Review Article

Novel Therapeutic Strategies in Acute Lymphoblastic Leukemia

Maria K. Angelopoulou, John V. Asimakopoulos, Theodoros P. Vassilakopoulos

Department of Hematology and Bone Marrow Transplantation Unit, National and Kapodistrian University of Athens, School of Medicine, Laikon General Hospital, Athens, Greece

ABSTRACT:
Adult acute lymphoblastic leukemia (ALL) is a rare and difficult to cure disease with a long-term survival of 30-40%. During recent years, a significant progress has been accomplished, especially for young patients. This is mainly due to the adaptation of “pediatric” type inspired protocols. Moreover, minimal residual disease (MRD) monitoring has become the most valuable tool for the discrimination of patients who will benefit from allogeneic hematopoietic stem cell transplantation at first complete remission. The bispecific anti-CD19/CD3 antibody blinatumomab and the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin represent two new effective treatment options for relapsed/refractory disease. The evolving technology of chimeric antigen receptor-T-cells breaks new ground in the treatment of B-ALL. Finally, the introduction of tyrosine-kinase inhibitors has reversed the dismal outcome of Philadelphia-chromosome positive ALL.

KEY WORDS: ALL, Acute lymphoblastic leukemia, Blinatumomab, Inotuzumab ozogamicin, CAR-T cells, Tyrosine-kinase inhibitors, Philadelphia-chromosome positive ALL

INTRODUCTION

Acute lymphoblastic leukemia (ALL) in adults is an extremely rare but highly fatal disease with annual incidence 1/100.000.1 Despite the unfavorable outcome (long-term survival 30-40%), the substantial progress in the treatment of ALL in the last two decades has led to the improvement of overall survival (OS) in all age groups, except from patients >60 years-old; 5-year OS >60% for age group 15-19, 45%, 34% and 24% for age-groups 20-29, 30-44 και 45-59, respectively.2

The majority of ALL cases are classified as precursor B-cell type, while T-ALL accounts for 25% of cases.3 Inferior outcomes in adults can be attributed to the combination of various factors, such as the unfavorable genetic basis of the adult ALL and its rarity, as well as the presence of co-morbidities, the treatment side-effects of active chemotherapeutic agents which affect the dose administration, and the complexity of these protocols.1,3

DEVELOPMENTS IN THERAPEUTIC STRATEGY

Intensification of initial treatment

The backbone of ALL therapeutic strategy during the early 21st century is the intensification of initial chemotherapeutic approaches. Pediatric-inspired therapies of the Berlin-Frankfurt-Munster (BFM) Study Group have revolutionized the management of the disease leading to a significant outcome improvement. Having been adapted from the majority of ALL Study Groups3,4 (GMAIL, GRAALL, GIMEMA, GNILG, PETHEMA, HOVON, UKALL, CALGB) these protocols are characterized by these main features; 1) multiple cycles of relatively low doses of antimetabolites with reduced myelotoxicity and...
without cross-link resistance, which lead to high cumulative doses, 2) repeated administration of asparaginase, 3) high-dose methotrexate, 4) early and frequent central nervous system (CNS) prophylaxis and 5) long-term consolidation and post-remission therapy. Contrariwise, adult-type approaches have been emerged from Hyper-CVAD protocol philosophy.

With the adoption of pediatric-type combination chemotherapy regimens, the 5-year OS has reached 50-60%. This outcome mainly results from the age group of adolescents and young adults (AYAs), who are in position to manage these intensive regimens. Indeed, the comparison with the historical studies suggests significantly more favorable outcome with the pediatric-inspired therapies than adult approach, at least in young patients. The 2-year event-free survival (EFS) and OS rates of 296 evaluable young adult patients with ALL enrolled in the US Intergroup C10403 trial were as high as 66% and 78%, respectively. The exact cut-off of age for AYAs usually is defined as the 40 years, however it can be expanded up to 45-50 years of age, for patients without co-morbidities.

Despite having been perceived as an extremely toxic drug in adults, asparaginase holds a critical role in modern therapeutic approach of ALL. The increased incidence of certain related side-effects has led to its omission or the use of inadequate doses in many adult-type regimens, a practice that should be avoided in patients <60 years-old, as most of these AEs are manageable. Indeed, hepatotoxicity related to asparaginase is very common as high-grade hyperbilirubinemia and transaminitis occur in a quarter and half of treated patients, respectively. Reversible hyperbilirunemia is mostly observed in the initial infusion and should not prevent further administration of additional doses, as the risk of recurrence is very low in subsequent cycles. However, clinical pancreatitis has a substantial risk of recurrence and it is included in life-threatening complications that preclude the re-administration of asparaginase. Hypersensitivity reactions to asparaginase are related with the generation of antibodies that result in drug inactivation and may not be clinically obvious. Pegylated form (PEG-Asparaginase) is less often involved with these reactions and, thus, it has substituted Escherichia Coli (E.Coli) Asparaginase. A third form of the drug, Erwinia Asparaginase, has been recently approved in the USA for patients who develop hypersensitivity to E Coli Asparaginase. As silent hypersensitivity is not rare and can result in loss of drug activity, measurement of asparaginase activity on day 14 after its administration is strongly recommended in clinical practice, with the target level being >0.1 IU/mL. On the other hand, due to limited tolerance to asparaginase in elderly, the Spanish Group Study has omitted asparaginase from induction leading to decrease in early mortality.

In T-cell ALL subcategory, pediatric-inspired regimen have improved outcomes making them comparable with those of precurcor B-cell ALL. These regimens mainly involve higher doses of methotrexate (5g/m²), as well as intensive use of asparaginase. Nelarabine activity is well-known in relapsed T-ALL, but recently its use has been introduced in upfront or in risk-adapted chemotherapy regimens with promising outcomes. Nelarabine is a purine nucleoside analog that is metabolized to arabinosylguanine nucleotide triphosphate (araGTP), which incorporates into DNA inhibiting its synthesis, and resulting in apoptosis. A phase II French study is evaluating nelarabine incorporated into consolidation and maintenance therapy in high-risk T-cell ALL (NCT02619630), as well as a phase III study will investigate the use of nelarabine as consolidation therapy in T-ALL (NCT02881086). On the contrary, asparaginase-free upfront protocols, such as hyper-CVAD, have demonstrated higher relapse rates in adult T-cell ALL.

