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Recent Advances in Adult Acute Lymphoblastic Leukemia

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Abstract

Purpose of Review This article reviews the recent advances in the pathophysiology and management of acute lymphoblastic leukemia (ALL) in adults.

Recent Findings Addition of rituximab to standard chemotherapy improves survival in the frontline treatment of B cell ALL, and measurable residual disease (MRD) is the most important prognostic factor. Tyrosine kinase inhibitors (TKI), particularly ponatinib, in combination with Hyper-CVAD significantly improve outcomes in Ph + ALL challenging the benefit of allogeneic stem cell transplant in first line for these patients. Blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor (CAR) T cells are better options than chemotherapy alone for the treatment of relapsed or refractory ALL. Combination of these agents with chemotherapy and their incorporation in the frontline setting show promises to improve cure rates of ALL.

Summary Development of monoclonal antibodies, CAR T, and potent TKI has improved the outcome of ALL. Advances in our understanding of ALL biology are expected to bring new therapeutic strategies in the upcoming years.

Keywords Acute lymphoblastic leukemia · Treatment · Management · Monoclonal antibodies · Chimeric antigen receptor T cells

Introduction

Acute lymphoblastic leukemia (ALL) is an aggressive neoplasm of lymphoid progenitor cells. The annual incidence of ALL is 1.7 cases per 100,000 people in the USA [1]. In 2018, the estimated number of new cases was 5960 and the estimated number of deaths was 1470 [1]. Age distribution is bimodal with peak of incidence in the childhood and around 60 years old. ALL is the most common neoplasm in children in whom its treatment has been a true success story in oncology. With contemporary chemotherapy protocols, pediatric ALL has become a highly curable disease with long-term survival rates above 90% [2]. In contrast, long-term overall survival (OS) in adults is about 35–45% [3, 4]. In the past decade, multiple advances in our understanding of the biology of ALL have led to significant breakthroughs, finally renewing hope for adult patients affected by this disease. This review will focus on the recent advances and therapeutic options now available for adult ALL and future directions to continue improving cure rates.

This article is part of the Topical Collection on *Acute Lymphocytic Leukemias*

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Diagnostic and Prognostic Evaluation

Diagnostic evaluation of ALL requires a bone marrow aspiration and biopsy with morphology, immunophenotyping by flow cytometry, and karyotype and fluorescence hybridization in situ hybridization (FISH) to identify *BCR-ABL1* fusion or *KMT2A* gene rearrangements. Mutational analysis of targeted genes is also useful to refine diagnosis and prognosis. A PET/CT scan is recommended to evaluate the presence of lymphadenopathies, hepatosplenomegaly, and mediastinal mass at diagnosis.

Multicolor flow cytometry (MFC) is required to differentiate B cell from T cell lineage ALL and to identify cell surface markers that can be targeted by monoclonal antibodies [5, 6]. B cell ALL accounts for ~ 75% of cases of ALL and is characterized by expression of CD19, CD22, and CD79a. Expression of CD20 is observed in 30–50% of B-ALL and was shown to be associated with poorer outcome, prior to standard administration of CD20 monoclonal antibodies [7,

8]. T cell lineage ALL comprises approximately 25% of adult cases and is characterized by TdT and cytoplasmic CD3 positivity and variable expression of CD1a, CD2, CD4, CD5, CD7, and CD8. In the past decade, early T cell precursor (ETP) ALL was defined as a subgroup of T-ALL arising from immature cells with the potential to differentiate into myeloid and T lineage [9, 10••]. ETP ALL lymphoblasts are negative for CD8 and CD1a, but positive for cytoplasmic CD3 and CD7 and one or more of the myeloid lineage markers (e.g., CD13, CD33). This subgroup accounts for ~ 20% of cases of T-ALL in adults and have a poor clinical outcome, with frequent induction failure and early relapse (Table 1) [11]. Intensified pediatric regimens with asparaginase might however mitigate this poor prognosis [12].

Cytogenetics

The karyotype is abnormal in approximately 75% of cases of ALL (Table 1) [13, 14]. The t(9;22)(q34;q11) or Philadelphia chromosome (Ph) is the most common cytogenetic abnormality observed in B-ALL occurring in ~ 20–30% of cases with an increasing frequency with age. Ph-positive ALL historically had an adverse outcome, but integration of TKI into the chemotherapy regimens has mitigated the poor prognosis of this subgroup.

