was seen at single center studies is being translated into multicenter studies, and results continue to be encouraging [108]. However, relapse after CAR T cells is manifested as either CD19-positive disease, or can be CD19-negative ALL in a subset of patients, with CD19-negative disease precluding any further CD19-targeted therapies. CD19-negative relapse tends to be seen in the context of ongoing CAR T cell persistence. This finding has prompted the search for other targets for CAR T cells in ALL. A pilot study of CD22CAR T cells is being conducted and so far has shown feasibility and activity [109]. Another proposed mechanism of resistance following CAR T cells was the development of antibodies toward murine-based parts of the CAR, which results in eliminating CAR T cells, and thus leads to leukemia relapse. This hypothesis led to developing humanized CAR T cells, and a pilot study has shown promising results among patients who failed prior murine-based CAR T cells [110]. Similarly, the addition of fludarabine to the lymphodepleting regimen has emerged as another potential approach that may abrogate the risk of transgene mediated rejection as well [100,103], as shown in improving survival in one study. Furthermore, combining immune checkpoint inhibitors with CAR T cells is an area of interest as the expression of programed cell death protein 1 (PD-1) increases following CAR T cells infusion [107]. The interest in CAR T cells in r/r ALL also led to introducing this novel therapy as a preemptive infusion after alloHCT for high risk ALL cases, and a pilot study has demonstrated feasibility in infusing CAR T cells early after alloHCT with no excess toxicity [75].

Antibodies in ALL

Blinatumomab

Blinatumomab is a bispecific CD3/CD19 antibody that redirects effector CD3+ T cells into close proximity to CD19+ ALL cells, creating a cytolytic synapse and resulting in ALL cell lysis [111]. Blinatumomab has a similar advantage to CAR T cell therapy in that T cells mediate leukemia eradication irrespective of TCR specificity, major histocompatibility complex context, or antigen processing and presentation. Blinatumomab has shown significant activity in MRD + and frank r/r ALL, independent of prior response to alloHCT or chemosensitivity [112].

For r/r MRD + ALL, two phase II studies examined blinatumomab in patients with morphological remission (<5% blasts) who had relapsed or refractory MRD (≥0.1%) and received ≥3 chemotherapy regimens before, but no prior alloHCT. Blinatumomab induced molecular response in around 80% of enrolled patients, and survival was similar among those who did and did not undergo subsequent alloHCT consolidation. Blinatumomab was used as a fixed dose with acceptable toxicities [113–116].

In a pilot study for adults with frank r/r ALL with blasts ≥5% ($N = 36$), blinatumomab induced CR in 69% of patients [117]. In a subsequent confirmatory phase II study enrolling 189 patients with r/r Ph − ALL, CR/CR with incomplete blood count recovery (CRi) was 43%, and the majority of responses were molecular remissions [112]. Only pretreatment disease burden was shown to correlate with response rate, but neither prior alloHCT nor chemosensitivity influenced response to blinatumomab [112]. A phase III randomized study (TOWER) compared blinatumomab to physician choice in 405 adults with r/r Ph- ALL in a randomized 2:1 fashion; blinatumomab was associated with superior response (CR/CRh/CRi =44% vs. 25%, $p < .001$) and

Table 4. Blinatumomab studies.

Study	ALL setting	*N*	Prior alloHCT (%)	CR/CRh % (MRD response %)	Median RFS (months)	Median OS (months)
Topp et al. (MRD pilot) [113,114]	MRD^+	21	0 (0)	N/A (80)	61% (at 33 months)	N/A
Goekbuget et al. (BLAST) [115,116]	MRD^+	116	0 (0)	N/A (80)	18.9	36.5
Topp et al. (phase 2 pilot) [117]	r/r Ph^-	36	15 (42)	69 (88)	7.6	9.8
Topp et al. (confirmatory) [112]	r/r Ph^-	189	64 (34)	43 (82)	5.9	6.1
Kantarjian et al. (TOWER) [118]	r/r Ph-	271	94 (35)	44 (76)	6-month EFS = 31%	7.7
Martinelli et al. (ALCANTARA) [150]	r/r Ph^+	45	20 (44)	36 (88)	6.7	7.1

ALL: acute lymphoblastic leukemia; alloHCT: allogeneic hematopoietic cell transplantation; CR: complete remission; CRh: complete remission with partial hematopoietic recovery; MRD: minimal residual disease; RFS: relapse free survival; EFS: event free survival; OS: overall survival; N/A: not available; r/r: relapsed/refractory; Ph: Philadelphia chromosome; NR: not reported.

median OS (7.7 vs. 4.0 months) [118]. Blinatumomab studies in ALL are summarized in Table 4.

Although blinatumomab can induce durable CR in MRD + ALL without subsequent treatments [114], responses are usually transient in patients with r/r disease, and consolidation with alloHCT is recommended to prevent imminent relapse [117,119]. Interestingly, relapses after initial response to blinatumomab are manifested by CD19− leukemia and overrepresentation of extramedullary sites in subsets of patients [113,114,117,119]. For those relapsing with CD19+ disease, a third of patients respond to retreatment with blinatumomab [120].