At the time of diagnosis, CNS disease is uncommon, but the risk of relapse in this sanctuary site is substantial in the absence of adequate CNS-directed prophylactic therapy. Historically, prophylactic cranial-spinal radiation was an integral part of CNS prophylaxis regimen. However, due to prohibitive late toxicities, this strategy has been abandoned. On the other hand, the mainstay of CNS prophylaxis in modern ALL therapeutic regimens, which has resulted in low risk CNS relapse, consists of early and frequent intrathecal administration of MTX in combination with intravenous chemotherapeutic agents that have sufficient blood-brain barrier penetration. Moreover, the prognosis of CNS involvement at diagnosis remains a matter of debate, while isolated CNS relapse portends systemic relapse and mandates systemic chemotherapy in addition to CNS-directed therapy. Allogeneic stem cell transplantation (allo-SCT) after local clearance of ALL has demonstrated promising outcomes, as the graft-versus-leukemia effect can potentially extend to cerebrospinal fluid. Contrariwise, radiation-based conditioning, administration of cranial radiation prior to allo-SCT or administration of post-allo-SCT prophylactic intrathecal chemotherapy do not seem to offer substantial benefit.

**Selection of candidate patients eligible for allogeneic stem-cell transplantation**

The second axis of development in therapeutic strategy involves the precise defining of high-risk patients for relapse and their selection for consolidation with allo-SCT. Classic criteria remain the high white blood cell count and certain cytogenetic features, such as t(9;22), t(4;11) and other types of MLL gene rearrangement. However,
recent data suggest a more pronounced benefit with early allo-SCT for standard-risk patients in complete response (CR) 1 compared with the high-risk subset.12

In modern era, the classic criteria are tend to be replaced by the detection of the minimal residual disease (MRD) in certain time points; usually between 4th and 16th week from induction.13 Despite that the molecular-based methods of MRD detection are strenuous, demanding and expensive, the great majority of study-groups are using them, as significant prognostic tools.14-17 The positive predictive value of MRD negativity, early in the disease course, has been proven in many studies. In example, the German Study Group demonstrated 67% relapse free survival (RFS) in patients with negative MRD compared to 25% in those with positive MRD, for age-group 15-55 years-old.13 MRD positivity constitutes the main selection criteria for allo-SCT (5-year RFS 44% vs. 11% with or without allo-SCT). In some studies, the risk stratification based on MRD has been expanded not only to standard-risk patients, but also to high-risk ones.13 Nevertheless, the elimination of MRD through the introduction of targeted therapies may alter the subsequent therapeutic strategy. At the same time, recent scientific data supports the increased relapse risk in MRD negative patients with deletion of IKAROS gene (IKZF1) and the distinct entity of bcr/abl1-like ALL.18,19 Thus, the incorporation of new molecular entities in ALL classification may further improve therapeutic approach.

**Anti-CD20 monoclonal antibodies**

CD20 molecule is expressed in 1/3 of B-ALL20 and is related with increased risk of relapse.21 Initially, the GMALL study group explored the combination of rituximab and chemotherapy in adult CD20+ precursor B ALL patients (15-55 years of age, n=181) which were compared with patients recruited earlier in the same study without rituximab (n=82), who received the same chemotherapy regimen. Although, there was not improvement in CR rate in the standard risk group, there was a higher rate of molecular CR (57% vs 27% at day 24 and 90% vs 59% at week 16). Moreover, there was a significant improved rate of 3-year continued CR for patients received rituximab (64% vs. 48%) and 5-year OS (80% vs. 47%). Notably, 5-year OS was increased in the high-risk group with addition of rituximab (55% versus 36%).22 Similar outcomes were presented in another study performed at MD Anderson Cancer Center (MDACC) in precursor B ALL CD20+ patients <60 years of age. However, the backbone chemotherapeutic regimen used was hyper-CVAD and patients >60 years of age were also included. In patients <60 years of age, the addition of rituximab was associated with an improved rate of CR duration and OS compared with historical controls at 3 years (91% vs. 66% and 89% vs. 53%, respectively). However, this benefit did not extend to patients ≥60 years of age.23 Recently, a randomized Phase III clinical trial in CD20+ precursor B ALL patients (18-59 years-old) demonstrated that treatment with rituximab is associated with significantly improved event-free survival (EFS) with significantly lower incidence of relapse and higher rates of proceeding allo-SCT during the first remission. Thus, the introduction of Rituximab in 1st line treatment improves the outcome of CD20+ B-ALL.24 Second generation anti-CD20 molecule ofatumumab in combination with hyper-CVAD led to 98% MRD negativity.25

**DEVELOPMENTS IN REFRACTORY/RELAPSE (R/R) DISEASE**

**Therapeutic Strategy**

In R/R disease, therapeutic strategy aims at achieving 2nd CR and proceeding to allo-SCT. In common practice, the outcome of this strategy is limited (20-30% of patients), since the presence of chemoresistance is usual with extremely dismal prognosis (median OS 3-6 months).26 The significance of MRD has not been sufficiently clarified in relapsed disease. Recent outcomes demonstrate that MRD negativity in salvage 1 (S1) is related with more favorable outcome, especially for patients who immediately underwent allo-SCT (2-year OS >60%). Contrariwise, patients in >S1 have dismal outcome, regardless of their MRD status.27

**Newer Chemotherapeutic Agents**

Among the chemotherapeutic agents incorporated in the management of R/R disease, mitoxantrone-containing regimens are related with higher response rates compared to that of idarubicin. Newer approaches include clofarabine, cyclophosphamide and etoposide for B-ALL, nelarabine for T-ALL and liposomal vincristine.28

**Anti-CD22 monoclonal antibodies**

Epratuzumab

CD22 antigen is expressed in 60-96% of B-ALL cases.20 Epratuzumab is naked anti-CD22 humanized monoclonal antibody (mAb). In adults, the addition of epratuzumab to the combination of clofarabine and cytarabine in adults with R/R precursor B ALL led to more favorable CR rate compared to historical studies.29 However, the combination epratuzumab/hyper-CVAD in CD22+ R/R ALL had disappointing outcomes.30 After binding, the receptor/antigen complex is internalized, without significant
therapeutic efficacy when used as monotherapy. On the other hand, this molecule is ideal for conjunction with toxins or chemotherapeutic agents.