In adult patients with Ph-negative B-ALL, t(4;11)(q21;q23)—*KMT2A-AFF1* (9–13% of cases), t(v;14)(v;q32)—*IGH*-r (2–5% of cases), and low hypodiploidy/near triploidy (Ho-Tr) (4–6% of cases) are the subgroups consistently associated with adverse prognosis (Table 1) [15–18]. Patients with complex cytogenetics (≥ 5 chromosomal abnormalities) had previously been associated with adverse prognosis [13], but its impact is inconsistent in recent series [17–19]. The t(1;19)(q23;p13)—*TCF3-PBX1*, observed in 5% of cases, is associated with central nervous system relapses, but does not confer adverse outcome with intensified chemotherapy protocols [17, 20–22]. The prognostic significance of t(12;21)(p13;q22)—*ETV6-RUNX1* and intrachromosomal amplification of chromosome 21 (iAMP21) are not clearly defined in adults because of their

Table 1 Genetic subgroups of acute lymphoblastic leukemia

Genetic subgroup	Cytogenetic lesions	Prevalence	Prognosis
B cell lineage ALL			
Ph+	t(9;22)(q34;q11)—BCR-ABL1	20–30%	Historically poor; improved with TKI
Ph-like ALL	t(X;14)(p22;q32), del (Xp22), t(9p24;v)	20–30%	Poor
HeH	51–65 chromosomes	6–10%	Favorable
Ho-Tr	30–39 or 60–78 chromosomes	4–6%	Poor
CK	≥ 5 chromosomal abnormalities	5–7%	Poor
KMT2A-AFF1	t(4;11)(q21;q23)	9–13%	Poor with t(4;11)
IGH-IL3	t(5;14)(q31;q32)	2–5%	Poor
MYC-r	t(8;14)(q24;q32), t(2;8)(q12;24), t(8;22)(q24;q11)	2%	Favorable
TCF3-PBX1 fusion	t(1;19)(q23;p13)	5–7%	Standard
ETV6-RUNX1 fusion	t(12;22)(p13;q22)	< 1%	Probably favorable
iAMP21	Intrachromosomal amplification of chromosome 21q22.11-21q22.12	< 1%	Probably poor
T cell lineage ALL			
ETP ALL	Various	17–22%	Poor
TAL1 dysregulation	del(1p32), t(1;7)(p32;q34), t(1;14)(p32;q11)	10–15%	Favorable
TLX1-r	t(10;14)(q24;q11), t(7;10)(q34;q24)	5–10%	Uncertain
TLX3-r	t(5;14)(q35;q32)	5–6%	Uncertain
LMO2 dysregulation	t(11;14)(p13;q11), t(7;11)(q34;p13), del(11)(p12p13)	2–6%	Uncertain
AF10-CALM	t(10;11)(p13;q14–21)	~ 3%	Uncertain
KMT2A-r	t(11;19)(q23;p13)—KMT2A-ENL	1–2%	Uncertain
NUP214-ABL1	Amplification of 9q34	~ 2%	Uncertain
Deletion 17p	del(17p)	~ 5%	Poor
CK	≥ 5 chromosomal abnormalities	~ 8%	Poor

ALL acute lymphoblastic leukemia, *Ph* Philadelphia chromosome, *TKI* tyrosine kinase inhibitors, *HeH* high hyperdiploidy, *Ho-Tr* low hypodiploidy/near triploidy, *CK* complex karyotype, *-r* rearrangement, *ETP* early T cell precursor

very low frequency (< 1%), but they are thought to confer favorable and adverse prognosis, respectively, by extrapolation from pediatric data and small reports in adults [22, 23].

In T cell ALL, complex karyotype and del(17p) are the two cytogenetic subgroups associated with a poor prognosis [14, 23]. The cytogenetic landscape of T cell ALL is otherwise broad and heterogeneous including translocations involving genes *TLX1*, *TLX3*, *LYL1*, *TAL1*, *TAL2*, *LMO1*, *LMO2*, and *MLL* associated with multiple various gene partners, notably T cell receptor *TCRA/D* and *TCRB/G* genes (Table 1) [14]. The prognostic significance of most of these rare cytogenetic subgroups is uncertain in adults.

Ph-Like ALL Is a Distinct Biological Entity with Poor Prognosis

Ph-like ALL is a high-risk subset of B-ALL with gene expression profile similar to Ph-positive ALL and with genetic alterations activating kinase signaling pathways (Table 1) [24, 25, 26••]. In adults, the incidence of Ph-like ALL varies between 20 and 30% with higher frequency in young adults and patients of Hispanic ethnicity [27, 28]. The clinical outcome of patients with Ph-like ALL is inferior with 5-year OS of 23–24% compared to 52–59% in other subgroups of B-ALL. Ph-like ALL harbors rearrangements in cytokine receptor-like factor 2 (*CRLF2*) in 50–60% of cases, most frequently partnered with *IGH* (76% of cases) or *P2RY8* (17% of cases). These cases are frequently associated with mutations in *JAK2* (25–45% of cases) or other kinases of the JAK-STAT or Ras pathway. In patients without *CRLF2* rearrangements or overexpression, Ph-like ALL is associated with rearrangements in ABL class genes (*ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB*), *JAK2*, *EPOR*, or point mutations in signaling pathways genes (*IL7R*, *SH2B3*, *JAK1*, *JAK3*, *KRAS*), highlighting the broad heterogeneity of the Ph-like genetic subgroup. *IKZF1* deletions are detected in 68–73% of all cases of Ph-like ALL, a common feature shared with Ph-positive ALL [29]. The importance of the identification of Ph-like ALL lies in the growing clinical data suggesting that patients harboring these genetic alterations may benefit from TKI or *JAK2* inhibitors [26••]. The benefit of these agents in addition to standard chemotherapy regimens is in evaluation in ongoing clinical trials (NCT02883049, NCT02420717).