Blinatumomab has a similar toxicity spectrum to CAR T cells, mainly CRS (grade $\geq 3 = 5\%$), neurotoxicity (grade $\geq 3 = 9\%$) and hypogammaglobulinemia [118]. The short half-life of blinatumomab allows rapid reversal of toxicity upon drug discontinuation. CRS is more pronounced in patients with higher burden disease at the time of initiating the antibody, and it is alleviated to some extent with the administration of pretreatment steroids and step-wise dose escalation of blinatumomab during the first cycle [117]. Neurotoxicity is usually reversible and appears more common with older age [121,122].

The promise of blinatumomab has encouraged investigators to incorporate its use in upfront therapy of ALL in combination with chemotherapy and/or TKIs, for Ph − and Ph + ALL (NCT#02143414).

Inotuzumab ozogamicin

Inotuzumab ozogamicin is a humanized anti-CD22 antibody conjugated to calicheamicin and has single-agent activity in CD22+ B-cell lymphoid malignancies [123,124]. CD22 is a B-lineage differentiation antigen that is frequently expressed on B-cell ALL cells (~90%) [94,125].

In a phase II study enrolling 49 patients with r/r ALL expressing CD22 in at least 20% of leukemia cells, inotuzumab was given at a dose of 1.8 mg/m^2 every 3–4 weeks and achieved an overall response rate (ORR) of 57% [126]. Subsequently, another 41 patients were treated with inotuzumab at weekly dosing (0.8 mg/m^2 on day 1, followed by 0.5 mg/m^2 on days 8 and 15 every 3–4 weeks), and the treatment achieved comparable ORR rates (59%). Overall, 36 (40%) out of 90 patients from the previous two reports underwent alloHCT after inotuzumab, and 17% ($n = 6$) developed veno-occlusive disease (VOD) [127]. In a phase III randomized study enrolling 326 patients with r/r ALL and allocating patients to inotuzumab or standard salvage choice, CR rate (81% vs. 29%, $p < .001$), MRD response (78% vs. 28%, $p < .001$), median PFS (5 vs. 1.8 months, $p < .001$) and median OS (7.7 vs. 6.7 months, $p = .04$) favored inotuzumab therapy. (Probability curves in this reference illuminate this notable improvement [128].) However, VOD occurred more frequently in inotuzumab compared to standard therapy (11% vs. 1%) [128].

Combining inotuzumab with other combination chemotherapies was feasible and encouraging [129,130]. The addition of inotuzumab was introduced as part of upfront therapy for older patients with ALL in combination with mini-hyperCVD (no anthracycline, and reduced doses of cyclophosphamide, dexamethasone, methotrexate, and cytarabine), which was feasible and yielded a high CR rate (95%). Four patients developed VOD, but no VOD occurred after reducing the inotuzumab dose to 0.8 mg/m^2 on day 1 and 1.3 mg/m^2 for subsequent doses [93].

VOD has emerged as a concern during and after inotuzumab therapy, especially for patients who later receive alloHCT [93,127,128,130,131]. The risk of VOD associated with inotuzumab is lower when weekly dosing or a lower dose is used, and when fewer alkylators are used as part of the conditioning regimen [127]. Identifying early markers and effective therapy for VOD will improve the use of inotuzumab, especially in r/r ALL where alloHCT is usually part of future treatment. Table 5 lists inotuzumab ozogamicin studies.

Table 5. Inotuzumab ozogamicin studies.

Study	ALL setting	*N*	Prior alloHCT (%)	CR/CRh % (MRD response %)	Median CRD/PFS (months)	Median OS (months)
Kantarjian et al. (Phase II) [126]	r/r Ph+ & Ph−	49	7 (14)	57 (63)	6.3	5.1
Phase II et al. (expansion of phase II) [127]	r/r Ph+ & Ph−	90	10 (11)	58 (72)	7	6.2
Kantarjian et al. (Phase III) [128]	r/r Ph+ & Ph−	109	17 (16)	81 (78)	5	7.7

ALL: acute lymphoblastic leukemia; alloHCT: allogeneic hematopoietic cell transplantation; CR: complete remission; CRh: complete remission with partial hematopoietic recovery; MRD: minimal residual disease; CRD: complete remission duration; PFS: progression free survival; OS: overall survival; r/r: relapsed/refractory; Ph: Philadelphia chromosome; NR: not reported.

CD20 antibodies (rituximab, ofatumumab)

CD20 is expressed in a subset of B-cell ALL, but the strength of expression varies among cases [94]. The expression of CD20 in ALL was correlated with inferior outcomes [132,133]. This finding led to combining the anti-CD20 monoclonal antibody rituximab with the chemotherapy backbone in ALL. The addition of rituximab to hyperCVAD compared favorably to a historic control of hyperCVAD alone in a non-randomized study in adults with Ph − ALL expressing at least 20% CD20, and the improvement was more pronounced in younger patients [134]. In a randomized study, the addition of rituximab improved EFS in younger adults with CD20+ ALL treated with the GRAALL-2005 regimen [135].