**Inotuzumab ozogamicin (INO)**

Inotuzumab ozogamicin (INO) is a mAb against CD22 that is bound to calicheamicin. Initially, the recommended dose was altered from 1 infusion every 3-4 weeks, to 3 weekly infusions every 28 days. The first phase 2 study demonstrated encouraging outcomes with overall response 57%. In the following study, the response rates were comparable, although the AEs were less frequent with the weekly schedule. Allo-SCT was decided for 44% of the patients, whom 17% developed veno-occlusive liver disease, with lower frequency in the arm of weekly administration schedule. Reproducible results have emerged from the following study in 35 B-ALL patients >S1; 67% of patients had CR, while 78% of them were MRD negative. The safety profile of the drug remained stable with main side-effects being haematological, gastroenterological and hepatotoxicity. In a phase III study on 326 patients with R/R B-ALL which compared the effectiveness of INO versus salvage treatment (FLAG, cytarabine and mitoxantrone, high-dose cytarabine), the complete response rates, median disease-free survival (DFS) and OS were better in the arm of INO. MRD response was also higher (78.4% vs 28.1% of those who responded). Moreover, allo-SCT was more likely to be performed in patients who received INO compared to those received systemic chemotherapy (41% vs 11%). From further analysis, the main advantage of INO regarding the achievement of CR has been appeared in all subcategories, except from those with t(4;11). Veno-occlusive liver disease in the INO arm was 11%. Extremely promising results are demonstrated combining INO with unintesified chemotherapy (mini- hyper-CVAD) both in R/R disease and in 1st line treatment in elderly. Main studies of INO are described in Table 1. Based on results of the Phase 3 INO-VATE ALL clinical trial (NCT01564784), which compared the effectiveness, safety and tolerability of INO with those of standard of care chemotherapy, INO received EU approval as monotherapy for the treatment of patients with R/R CD22-positive B cell precursor ALL. Moreover, INO is indicated for patients with Philadelphia positive (Ph+) R/R B cell precursor ALL who have failed treatment with at least one TKI.

**Moxetumomab Pasudotox (CAT-8015)**

This is another anti-CD22 mAb, which is composed by the variable region against CD22 fused to Pseudomonas Aeruginosa exotoxin A. Its efficacy in R/R disease is currently evaluated.

**Combotox**

Combotox is a combination immunotoxin that contains a 1:1 mixture of anti-CD19 and anti-CD22 antibodies, both conjugated to the cytotoxin deglycosylated ricin-A chain. A phase 1 trial is currently studying the drug efficacy in combination with cytarabine for adults with R/R disease (NCT01408160).

**Anti-CD19 monoclonal antibodies**

CD19 is widely expressed in B-ALL (>90%). Like CD22 molecule, CD19 is rapidly internalized upon binding of an antibody making it an ideal candidate for immunoconjugate therapy. Two main immunoconjugates have been developed so far: SAR3419 (Coltuximab Ravtansine), an anti-CD19 humanized mAb conjugated to a semisynthetic maytansinoid compound, an anti-tubulin molecule similar to vincristine, and SGN-CD19 (Denintuzumab Mafodotin), an antibody conjugated to monomethylauristatin. Both antibodies have been studied in phase I trials, whose outcomes were not very promising, while significant AEs from the cornea were described.

**Immunotherapies mediated by T-lymphocytes**

**Blinatumomab**

Blinatumomab is the first clinically applied bispecific, single-chain mAb based on BiTE technology (Bi-specific T-cell engagers), a construct specific for CD19 and CD3, which links cytotoxic CD3 positive T cells to malignant cells. It has two single chain variable fragments, each with an antigen-binding domain, linked by a glycine-serine domain. One antigen-binding domain has affinity for CD3ε, which forms part of the T-cell receptor (TCR) complex, while the other engages CD19, a pan-B cell marker expressed in ALL. This technology exploits the anti-neoplasmatic cytotoxic activity of naturally circulating T-lymphocytes, independently of TCR specificity or MHC-mediated target-antigen presentation. The linkage between T-lymphocytes and lymphoblasts provoke the activation of T-lymphocytes leading to cytotoxic effect, through the production of inflammatory molecules and cytokines, such as IL-6, IL-10, IFN-γ, granzymes and perforin. Moreover, each activated T cell is able to engage serially multiple leukemic cells, while there is a polyclonal expansion of activated T cells.