Measurable Residual Disease: a Powerful Prognostic Factor in ALL

Evaluation of measurable residual disease (MRD) by flow cytometry has been demonstrated to be one of the most important prognostic tools in ALL [30–33]. A recent meta-analysis with pooled data from multiple studies recently confirmed the prognostic impact of MRD positivity [34]. MRD assessment should be performed after the first cycle of induction, at time of complete remission (CR), at 3 months, and every 3 to 6 months thereafter. Persistence or reappearance of MRD with $> 10^{-3}$ (> 0.1%) of aberrant cells is associated with a poorer prognosis. MRD evaluation should only be performed in laboratories with extensive experience and expertise in flow cytometry and MRD testing as technical aspects are complex, but critical [35]. Patients with MRD positivity at any time after induction should be referred for allogeneic stem cell transplant (HSCT) or other intensification strategies including blinatumomab (discussed below).

Mature B Cell ALL

Burkitt leukemia/lymphoma (BL) is a mature B cell neoplasm characterized by rearrangement of the gene *MYC*, most commonly partnered with the *IGH* gene. Neoplastic cells originate from the germinal center and express B cell antigens (CD19, CD20, CD22, CD79a), membrane IgM with light chain restriction and germinal center markers (CD10, BCL6) [5]. With intensive chemotherapy regimens incorporating rituximab, long-term remissions are now achieved in ~ 80% of patients [36–38, 39••, 40]. In a phase 2 trial of Hyper-CVAD in combination with rituximab (two doses for each of the first 4 cycles), CR rate was 86% and 3-year OS was 89%, comparing favorably to historical controls without rituximab (CR rate of 81% and 3-year OS of 49%) [36]. The benefit of the addition of rituximab to chemotherapy in BL was confirmed by a multicenter randomized controlled phase 3 trial in which 260 patients were allocated to receive or not four doses of rituximab with the LMB (lymphoma malin B) protocol during the COPADM induction phase (fractionated cyclophosphamide, adriamycin, high-dose methotrexate, vincristine, and prednisone) [39••]. Patients randomized to receive rituximab had an improved 3-year event-free survival (EFS) of 75% compared to 62% in patients who did not receive rituximab ($p = 0.024$). The 3-year OS was also better in patients receiving rituximab (83% vs 70%, $p = 0.011$) and was particularly favorable in patients younger than 40 years old (94% vs 88%, $p = 0.03$). In results from other groups, the addition of rituximab to chemotherapy regimens increased the CR rates from ~ 70 to 85–90% and the cure rates from 40 to 50 to ~ 80% [37, 38]. Dose-adjusted EPOCH with rituximab (DA-EPOCH-R) showed promising results in a single-institution study including 30 patients with BL [40]. In a multicenter phase 2 trial including 112 patients so far, DA-EPOCH-R was associated with a progression-free survival (PFS) of 84.6% and OS of 84.7% at a median follow-up of 34 months [41]. A randomized phase 3 trial is ongoing to compare this regimen to another established protocol for Burkitt leukemia/lymphoma (EudraCT 2013-004394-27).

Adolescents and Young Adults

In the past decade, retrospective studies have shown that adolescents and young adults (AYA) had better outcomes when treated in pediatric centers or with intensive pediatric chemotherapy regimens [42–46]. A series of prospective trials with pediatric-inspired intensive chemotherapy regimens for AYA patients yielded improved long-term OS of 60–70% [47–54]. These regimens include higher doses and prolonged intensifications with asparaginase and corticosteroids which can be associated significant toxicities including pancreatitis, thrombotic events and avascular osteonecrosis. The Hyper-CVAD regimen, which does not include asparaginase, showed comparable results to the Augmented Berlin-Frankfurt-Münster (A-BFM) regimen in a non-randomized study including AYA patients treated at the MD Anderson Cancer Center (MDACC) [55]. The 5-year complete remission duration (CRD) was 53% with Hyper-CVAD and 55% with A-BFM, and the 5-year OS was 60% in both groups [55]. Although significant improvements have been made, the survival of AYA patients with ALL is still not optimal. Compared to children, AYA patients have higher frequency of adverse risk features (e.g., Ph-like ALL), lower frequency of favorable risk features (e.g., t(12;21)—*ETV6-RUNX1*), higher treatment-related toxicities, and poorer compliance. These patients also have specific psychological and social issues that are best addressed by multidisciplinary teams with expertise in the care of this population [56].