On the other hand, ofatumumab is another CD20 monoclonal antibody that binds to a different CD20 epitope, and it has higher potency compared to rituximab. Therefore, ofatumumab was combined with hyperCVAD in a phase II study enrolling 55 patients with ALL expressing $\geq$20% CD20 and showed safety and feasibility. Activity was promising, as 93% of those treated attained MRD-negative CR, and 3-year complete remission duration and OS were 78% and 68%, respectively [136].

T cell ALL

T cell ALL was considered historically as a high risk disease, with outcomes generally inferior to B cell ALL. However, this result has changed in recent years with the introduction of modern pediatric-inspired ALL regimens for T cell ALL, with outcomes comparable to B cell ALL [8,37,38,40]. The progress that was witnessed in T cell ALL was attributed to the use of intensive ALL regimens, particularly the frequent administration of asparaginase [137]. On the other hand, relapse risk is high when non-asparaginase regimens are used, especially when alloHCT consolidation was not offered in first CR [138]. The use of higher doses of methotrexate (up to 5 g/m^2) has also emerged as another approach to improve long-term outcomes of T cell ALL [139,140].

Expression of CD13, lack of CD1a expression, and a complex karyotype were factors associated with worse OS among adult T cell ALL treated with frontline therapy on the UKALL XII/ECOG 2993 study [141]. Nonetheless, the T cell phenotype is a poor prognostic feature in relapsed ALL and has limited salvage options [142]. Therefore, every effort should be made to cure T cell ALL with active frontline therapies, and early referral for alloHCT should be emphasized for high-risk features based on genetics, MRD response and possibly phenotype (early thymic T cell). In a retrospective analysis, alloHCT produced a 3-year OS of 62% for adults with T cell ALL in first CR, and no difference in outcomes was noted on the basis of leukemia phenotype (early thymic vs. others) [143].

Nelarabine has single agent activity in r/r T cell ALL [144]. Therefore, interest has emerged to incorporate nelarabine in upfront therapy for T cell ALL. Nelarabine was combined with hyperCVAD in a phase II study for newly diagnosed T cell ALL in adults, initially given after cycle 8 and then moved earlier to cycle 4 in an attempt to reduce early relapses. The study showed feasibility and encouraging activity (3-year OS =65%), but no difference in outcomes was noted on the basis of the timing of nelarabine administration [145].

The NOTCH1 pathway is frequently mutated in T cell ALL [141], and inhibition of gamma (γ) secretase results in decreased levels of intracellular NOTCH-1 and downregulation of its target genes. Single agent activity of (γ) secretase inhibitors has been reported in patients with r/r T cell ALL; however, gastrointestinal toxicity has emerged as a limiting toxicity [146,147]. Dexamethasone induced a synergistic effect when combined with a NOTCH inhibitor, and lessened gastrointestinal toxicity in a xenograft model [148]. A phase I/II study combining dexamethasone with LY3039478, a potent and selective NOTCH inhibitor, is ongoing and will address the activity of the combination regimen (NCT02518113).

Table 6. Novel treatment strategies and their mechanisms.

Strategy	Mechanism
TKIs for Ph-like ALL	Tyrosine kinase inhibition for activating mutations
Asparaginase	Deprivation of ALL blasts from circulating asparagine
2nd and 3rd generation TKIs	Higher potency and activity against more frequently encountered mutations in Ph + ALL
CAR T cells	Genetic reprograming of T cells to target a surface antigen on tumor cells
Blinatumomab	Redirection of effector CD3+ T cells in close proximity to CD19+ ALL cells, creating cytolytic synapse
Inotuzumab ozogamicin	Targeted delivery of antitumor agent (calicheamicin) to CD22+ cells
CD20 antibodies	Targeting of CD20+ ALL and mediating cell lysis
Nelarabine for T cell ALL	Inhibition of DNA synthesis
Gamma secretase inhibitors for T cell ALL	Inhibition of NOTCH-1 signaling and downregulation of target genes.

ALL: acute lymphoblastic leukemia; TKI: tyrosine kinase inhibitor.

Future directions

Recently, multiple factors have contributed to the progress of adult ALL therapy, and we anticipate one day we will observe outcomes in adult ALL comparable to those seen in pediatrics. This progress will occur with earlier referral of adult ALL patients to specialized centers to accommodate complex disease treatment, extending the use of pediatric-inspired ALL regimens in adults, incorporating new genomic and MRD response factors to more rapidly determine the necessity of changing therapy, integrating novel therapies in upfront therapy, testing TKIs in Ph-like ALL, and earlier identifying HLA-matched donors so that newly diagnosed patients proceed to transplant faster when recommended. Novel treatment strategies and their mechanisms are displayed in Table 6.

On the other hand, older adults with ALL remain a difficult to treat population, with only minimal improvement in ALL outcomes observed lately. The use of pediatric-inspired regimens in this age group is limited by toxicity and tolerability, as well as reduced activity due to high risk genetics. Nonetheless, new novel immunotherapeutics, antibodies and TKIs have shown promising activity and toxicity profiles irrespective of patient age, and introducing these therapies in the frontline setting is being studied and will likely help to advance the treatment of older adults with ALL.

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