Blinatumomab is actually the only innovative treatment of B-ALL applied in daily clinical practice. For the time being, its indication is for R/R Ph- ALL. Table 2 represents the characteristics and outcomes of the main clinical studies in detail. Phase II/III studies concluded at significant outcomes in efficacy, as they demonstrated CR rates 43-67% and MRD negativity 73-88% of those who responded.
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<th>Study Data</th>
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<tr>
<td>B-ALL, infants-adults, R/R, single-arm, single-center Phase II, NCT01134575 (32)</td>
<td>N=49  &lt;br&gt;• R1: 27%, R2: 49%, ≥R3: 24%  &lt;br&gt;• Ph+: 14%  &lt;br&gt;• Previous allo-SCT: 14%  &lt;br&gt;• Median age: 36 years-old  &lt;br&gt;• Dose: 1.8mg/m2 every 3-4 weeks</td>
<td>• CR/CRh: 57%  &lt;br&gt;• CR/CRh in Ph+: 42%  &lt;br&gt;• MRD: 63% of responders  &lt;br&gt;• CR/CRh in Ph+: 43%  &lt;br&gt;• Median OS: 5.1 m  &lt;br&gt;• Median duration of CR/CRh: 6 m</td>
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<td>B-ALL infants-adults, R/R, single-arm, single-center Phase II, NCT01134575 (validation) (31)</td>
<td>N=90  &lt;br&gt;• R1: 32%, R2: 38%, ≥R3: 30%  &lt;br&gt;• Ph+: 17%  &lt;br&gt;• Previous allo-SCT: 11%  &lt;br&gt;• Median age: 39.5 years-old  &lt;br&gt;• Dose: 1.3-1.8mg/m2 every 3-4 weeks (N=49)  &lt;br&gt;• 3 weekly infusions every 3-4 weeks (day1: 0.8mg/m2, days 8,15: 0.5mg/m2) (N=41)</td>
<td>• CR/CRh: 58%  &lt;br&gt;• MRD: 72% of responders  &lt;br&gt;• CR/CRh in Ph+: 67%  &lt;br&gt;• Median OS: 7.4 m</td>
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<td>B-ALL, adults R/R, single-arm, multicenter Phase II (33)</td>
<td>N=35  &lt;br&gt;• ≥R2, 17%≥R5  &lt;br&gt;• Ph+: 26%  &lt;br&gt;• Previous allo-SCT: 43%  &lt;br&gt;• ≥ 18 years-old, median age: 34 years-old  &lt;br&gt;• Dose: 3 weekly infusions every 4 weeks (day1: 0.8mg/m2, days 8,15: 0.5mg/m2) (N=41)</td>
<td>• CR/CRh: 65.7%  &lt;br&gt;• MRD: 78% of responders  &lt;br&gt;• CR/CRh in Ph+: 67%  &lt;br&gt;• Median OS: 7.4 m</td>
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<td>B-ALL adults, R/R, open-label, 2-arm, randomized (INO vs CHEMO), multicenter, international Phase III (NCT01564784) (34)</td>
<td>N=218, (INO: 109 – CHEMO: 109)  &lt;br&gt;• ≥ 18 years-old, median age: 47 years-old  &lt;br&gt;• INO 67%/32% vs CHEMO: 63%/36%  &lt;br&gt;• Ph+: 41% vs 11% underwent allo-SCT  &lt;br&gt;• Previous allo-SCT: 16% vs 20%  &lt;br&gt;• Ph+: 41% vs 11% underwent allo-SCT  &lt;br&gt;• Median OS: 13.9 m vs 9.9 m</td>
<td>Results INO vs CHEMO  &lt;br&gt;• CR/CRh: 80.7% vs 29.4%  &lt;br&gt;• MRD: 78.4% vs 28.1%  &lt;br&gt;• Median PFS: 5 m vs 1.8 m.  &lt;br&gt;• Median OS: 13.9 m vs 9.9 m (all the differences were statistically significant)</td>
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<td>B-ALL, adults R/R, single-arm, single-center Phase II (NCT01371630) (35)</td>
<td>N=59  &lt;br&gt;• ≥ 18 years-old, median age: 35 years-old  &lt;br&gt;• Combination INO + mini- hyper-CVAD (INO: 1.8-1.3 mg/m2, day 3 (cycle 1), 1.3-1.0 mg/m2 (next cycles)</td>
<td>• CR: 59%  &lt;br&gt;• MRD: 82% of responders  &lt;br&gt;• Post-response allo-SCT: 44%  &lt;br&gt;• Median PFS: 8 m  &lt;br&gt;• Median OS: 11 m</td>
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**ALL:** Acute lymphoblastic Leukemia, R/R: Relapse/Refractory disease, R: relapse, m: months, N: number of patients, INO: inotuzumab ozogamicin, CHEMO: chemotherapy, CR: complete remission, CRh: Complete remission without normal complete blood count, Ph: Philadelphia chromosome, allo-SCT: allogeneic stem cell transplantation, MRD: minimal residual disease, OS: overall survival, PFS: progression free survival, RFS: relapse free survival
ver, 25–50% of these patients underwent allo-SCT. Median RFS and OS may vary between 5.9–8.8 and 6.1–13 months, respectively. Nevertheless, a group of MRD negative patients seems to have achieved a significant long-term survival. The comparison of blinatumomab with historical studies highlights the superiority of the first regarding the CR and OS rates. In addition, the use of blinatumomab in older adults seems promising, considering that the therapeutic choices in elderly are extremely limited.41

The recently published multinational phase III study (TOWER) compared blinatumomab with standard-of-care S1 chemotherapy. In the blinatumomab arm, OS and RFS were significantly longer (median OS: 7.7 versus 4 months, HR=0.71, p=0.01; median RFS: 7.3 versus 4.6 months). The superiority of blinatumomab on OS extends on all subgroups, except from patients >S2. It is worth mentioning that OS curves for the blinatumomab and chemotherapy groups separated within 3 months and converged again between 15 and 18 months. This observation indicates that blinatumomab is mostly suitable for the achievement of CR and the immediate proceeding to allo-SCT. Indeed, OS curves were separated showing superiority for blinatumomab, when allo-SCT was taken into account. It should be mentioned that the basic characteristics of TOWER study patients were unfavorable in comparison with phase III study of INO.

Except from its efficacy in R/R B-ALL, blinatumomab could also be applied in the MRD elimination after 1st line treatment: in a limited number of patients with persistent MRD after consolidation treatment, 80% of them achieved MRD negativity. Notably, RFS did not differ between those who respond and underwent allo-SCT from those who achieved MRD negativity and did not received any further treatment. The recent study update revealed that approximately half the patients remain in remission 5 years after treatment with blinatumomab (median follow-up time 50.8 months), regardless of allo-SCT. What remains to be proven is if the elimination of MRD with blinatumomab could substitute the necessity for allo-SCT. Current studies examine the efficacy of blinatumomab in first-line treatment in combination or in comparison with chemotherapy (NCT02877303, NCT0203222, NCT02101853).

Negative predictors of response to blinatumomab include high disease burden (defined as bone marrow blast >50%), the presence of extramedullary disease and the frequency of the circulating T regulatory cells (Tregs). With a cut-off of Tregs <8.525%, Tregs enumeration can identify 100% of all blinatumomab responders and exclude 70% of non-responders. Thus, therapeutic removal of Tregs may convert blinatumomab non-responders to responders. Multiple mechanisms may be involved in resistance to blinatumomab, such as the emergence of CD19-negative clones, the increased frequency of Tregs, the overexpression of programmed cell death-1 receptor (PD-L1) on the leukemic blasts or PD-1 from Tregs. In addition, a group of patients can develop extramedullary disease in relapse following blinatumomab therapy.

Due to its short half-life, blinatumomab should be administered in continuous intravenous infusion, while its final approved dose is 9 μg/day on days 1–7 of the first cycle, followed by 28 μg/day on days 8–28. Remarkably, T-cell expansion within 4 weeks of administration is related with increased MRD-negativity rates and more favorable prognosis. Besides the hematologic toxicity, cytokine-release syndrome (CRS) and CNS-related events are the most significant AEs. Thus, pre-emptive administration of dexamethasone is recommended in patients with high leukemic burden (>50% BM blasts) or rapidly progressive disease. CRS management consists of transient discontinuation of treatment, administration of high-dose corticosteroids or the use of tocilizumab, a monoclonal antibody against IL-6 receptor. CNS AEs may be caused by the small size of the antibody, that surpass the blood-brain barrier and results in rapid neurotoxic cytokine release. Grade ≥3 AEs occur in 9–11% of patients. CNS-related events usually present after 1st week of infusion and are reversible with corticosteroids and supportive care.

Currently, blinatumomab is indicated as monotherapy for the treatment of adults with Ph(-) CD19 positive relapsed or refractory B-precursor ALL, as well as monotherapy for the treatment of paediatric patients aged 1 year or older with Ph(-) CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

**Chimeric antigen receptor (CAR) T cells**

Chimeric antigen receptor (CAR) T cells (CAR-Ts) are genetically engineered T cells that express the antigen-binding domain of an immunoglobulin linked via transmembrane domains to the intracellular T-cell receptor signaling moieties. This allows the T cells to recognize unprocessed antigens and to be activated in a major histocompatibility complex (MHC)-independent manner. First generation CAR-Ts contain intracellular signaling moieties derived only from the T-cell receptor/CD3ξ complex. In contrast, second- and third-generation CAR-Ts include co-stimulatory signals in the CAR gene constructs (CD137, CD27, CD28 ή CD134). More recently, fourth-generation CAR-Ts have been engineered to include a cytokine-expressing cassette.