CD20-Directed Antibodies in B-ALL

Addition of CD20-directed monoclonal antibodies to chemotherapy regimens improved the survival of patients with Ph-negative B-ALL. In a trial at the MDACC, addition of 12 doses of rituximab to the Hyper-CVAD regimen increased the 3-year OS rate from 47 to 75% ($p = 0.003$) compared with historical controls [57]. These results were validated in the phase III randomized trial GRAALL-2005/R in which patients < 60 years old with Ph-negative CD20-positive B-ALL were randomized to receive 16 to 18 doses of rituximab in addition to standard chemotherapy [58••]. The 2-year EFS was 65% in the rituximab group vs 52% in the control group ($p = 0.04$). The 2-year OS was 71% in the rituximab group vs 64% in the control group, although not statistically significant ($p = 0.10$). In sensitivity analyses with censoring at time of HSCT, rituximab was associated with a statistically significant improvement in OS (hazard ratio, 0.55; $p = 0.02$).

Ofatumumab binds to a juxta-membrane small-loop epitope of CD20 and has increased complement-dependent cytotoxicity (CDC) compared to rituximab [59, 60]. A phase 2 trial evaluated ofatumumab in combination to the Hyper-CVAD in CD20-positive Ph-negative B-ALL [61]. In a total of 65 evaluable patients, CR or CRp was achieved in 64 (98%) and the rate of MRD negativity was 93% overall. With a median follow-up of 27 months, the estimated 2-year CRD and OS were 79% and 81%, respectively. Patients with either 1–19% or ≥ 20% of CD20 expression may equally benefit from CD20-directed therapy.

Obinutuzumab is a highly potent anti-CD20 monoclonal antibody with increased direct cytotoxicity in vitro. It is superior to rituximab in the treatment of chronic lymphocytic leukemia [62]. The safety and efficacy of obinutuzumab in combination with chemotherapy regimens has not been evaluated yet and represents an open field for study.

Nelarabine for T Cell ALL

Nelarabine, a water-soluble prodrug of 9-β-D-arabinofuranosylguanine (ara-G), is a purine nucleoside analogue preferentially accumulating in T-lymphoblasts. Its single agent activity was demonstrated in patients with relapsed or refractory T-ALL in two independent phase 2 trials achieving CR rates of 31–36% [63, 64].

Nelarabine was recently evaluated in combination with Hyper-CVAD in the frontline setting for T-ALL [65]. CR rate was 96% with a 3-year CRD and OS of 66% and 65%, respectively, which was not significantly improved compared to historical controls. However, incorporation of nelarabine into standard treatment improved disease-free survival (DFS) in the Children Oncology Group (COG) AALL0434 trial in which patients up to 31 years old with T-ALL were randomized to receive or not six 5-day courses of nelarabine at a dose of 650 mg/m^2/day [66]. The 4-year DFS was 88.9% for patients randomized to receive nelarabine compared to 83.3% for patients randomized not to receive nelarabine ($p = 0.00332$). Although these results might be relevant for the AYA population, benefit of nelarabine in the frontline setting remains uncertain in adults.

Treatment for Ph-Positive ALL

Addition of TKI to the treatment of Ph + ALL has significantly improved the outcome of this historically classified adverse-risk subgroup. Addition of imatinib to chemotherapy improved CR rates to > 90–95% and long-term survival to 40–50% [67–69]. Second- and third-generation TKIs have been tested to improve further on these results. In a study by the Korean group, addition of nilotinib to chemotherapy resulted in 2-year RFS and OS rates of 72% [70]. When adding dasatinib to the Hyper-CVAD regimen, 2-year DFS and OS were 60% and 64%, respectively, showing improvements upon imatinib [71, 72••]. These results were validated in a US intergroup multicenter study evaluating Hyper-CVAD plus dasatinib in 94 young

patients with Ph-positive ALL. In this study, the 3-year RFS and OS were 62% and 69%, respectively. Outcomes are further improved with the combination of Hyper-CVAD and ponatinib, a third-generation TKI, at a dose of 45 mg [72••]. In a follow-up on 64 patients, this regimen yielded CR rate of 98%, major molecular remission (MMR) rate of 97%, and complete major remission (CMR) rate of 84% [72••, 73]. The 3-year CRD and OS were 79% and 76%, respectively. Grade ≥ 3 pancreatitis occurred in 12 (19%) patients, thrombotic events in 4 (6%) patients, and myocardial infarction in 3 (5%) patients. Among eight deaths, two were related to ponatinib. After a protocol amendment reducing the dose of ponatinib to 30 mg once patients achieve CR and to 15 mg once patients achieve CMR, no grade ≥ 3 vascular events were reported. Importantly, ponatinib is effective against ALL cells harboring the *ABL1* T315I mutation which is a known mechanism of resistance and relapse in Ph-positive ALL [74].

The treatment-related toxicities are a major concern for Ph + ALL. Chalandon et al. showed fewer early deaths (0.7% vs 6.7%, $p = 0.010$) and 60-day mortality (2.2% vs 9.0%, $p = 0.017$) with a Hyper-CVAD-inspired induction regimen without doxorubicine and cyclophosphamide [75]. The 5-year EFS and OS rates were 37.1% and 45.6%, respectively, and no difference was observed compared to Hyper-CVAD. However, the 60-day mortality of 9% in the Hyper-CVAD induction arm is much higher than observed at the MDACC potentially negating any benefit. Furthermore, the intermittent schedule of imatinib may not be an optimal strategy for suppression and eradiation of the Ph-positive clone.