The process of CAR-Ts therapy involves collecting T cells, introducing the CAR construct, cell amplification ex-vivo to a goal volume approximately 3x10^6 cells/kg and...
### TABLE 2. Major clinical studies of blinatumomab in B-cell Acute Lymphoblastic Leukemia

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<th>Study Data</th>
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| B-ALL adults, R/R randomized (blinatumomab vs CHEMO), multicenter international, Phase III, TOWER, NTC02013167 (39) | N=405  
Blinatumomab=271, CHEMO=134  
• R ≤ 12 m after CR1 or allo-SCT or refractory in 1st line treatment or ≥R2  
• Only Ph− patients  
• Previous allo-SCT: 104/403 (35%)  
• Median age: 40.9 years-old | Results blinatumomab vs CHEMO:  
• Median OS 7.7m vs 4.0m after median F/U time 11.7m, p=0.01  
• CR/CRh in 44% vs 25%, p<0.001  
MRD−: 33% vs 12%  
• Median RFS: 7.3m vs 4.6m  
In both groups, 24% underwent allo-SCT |
| B-ALL adults, R/R, single-arm, multicenter, international, Phase II, NCT01466179, NTC020003612 (38) | N=189  
• R ≤ 12 m after CR1 or allo-SCT or refractory in 1st line treatment or ≥R2  
• Only Ph− patients  
• Previous allo-SCT: 64/189 (34%)  
• Median age: 39 years-old | CR/CRh: 81/189 (43%)  
• MRD− after 2 cycles: 60/181 (33%)  
(1st=59, 2nd=1)  
Post response allo-SCT: 32/81 (40%)  
After median F/U time 8.9m:  
In CR/CRh patients: median RFS 5.9m  
(MRD−: 6.9m vs MRD+:2.3m)  
Median OS (189 patients): 6.1m with median F/U time 9.8m |
| B-ALL adults, R/R, single-arm, multicenter, Germany (GMALL Study Group), Phase I/II NCT01209286 (37) | N=36  
• Only Ph− patients  
• Previous allo-SCT: 15/36 (42%)  
• Median age: 32 years-old | CR/CRh: 25/36 (69%)  
• CR/CRh after allo-SCT: 8/15 (52%)  
MRD−: 22/36 (61%)  
Post-response allo-SCT: 13/25 (52%)  
(R=2, TRM=6)  
without allo-SCT after CR/CRh: 12/25 (48%)  
(R=8)  
After median F/U time 28.9m:  
12 patients with CR (RFS 61%)  
Post-response allo-SCT (N=9): CR=6, R=2, TRM=1 |
| B-ALL adults in CR but with persistent/recurrent MRD, single-arm, multicenter, Germany (GMALL Study Group), Phase II, NCT00198991, NCT00198978 (41,43) | N=20/21  
• Persistent MRD: 15  
• Recurrent MRD: 5  
• Ph+ ALL TKI-resistant: 5  
• No previous allo-SCT  
• Median age 47 years-old | MRD− after 1st cycle: 16/20 (80%)  
3/5 Ph+ ALL achieved response  
allo-SCT, N=9  
After media F/U time 50.8 m:  
CR: 10 (long-term RFS 50%)  
Post-response allo-SCT(10): CR=5, R=3, TRM=1  
without allo-SCT(11): CR=5, R=5, TRM=1 |
| B-ALL adults, R/R, single-arm, multicenter, Phase II, NCT02000427 (ALCANTARA) (74) | N=45  
• Ph+: all patients  
• R/R in ≥2nd generation TKI and/or with intolerance to imatinib  
≥18 years-old, median age: 55 years-old  
• Previous allo-SCT: 44%  
• Mutation T315I: 27%  
| CR/CRh: 36%  
MRD−: 88% of CR/CRh  
Median RFS: 6.7m  
Median OS: 7.1m  
44% underwent allo-SCT |

ALL: Acute Lymphoblastic Leukemia, R/R: Relapse/Refractory disease, R: relapse, m: months, N: number of patients, CHEMO: chemotherapy, CR: complete remission, Ph: Philadelphia chromosome, allo-SCT: allogeneic stem cell transplantation, F/U: follow-up, CRh: complete remission without normal complete blood count, MRD: minimal residual disease, RFS: relapse free survival, OS: overall survival, GMALL: German Multistudy Group for Adult Acute Lymphoblastic Leukemia, TRM: treatment related mortality, TKI: tyrosine-kinase inhibitors
then an autologous transplantation of the modified cells into the patient after lymphoablative conditioning regimen. Following infusion, cells can multiple up to 103 fold in vivo within 7-14 days. Degree of expansion in vivo as well as B cell depletion correlates with response to therapy. Options for gene delivery methods include viral vectors and RNA-based methods. The use of viruses induce permanent gene expression, however it involves the risk of oncogene activation through random gene integration.54-55

Clinical studies are being elaborated by four major centers: University of Pennsylvania (UPenn), National Cancer Institute (NCI), Fred Hutchinson Cancer Research Center (FHCRC) and Memorial Sloan Kettering Cancer Center (MSKCC).49-55 (Table 3). The outcomes appear to be outstanding. Near all of these studies have demonstrated CR rates 80-90%, while the vast majority of those who respond achieve MRD negativity.49-55 Nevertheless, half the patients experience relapse within 1 year during follow-up. Thus, CAR-Ts therapy is proposed as a “bridge” to allo-ASCT.51 Albeit, scientific data from MSKCC revealed that outcome did not differ regardless performing or not allo-SCT. In addition, the same researchers have highlighted the significant negative predictive value of post-treatment MRD.55 The persistence of cells in the circulation depends on the manufacturing method of CAR-Ts and the chemotherapeutic regimen.51 It would be worthy to mention that CAR-Ts therapy is related with serious AEs.51 Thus, grade III CRS and neurotoxicity are frequently observed (23-100% and 15-50%, respectively). Limitations in efficacy of CAR-Ts and neurotoxicity are frequently observed (23-100% and therapy is related with serious AEs.51 Thus, grade III CRS and neurotoxicity are frequently observed (23-100% and 15-50%, respectively). Limitations in efficacy of CAR-Ts and neurotoxicity are frequently observed (23-100% and 15-50%, respectively). Limitations in efficacy of CAR-Ts and neurotoxicity are frequently observed (23-100% and 15-50%, respectively). Limitations in efficacy of CAR-Ts and neurotoxicity are frequently observed (23-100% and 15-50%, respectively). Limitations in efficacy of CAR-Ts and neurotoxicity are frequently observed (23-100% and 15-50%, respectively). Limitations in efficacy of CAR-Ts and neurotoxicity are frequently observed (23-100% and 15-50%, respectively).

Proteasome inhibitors

Nuclear factor kappa-B (NF-κB) is a transcriptional activator with anti-apoptotic properties which plays a role in a variety of malignancies. Proteasome inhibitors inactivate NF-κB and impair tumor growth. The induction of apoptosis through the inhibition of proteasome is examined in ALL. Several preclinical studies have suggested a synergistic role of bortezomib, which first approved for the treatment of multiple myeloma, with dexamethasone and additive effects to standard chemotherapy agents in acute leukemias. Yet, a single agent, bortezomib did not produce durable responses in patients with R/R ALL. Current studies examine its efficacy as frontline therapy in combination with chemotherapy in T-ALL, due to its ability to inhibit the NF-κB and NOTCH1 signaling pathways.56 The phase II ALL07P1 COG study investigated the efficacy of bortezomib with re-induction chemotherapy vincristine, prednisone, peg-asparaginase, and doxorubicin for relapsed ALL. The CR rate was 69% in precursor B-ALL (n=61) and 65% in T-ALL (n=17).9 In adults, recruitment has begun for a phase 2 trial of bortezomib with combination chemotherapy in R/R ALL (NCT01769209), while another phase II trial is investigating the same question in pediatric and young adults patients (NCT02535806). A randomized phase III COG study (AALL1231) is studying combination chemotherapy with or without bortezomib for younger patients with newly diagnosed T-ALL or stage II-IV T-cell lymphoblastic lymphoma (NCT02112916).

Carfilzomib achieves a higher degree of proteasome inhibition compared to bortezomib with fewer off-target effects. The maximum tolerated dose of carfilzomib combined with hyper-CVAD is being studied in a phase I study (NCT02293109). In addition the safety and tolerability of carfilzomib for relapsed ALL in combination with re-induction therapy are being evaluated as well (NCT02303821). Ixazomib, the newest proteasome inhibitor that is also orally administered, is being studied in a phase I trial, in combination with chemotherapy for ALL (NCT02228772).

JAK inhibitor (ruxolitinib)

Bcr-abl1 -like B-ALL is a recent recognized entity with similar expression profile with bcr/abl1+ ALL, which is characterized by IZKF1 deletion, CRLF-rearrangements and coexpression of JAK1/2 mutations, as well as translocations of PDGFRβ, abl1, abl2, JAK2 and EPOR.19 The JAK/STAT signaling pathway has been identified as a significant
### TABLE 3. Major clinical trials of anti-CD19 Chimeric Antigen Receptor T-cells in Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Center/Study Data</th>
<th>Patients’ characteristic</th>
<th>Study Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSKCC/</strong> B-ALL adults, R/R, single-scale, Phase I (49)</td>
<td>N=16</td>
<td>CR/CRh: 88% (median F/U time 24.5 days)</td>
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<tr>
<td></td>
<td>Median age=50 years-old</td>
<td>MRD-: 12/16 (75%)</td>
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<tr>
<td></td>
<td>≥R2: 7 (44%)</td>
<td>Post-response allo-SCT: 7/10 (70%)</td>
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<tr>
<td></td>
<td>Ph+ patients: 4 (25%)</td>
<td>Before CAR-Ts infusion:</td>
</tr>
<tr>
<td></td>
<td>CNS disease: 2 (12%)</td>
<td>• Blasts≥50%: 6/15 (40%)</td>
</tr>
<tr>
<td></td>
<td>Previous allo-SCT: 4 (25%)</td>
<td>• MRD-: 12/16 (75%)</td>
</tr>
<tr>
<td></td>
<td>Before CAR-Ts infusion:</td>
<td>• Post-response allo-SCT: 7/10 (70%)</td>
</tr>
<tr>
<td></td>
<td>• Blasts≥50%: 6/15 (40%)</td>
<td>After CAR-Ts administration, post-response allo-SCT (12/35, 33%):</td>
</tr>
<tr>
<td></td>
<td>• MRD-: 12/16 (75%)</td>
<td>• 6m-OS: 70% allo-SCT(+) vs 64% allo-SCT(-)</td>
</tr>
<tr>
<td></td>
<td>≥R2: 7 (44%)</td>
<td>Median 18m-LFS: 85.7% allo-SCT+ vs 9.5% allo-SCT-</td>
</tr>
<tr>
<td></td>
<td>Ph+ patients: 4 (25%)</td>
<td>CNS disease CR rate: 100% (6/6)</td>
</tr>
<tr>
<td></td>
<td>CNS disease: 2 (12%)</td>
<td>Response rate Flu/Cy(+) 66% vs Flu/Cy(-) 25%, p=0.03:</td>
</tr>
<tr>
<td></td>
<td>Previous allo-SCT: 4 (25%)</td>
<td>• OS (Flu/Cy+): 34.7% at 38m</td>
</tr>
<tr>
<td></td>
<td>Before CAR-Ts infusion:</td>
<td>• Flu/Cy(-): HR=6.35, p=0.0026</td>
</tr>
<tr>
<td></td>
<td>• Blasts≥50%: 6/15 (40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MRD-: 12/16 (75%)</td>
<td></td>
</tr>
<tr>
<td><strong>NCI/</strong> B-ALL adults, R/R, Phase I (54)</td>
<td>N=44</td>
<td>CR: 36/44 (64%)</td>
</tr>
<tr>
<td></td>
<td>Median age=45 years-old</td>
<td>MRD-: 29/35 (83%)</td>
</tr>
<tr>
<td></td>
<td>≥3 treatment lines: 22 (55%)</td>
<td>6m-OS: 76% MRD-CR+ vs 14% MRD+CR+</td>
</tr>
<tr>
<td></td>
<td>Ph+ patients: 14/32 (25%)</td>
<td>After CAR-Ts administration, post-response allo-SCT (12/35, 33%):</td>
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<tr>
<td></td>
<td>Primary resistant disease: 11</td>
<td>• 6m-OS: 70% allo-SCT(+) vs 64% allo-SCT(-)</td>
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<tr>
<td></td>
<td>Ph+ patients: 5</td>
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<td></td>
<td>CNS disease: 6</td>
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<td></td>
<td>Type of lymphoblastic treatment</td>
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<tr>
<td></td>
<td>LD Flu/Cy: 43</td>
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<tr>
<td></td>
<td>FLAG: 6</td>
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<tr>
<td></td>
<td>Ifo/Eto: 2</td>
<td></td>
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<tr>
<td></td>
<td>HD Flu/Cy: 8</td>
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<tr>
<td><strong>MULTICENTER/</strong> B-ALL infants and young adults, R/R, Phase I (ZUMA-3 και -4) (55)</td>
<td>N=51</td>
<td>CR: 31/51 (60.8%) with MRD-: 28/31 (90%)</td>
</tr>
<tr>
<td></td>
<td>Primary resistant disease: 11</td>
<td>Median 18m-LFS in MRD-: 49.5%</td>
</tr>
<tr>
<td></td>
<td>Ph+ patients: 5</td>
<td>Median 18m-LFS: 85.7% allo-SCT+ vs 9.5% allo-SCT-</td>
</tr>
<tr>
<td></td>
<td>CNS disease: 6</td>
<td>CNS disease CR rate: 100% (6/6)</td>
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<tr>
<td></td>
<td>HD Flu/Cy: 8</td>
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<tr>
<td><strong>CHOP/UPenn/</strong> CD19+ ALL infants and young adults, R/R, Phase I (51)</td>
<td>N=53</td>
<td>CR: 50/53 (94%) (and T-ALL case responded)</td>
</tr>
<tr>
<td></td>
<td>CD19+ T-ALL: 1/53</td>
<td>MRD-: 42/45 (93%)</td>
</tr>
<tr>
<td></td>
<td>MRD-: 12/53 (23%)</td>
<td>After median F/U time 10.6m, CR:29/53 (55%)</td>
</tr>
<tr>
<td></td>
<td>After median F/U time 10.6m, CR:29/53 (55%)</td>
<td>6m-EFS: 70%, 6m-RFS: 72%, 12m-OS: 78%</td>
</tr>
<tr>
<td><strong>FHCRC/</strong> B-ALL infants and young adults, R/R after allo-SCT, Phase I (50)</td>
<td>N=43/45</td>
<td>MRD-: 40/43 (93%)</td>
</tr>
<tr>
<td></td>
<td>After median F/U time 10.6m, CR:29/53 (55%)</td>
<td>12m-EFS: 50.8%, 12m-OS: 69.5%</td>
</tr>
</tbody>
</table>