In older patients with Ph-positive ALL, reduced intensity chemotherapy regimens in combination with TKIs have been evaluated to decrease treatment-related toxicities and the rate of induction mortality [76–79]. In the European Working Group on Adult ALL (EWALL) study for Ph-positive ALL, patients older than 55 years old were treated with dasatinib 140 mg per day with vincristine, dexamethasone, and intrathecal chemotherapy for induction followed by consolidation with dasatinib 100 mg per day with intermediate-dose cytarabine, asparaginase, and methotrexate for 6 months and maintenance therapy for 18 months [78]. With this regimen, 96% of patients achieved CR and 65% of evaluable patients achieved MMR during consolidation. The estimated RFS and OS were 28% and 36%, respectively, at 5 years. In this study, 23% of evaluable patients had the T315I mutation at diagnosis and it was detected in two thirds of patients at relapse confirming its role in the resistance and recurrence of Ph-positive ALL. The combination of nilotinib 400 mg twice daily with the same chemotherapy backbone in the EWALL-PH02 trial was associated with a CR rate of 94.4% and 4-year EFS and OS of 42% and 47%, respectively, comparing favorably to the results obtained with dasatinib [80]. A combination of ponatinib with corticosteroids without chemotherapy resulted in CR rate of 95.2% and 1-year OS of 87.5% with limited toxicity [79]. Reduced intensity regimens with TKIs and inclusion of monoclonal antibodies in the frontline setting of elderly patients with Ph-positive ALL may further improve cure rates without chemotherapy-related adverse events. The combination of ponatinib with blinatumomab is currently in evaluation at the MDACC in a cohort of untreated elderly patients with Ph-positive ALL (NCT03263572). Various other combinations of TKIs and blinatumomab (NCT02143414, NCT02744768) or inotuzumab (NCT02311998) are also being evaluated in ongoing clinical trials.

The Role of Stem Cell Transplant in ALL

Patients with high risk of relapse are referred for a stem cell transplant in first CR. These high-risk features are low hypodiploidy/near triploidy (Ho-Tr), t(4;11), t(9;22), and complex karyotype [13]. With the recent advances in risk stratification of ALL, patients who do not achieve MRD negativity after induction chemotherapy, Ph-like ALL and ETP ALL should also be considered for HSCT [28, 33, 34]. The French group identified in the GRAALL-2003/2005 trials that the main factors predicting for the benefit of SCT in CR1 were MRD positivity after induction, the presence of *IKZF1* in B-ALL, and absence of *NOTCH1* or *FBXW7* mutations in T-ALL [33, 81]. Whether patients with positive MRD who achieve MRD negativity after treatment with blinatumomab should still be referred for HSCT remains an open question.

The benefit of HSCT in CR1 for patients with Ph + ALL becomes uncertain with the addition of potent TKIs to conventional first-line therapy. Patients achieving CMR or MMR after chemotherapy and TKIs have a very good prognosis and may not benefit from additional intensification with HSCT [82, 83]. In the study by Chalandon et al., HSCT in CR1 was associated with significant improvements in RFS (HR, 0.69) and OS (HR, 0.64) in the overall population, but these benefits were restricted in patients with white blood cell counts $> 30 \times 10^9$/L at diagnosis and patients who did not achieve MMR after 2 cycles of chemotherapy [75]. Furthermore, in patients who received Hyper-CVAD plus ponatinib as frontline treatment of Ph + ALL, long-term survival probability was not modified when data were censored at time of transplant suggesting that most of these patients may be cured without transplant [72••, 73]. Considering these data, we usually refer Ph-positive ALL patients to HSCT at our center when they do not achieve CMR after 3 cycles of therapy and after a trial with blinatumomab.

Relapsed and Refractory ALL

Relapsed or refractory ALL is associated with a dismal prognosis with a cure rate of less than 10% [84–86]. The CR rates

with standard chemotherapy regimens are 30–40% in first relapse and 20–25% in second relapse [87, 88]. Accordingly, only 10–30% adult patients with relapsed ALL proceed to HSCT, which is the only curative option in this setting. Recent developments of monoclonal antibodies and chimeric antigen receptor (CAR) T cells have significantly improved the outcomes of patients with relapsed or refractory ALL and have become standard treatments in this setting (Table 2).