**CAR-Ts**: chimeric antigen receptor T-cells, **MSKCC**: Memorial Sloan Kettering Cancer Center, **ALL**: acute lymphoblastic leukemia, **R/R**: relapse/refractory, **Ph**: Philadelphia chromosome, **CNS**: central nervous system, **allo-SCT**: allogeneic stem cell transplantation, **MRD**: minimal residual disease, **CR**: complete remission, **CRh**: complete remission without normal complete blood count, **6m**: 6-month, **OS**: overall survival, **LD**: low dose, **Flu**: fludarabine, **Cy**: cyclophosphamide, **FLAG**: fludarabine-aracytine, **Ifo**: ifosfamide, **Eto**: etoposide, **HD**: high dose, **18m**: 18-months, **LFS**: leukemia free survival, **HR**: hazard ratio, **F/U**: follow-up, **EFS**: event free survival, **RFS**: relapse free survival
Results from these trials are pending. HIBITORS sapnisertib in R/R ALL in adults (NCT02484430). sponsored multi-center phase II trial with TORC1/2 in-
corticosteroids in R/R ALL (NCT00874562) and NCI-
ALL (NCT01403415), phase I trial evaluating sirolimus
combination with intensive re-induction therapy for R/R
phase I COG study ADVL1114 exploring temsirolimus in
trial studying temsirolimus in R/R ALL (NCT00084916),
trials include National Cancer Institute (NCI) phase II
with first line chemotherapy and R/R disease.28 Ongoing
highlightened in several clinical trials in combination
as therapeutic target in T-ALL management has been
mTOR signaling. The significance of PI3K/AKT/mTOR
PI3K/mTOR pathways
The phosphatidylinositol 3-kinase/protein kinase
and mammalian target of rapamycin (mTOR) pathways
are shown to be constitutively activated in 50-75% of
T-ALL. Constitutive activation may also play a role in
chemotherapy resistance. Everolimus, temsirolimus and
sirolimus inhibit mTOR kinase activity by binding intra-
chemotherapy resistance. Everolimus, temsirolimus and
sirolimus inhibit mTOR kinase activity by binding intra-
cellular protein FKBP-1, forming a complex that inhibits
mTOR signaling. The significance of PI3K/AKT/mTOR
as therapeutic target in T-ALL management has been
highlightened in several clinical trials in combination with
first line chemotherapy and R/R disease.28 Ongoing
trials include National Cancer Institute (NCI) phase II
trial studying temsirolimus in R/R ALL (NCT0084916),
phase I COG study ADVLI1114 exploring temsirolimus in
combination with intensive re-induction therapy for R/R
ALL (NCT01403415), phase I trial evaluating sirolimus and
corticosteroids in R/R ALL (NCT00874562) and NCI-
sponsored multi-center phase II trial with TORC1/2 in-
hibitor sapniserrith in R/R ALL in adults (NCT02484430).
Results from these trials are pending.

BTK, BCL2 and PD-1 Inhibitors

The BCR signaling pathway plays an essential role
in B-cell development and function, which includes the
Bruton’s tyrosine kinase (BTK). Preclinical studies have
investigated the activity of ibrutinib, an oral selective ir-
reversible inhibitor of BTK, in B-ALL, demonstrating
suppression of BCR-positive ALL proliferation in vitro and
in vivo. These data provide a rationale for clinical testing
of B-ALL with active pre-BCR signaling, either as a single
agent or in combination with other therapies. A phase II
study of ibrutinib and blinatumomab in patients with R/R
B-ALL will soon be opened to recruitment (NCT02997761).