Inotuzumab

Inotuzumab is a humanized antibody drug conjugate (ADC) coupled with calicheamicin which targets CD22, a glycoprotein expressed on lymphoblasts in ~ 90% of patients with B-ALL [6]. Phase I and II trials with single agent inotuzumab in relapsed or refractory ALL have shown overall remission rates (ORR) of 58–68% with MRD negativity rates of 72–84% (Table 2) [96, 97]. The safety and efficacy of inotuzumab in relapse or refractory B-ALL was further evaluated in a multicenter randomized phase 3 trial comparing 6 cycles of inotuzumab to standard of care intensive chemotherapy [95••]. Inotuzumab was administered weekly for a total dose of 1.8 mg/m^2 per cycle, reduced to 1.5 mg/m^2 once patients achieved CR. In patients randomized to inotuzumab, the CR rate was 80.7% and the MRD negativity rate was 78.4%, whereas in patients randomized to chemotherapy, the CR rate was 29.4% and the MRD negativity rate was 28.1%. Median OS was 7.7 months in the inotuzumab group and 6.7 months in the chemotherapy group, but this did not meet the prespecified statistical boundary. However, the 2-year OS was 23% in the inotuzumab group and 10% in the chemotherapy group, a difference that can be explained by the greater proportion of patients proceeding to HSCT in the inotuzumab group (41% vs 11%, $p < 0.001$).

Inotuzumab was also evaluated in combination with mini-Hyper-CVD, a reduced-dose Hyper-CVAD without doxorubicin, in a phase 2 clinical trial of patients with relapsed or refractory B-ALL (Table 2) [98]. Inotuzumab was given on day 3 of cycles 1 to 4 at doses of 1.0 to 1.8 mg/m^2 per cycle. The ORR was 80%, and among 64 evaluable patients, the MRD negativity rate after 3 cycles was 80%. The median OS was 14 months, and the 3-year CRD and OS were 33% and 49%, respectively [100]. Patients treated in first salvage particularly benefited from this regimen with an ORR rate of 92%, a median OS of 25 months, and an estimated 2-year OS rate of 54% [101]. Using inverse probability of treatment weighting analysis, the inotuzumab plus mini-Hyper-CVD had better ORR (75% vs 63%, $p = 0.02$) and median OS (9.3 months vs 5.6 months, $p = 0.02$), compared with historical controls who received inotuzumab alone [98]. This study was later amended to incorporate 4 cycles of blinatumomab after 4 initial cycles of mini-Hyper-CVD plus inotuzumab to improve outcomes and further decrease chemotherapy administration [100].

Inotuzumab is associated with increases in liver function tests in 20–25% of patients, mostly reversible and grade 1 or 2.

Table 2 Efficacy of FDA-approved therapies for relapsed or refractory ALL

Clinical trial	Patients	Number	ORR	MRD rate	HSCT rate	Median OS	Reference
Blinatumomab (Blincyto)							
Phase III	R/R (Ph-)	405	Blina 44% SOC 25%	Blina 76% SOC 48%	Blina 24% SOC 24%	Blina 7.7 m SOC 4.0 m	[89••]
Phase II	R/R (Ph-)	189	43%	82%	40%	6.1 m	[90]
Phase II	R/R	36	69%	88%	52%	9.8 m	[91]
Phase II	R/R (Ph+)	45	36%	88%	44%	7.1 m	[92]
Phase II	MRD+ $\geq 1 \times 10^{-4}$	21	N/A	80%	38%	NR	[93]
Phase II	MRD+ $\geq 1 \times 10^{-3}$	116	N/A	78%	67%	36.5 m	[94••]
Inotuzumab (Besponsa)							
Phase III	R/R	218	Ino 81% SOC 29%	Ino 78% SOC 28%	Ino 41% SOC 11%	Ino 7.7 m SOC 6.7 m	[95••]
Phase II	R/R	90	58%	72%	40%	6.2 m	[96]
Phase I/II	R/R	72	68%	84%	33%	7.4 m	[97]
Inotuzumab (Besponsa) + mini-Hyper-CVD							
Phase II	R/R (Ph-)	59	78%	82%	44%	11 m	[98]
Tisagenlecleucel (Kymriah)							
Phase II	R/R	75	81%	100%	13%	NR	[99]

ORR overall remission rate (includes complete remission (CR) and complete remission with incomplete hematological recovery (CRi)), *MRD* minimal residual disease, *HSCT* hematopoietic stem cell transplant, *OS* overall survival, *R/R* relapsed or refractory, *Ph* Philadelphia chromosome, *Blina* blinatumomab, *SOC* standard of care, *m* months, *NR* not reached, *Hyper-CVD* hyper-fractionated cyclophosphamide plus vincristine and dexamethasone

Veno-occlusive disease (VOD) is a potential fatal condition observed in 5–15% of patients receiving inotuzumab. This complication occurs mainly in patients who undergo or had prior HSCT especially if a dual-alkylator conditioning regimen was given. Weekly administration of inotuzumab with lower doses after first cycle (0.6 mg/m^2 on day 1 and 0.3 mg/m^2 on days 8 and 15) is in evaluation to reduce the frequency of this adverse event (NCT03094611). In 18 patients treated with mini-Hyper-CVD plus inotuzumab at reduced weekly dose of 0.6 and 0.3 mg/m^2 on cycle 1 then 0.3 and 0.3 mg/m^2 on subsequent cycles, no case of VOD has been observed so far suggesting that dose reductions may decrease incidence of this toxicity [100].

Blinatumomab

Blinatumomab is a bispecific T cell engager (BiTE) with dual affinity for CD19 and CD3 allowing T cells to recognize and exert their cytotoxic activity against CD19-positive lymphoblasts. A multicenter phase 2 trial initially reported CR rate of 43% in patients with relapsed or refractory B-ALL (Table 2) [90]. In the phase 3 multicenter trial TOWER, blinatumomab was compared to standard of care chemotherapy regimens [89••]. Blinatumomab was administered for 2 cycles of induction consisting of 4 weeks of continuous infusion at a dose of 28 mcg daily (9 mcg for the first week of cycle 1) followed by 2 weeks off treatment. Patients achieving CR after induction were eligible to pursue up to 3 cycles of consolidation followed by maintenance treatment every 3 months for 1 year. The median OS was 7.7 months in patients randomized to blinatumomab compared to 4.0 months in patients randomized to chemotherapy. Within 12 weeks of treatment, the ORR was 44% with blinatumomab compared to 25% with chemotherapy. Among patients who achieved remission, 76% of the patients in the blinatumomab group had negative MRD compared to 48% of the patients allocated to chemotherapy.

Blinatumomab was also evaluated in patients achieving CR, but with persistent MRD [94••]. In the BLAST multicenter phase 2 trial, patients in CR with $\geq 10^{-3}$ MRD received blinatumomab 15 mcg/m^2 IV daily as a 4-week continuous infusion for up to 4 cycles. In the primary endpoint efficacy set of 103 patients, 82 (80%) patients achieved complete MRD response after 1 cycle and 91 (88%) at any time. The 18-month RFS estimate without censor at time of transplant was 54%. Median RFS was longer for patients who achieved MRD negativity (23.6 vs 5.7 months, $p = 0.002$) and for those who were treated in first CR compared to later CR (24.6 vs 11.0 months, $p = 0.004$). Seventy-four patients (67%) underwent HSCT, and 36 of these patients (49%) remained in prolonged remission with a median follow-up of 24.0 months. In comparison, 9 of 36 patients (25%) without additional treatment after blinatumomab remained in CR. Albeit exploratory and limited by small numbers, this data may continue to suggest a role for HSCT in patients with MRD positivity after induction even if they achieve MRD negativity with blinatumomab. Further studies are needed to answer that question.

Blinatumomab is also effective in patients with relapsed or refractory Ph + ALL in whom few therapeutic options exist after failure to TKIs [92]. In a phase 2 multicenter trial, 16 of 45 (36%) patients with relapsed or refractory Ph + ALL treated with blinatumomab achieved CR with or without hematologic recovery, including some patients with T315I mutation. Of these responders, 88% achieved CMR by *BCR-ABL1* qPCR testing. Median RFS was 6.7 months, and median OS was 7.1 months. Combination of blinatumomab with TKIs, especially ponatinib, may further increase the responses rates and survival of these patients and are evaluated in ongoing clinical trials (NCT03263572, NCT02143414) [102].

Blinatumomab is better tolerated than chemotherapy with lower grade ≥ 3 adverse events when rates were adjusted for the treatment exposure in the phase 3 TOWER study [103]. Neurological events, including tremor, dizziness, confusion, and aphasia, occur in nearly half of patients receiving blinatumomab, with grade ≥ 3 neurological events occurring in 10–15% of patients [89••, 90, 94••]. Most of these events can however be treated with dexamethasone and interruption of blinatumomab infusion in more severe cases. Blinatumomab can then be safely resumed after resolution of symptoms. Grade 3–4 cytokine release syndrome (CRS) occurs in 2 to 6% of patients and can also be treated with dexamethasone and interruption of blinatumomab. Because CRS is associated with higher burden of disease, a sequential combination approach of low-dose chemotherapy followed by blinatumomab may decrease the rate of this adverse event [104].

CAR T Cells

Chimeric antigen receptor (CAR) T cells have emerged as another option for the treatment of relapsed or refractory B-ALL producing CR rates of ~ 80% in cohorts of heavily pretreated patients [99, 105]. In a phase 2 multicenter study, 75 children and young adults with relapsed or refractory CD19+ B-ALL received a single infusion of tisagenlecleucel, CD19 CAR T cells produced by Novartis (Table 2) [99]. Among evaluable patients, the ORR was 81% with all responding patients achieving negative MRD. The 12-month EFS and OS were 73% and 90%, respectively, and median OS was 19.1 months. The CAR T cells persisted for a median of 168 days (from 20 to 617 days) suggesting that immunosurveillance with these products may be long lasting. Similar results have been obtained with CAR T cells developed and evaluated at the Memorial Sloan Kettering Cancer Center (MSKCC) in a phase 1 single-center trial [105]. Among the 53 adult patients with heavily pretreated B-ALL who received the CAR T cell infusion, the CR rate was 83%

including 32 of 48 (67%) evaluable patients achieving negative MRD. Better outcomes were observed in patients with low disease burden (≤ 5% bone marrow blasts) at time of CAR T cell infusion with a median EFS of 10.6 months compared to 5.3 months and median OS of 20.1 months compared to 12.4 months in patients with a high disease burden [105].