The B cell lymphoma-2 (BCL-2) protein tightly regu-
lates cell death. BCL-2 inhibitors block the binding of
BCL-2 to anti-apoptotic proteins, triggering cell death. While
Navitoclax (ABT-263) has been abandoned due to
dose-limiting thrombocytopenia, a second-generation,
selective BCL-2 inhibitor Venetoclax (ABT-199) has
demonstrated activity against ALL in xenograft models,
without yet being tested in ALL.9

Nivolumab is a human IgG4 monoclonal antibody
against anti-programmed cell death protein-1 (PD-1).
Malignant cells evade immunosurveillance as they lack
expression of costimulatory molecules and induce T-cell
anergy. Nivolumab dampens T-cell anergy and allows
immunosurveillance of malignant cells to take place. A phase
I study is recruiting patients to investigate nivolumab plus
dasatinib in patients with R/R Ph+ ALL (NCT02819804).
A phase I study is investigating blinatumomab, nivolumab
with or without ipilimumab in patients with poor risk R/R
CD19+ precursor B-ALL (NCT02879695).

DEVELOPMENTS IN PHILADELPHIA
CHROMOSOME-POSITIVE ALL

Ph+ ALL is the most common B-ALL subtype in
adults, comprising 20-30% of all cases, while its inci-
dence increases with age. Traditionally, Ph+ ALL was
considered as the subcategory with the worst prognosis
having 5-year OS <10%.50 However, the introduction of
TKI inhibitors has improved dramatically the outcome
with CR rates and 5-year OS >40%,61-67 Furthermore, in
the majority of studies, the use of TKIs has improved the
number of patients who proceed to allo-SCT (in most tri-
als >50%).61,62,64,65 Thus, the common therapeutic strategy
includes the introduction of imatinib or dasatinib in in-
duction, consolidation and maintenance, with continuous
administration being more preferable than interrupted.62

Issues to be clarified remain: 1. the choice of suitable
TKI, 2. the de-escalation of induction chemotherapy regi-
men, 3. the significance of MRD, 4. the need for allo-SCT
and 5.the resistance to TKIs.
Regarding the first issue, only imatinib and dasatinib have gained approval from the FDA. Most scientific studies conducted with imatinib at doses between 600-800mg. 68 Although comparative studies do not exist, the outcomes are similar. 69 However, treatment with dasatinib results in more stable molecular responses, having more toxicities. 60 Moreover, dasatinib has been reported to have a higher CNS penetration. 69 Certainly, the use of second generation TKIs is related with increased incidence of T315I mutations, possibly due to selection of pre-existing mutated clones. 60 Dasatinib was approved for the treatment of patients with Ph+ ALL resistant or intolerant to prior therapy with imatinib following the results of the pivotal START-L study. This study, which included patients with Ph+ ALL resistant or intolerant to imatinib (29% with T315I), revealed complete cytogenetic response in 58%. Major hematologic responses were achieved in 42% of patients, 67% of whom remained progression-free. Meanwhile, dasatinib as first-line treatment leads to 2-year OS>60%. 68 Substantial hematologic and cytogenetic responses have been also achieved with nilotinib and ponatinib.

Especially ponatinib has the potential of minimizing the evolution of TKI-resistant clones with T315I mutation, decreasing the risk of relapse. The T315I mutation is rarely present at the initial diagnosis but more often appears after an initial response to therapy. This mutation can be detected in 70% of patients relapsing after being treated with a second-generation TKI. However, although ponatinib can achieve 41% major haematologic response and 47% major cytogenetic response, many patients relapsed early and the median OS was less than 1 year, according to phase 2 PACE study. The superior outcomes of ponatinib in comparison with dasatinib when they were used in combination with hyper-CVAD, include CR rates 100%, complete molecular response 78% and 3-year overall survival 83%. 70 Yet, the development of novel "compounds" against T315L mutations, which are resistant to ponatinib is a matter of concern. 68

Regarding the de-escalation of induction treatment, the addition of TKIs in systemic chemotherapy leads to early mortality ~10% in AYAs, while is higher in older patients. 65,66 In contrast, a less toxic therapeutic approach combining steroids or low-dose chemotherapy with a TKI demonstrates CR rates of almost 100%. While this strategy is commonly adopted in older patients, 60 the use of de-escalated chemotherapeutic regimens in AYAs remains strongly doubtful. In a GRAALL group study, 268 patients, 18-59 years old, were randomized between imatinib/vincristine/dexamethasone and imatinib/hyper-CVAD. In the arm of less intensive chemotherapy, increased incidence of CR rates was observed (98% vs. 91%, p=0.006) due to decreased early mortality, but without significant difference in major molecular response and OS. 71 Similar strategy is followed by other study groups for ALL, such as GIMEMA and PETHEMA. 60

There is interesting scientific evidence concerning the significance of MRD and the level of the molecular response, during the last 2-3 years. 71-73 The achievement of early complete molecular response is related with lower relapse risk and more favorable outcome. Though, the aim is not clearly defined, in contrast with chronic myeloid leukemia, regarding not only the level of molecular response but also the time it should be studied. Complete molecular response with sensitivity 0.01% within 3 months from treatment initiation using the combination hyper-CVAD/TKI is related with more favorable OS and RFS, while allo-SCT is not performed. (median OS: 127 vs. 38 months and RFS 126 vs. 18 months). The group of patients having WBC<30X10^9/L and p190 transcript demonstrate higher possibility of achieving major and complete molecular remission. 71

Given that the only possibility of cure in Ph+ ALL is hematopoietic stem cell transplantation, even if remission is achieved by chemotherapy combined with a TKI, Ph+ ALL patients in remission should be referred to allo-SCT. 66 However, the long-term results of regimens combining chemotherapy with TKIs suggest the possibility of long-term survival in a proportion of patients who do not undergo a transplant. 71,72 Patients with early complete molecular response are likely to have similar outcome with or without allo-SCT. Currently, the role of autologous transplantation is being also re-examined in these patients. 71

Concerning the management of TKI-resistance, both blinatumomab and INO are efficient in R/R disease. Despite blinatumomab has not gained formal approval for R/R disease, ALCANTARA study 74 revealed CR rates 36%, while 44% of patients underwent allo-SCT. Similar results have been achieved with INO. 33 An ECOG study group trial compares the efficacy of TKIs/corticosteroid/blinatumomab combination with TKIs/chemotherapy combination, while SWOG study group examines the role of dasatinib/blinatumomab in first-line treatment for older patients (>65 years-old). 60

CONCLUSION

The adoption of pediatric-type intensive chemotherapeutic protocols has definitely improved the outcome of ALL in younger patients, while the monitoring of MRD is the most important tool for the choice of patients who are eligible for allo-SCT. The development of two novel monoclonal antibodies, blinatumomab and INO constitute important therapeutic option for R/R disease. Yet, the evolving technology of CAR-Ts has already revolutionized the treatment of adult B-ALL.
**Conflict of Interest:** Advisory Board: Amgen, Advisory Board-Honoraria: Pfizer, Gilead, Honoraria: Novartis.

**REFERENCES**