The two main adverse events with CAR T cells are CRS and neurologic events which occur in 77–83% and 40–43% of patients, respectively. The frequency of these side effects correlates with the patients' disease burden and is less likely to occur in patients with less than 5% bone marrow blasts. Grade ≥ 3 CRS, including one death in the MSKCC study, were observed in 26% and 46% of patients, and most of them required treatment with tocilizumab, an anti-IL6 antibody. The assessment and management of CRS in patients receiving CAR T cells is reviewed elsewhere [106].

In addition to significant toxicities, CAR T cell therapy is complex to produce which implies delays in treatment initiation. In the trial with tisagenlecleucel, the median time from enrollment to infusion of CAR T cells was 45 days, and many patients in both trials (18–36%) did not receive the planned treatment for various reasons including infection, progressive disease, CAR T cell production failure, or premature death [99, 105]. Further studies are needed to improve the safety profile and feasibility of this therapeutic approach.

Future Directions

To further improve cure rates, monoclonal antibodies are now being evaluated in combination with chemotherapy in the frontline setting of B-ALL. In a phase 2 trial at the MDACC, the addition of inotuzumab to mini-Hyper-CVD in 52 elderly patients with untreated B-ALL resulted in an ORR of 98%, 2-year PFS of 59%, and 3-year OS of 56% with manageable toxicity [107]. Based on these impressive results, incorporation of either or both inotuzumab and blinatumomab to Hyper-CVAD in young patients with B-ALL is being evaluated in phase 2 trials at the MDACC (NCT02877303, NCT03488225). The sequential combination of 4 cycles of Hyper-CVAD and 4 cycles of blinatumomab followed by 12-month maintenance was associated with a CR rate of 100% and 1-year RFS and OS rates of 77% and 90%, respectively, in 17 patients [104]. Two phase 3 multicenter randomized trials are underway to evaluate monoclonal antibodies in combination with chemotherapy backbones for patients with untreated B-ALL. Blinatumomab consolidation is evaluated in patients aged 30–70 years in the ECOG1910 trial (NCT02003222), and addition of inotuzumab to the pediatric inspired protocol C10403 is under evaluation for young adults aged 18–39 years in the Alliance A041501 trial (NCT03150693).

In Ph-positive ALL, ponatinib in combination with Hyper-CVAD achieves the best outcomes in first-line treatment of younger patients. Studies are warranted to evaluate the possibility to reduce chemotherapy intensity without compromising outcomes in these patients. Several studies are evaluating the combination of blinatumomab with TKI in older patients with Ph-ALL. The results of these studies may give insight on how incorporation of blinatumomab to chemotherapy and TKI combinations could benefit younger patients.

The role of CAR T cells in our therapeutic arsenal will need to be defined in the upcoming years. Their high rate of toxicity, their complexity in manufacturing, and their cost may limit their broad utilization, and further studies are warranted. Similarly, the role of HSCT will need to be re-evaluated with evolving treatment strategies achieving better results. For example, patients with Ph + ALL who achieve CMR do not seem to benefit from HSCT changing the paradigm for this previously categorized high-risk patient population [72••, 73].

Although many major advances have been made, patients with ETP ALL, t(4;11), and Ph-like ALL remain at very high risk and are eagerly awaiting for novel effective therapeutic strategies. Hopefully, a plethora of new treatment strategies with targeted mechanisms of action are making their way in early phase clinical trials [108]. Reference of patients to academic institutions and enrollment into clinical trials are of paramount importance to continue to achieve major breakthroughs in the management and outcomes of adult ALL.

Compliance with Ethical Standards

Conflict of Interest Guillaume Richard-Carpentier reports grants from Cole Foundation, outside the submitted work. Hagop Kantarjian reports grants from Abb Vie, grants from Agios, grants from Amgen, grants from Ariad, grants from Astex, grants from BMS, grants from Cyclacel, grants from Daiichi-Sankyo, grants from Immunogen, grants from Jazz Pharma, grants from Novartis, grants from Pfizer, other from AbbVie, other from Actinium (Advisory Board), other from Agios, other from Amgen, other from Immunogen, other from Orsinex, other from Pfizer, and other from Takeda, during the conduct of the study. Elias Jabbour reports grants and personal fees from Takeda, grants and personal fees from Pfizer, grants and personal fees from Amgen, grants and personal fees from Abbvie, grants and personal fees from Spectrum, grants from Novartis, and from Bristol-Myers Squibb, during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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demonstrated that inotuzumab achieves higher rates of complete remission and improves overall survival compared to chemotherapy in patients with relapsed or refractory B-ALL. This led to the FDA-approval of inotuzumab for adult patients with relapsed or refractory B-cell precursor ALL.

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