Pharmacotherapy for adult acute lymphoblastic leukemia: an update from recent clinical trials and future directions


In adults, acute lymphoblastic leukemia (ALL) is an aggressive malignancy that, while initially highly responsive to chemotherapy, has a high relapse rate and poor survival. The role of allogeneic transplantation in ALL, the use of pediatric strategies in adolescents and young adults, the administration of rituximab for CD20-positive B-lineage ALL, tyrosine kinase inhibitors for Philadelphia chromosome-positive ALL, and nelarabine for T-lineage ALL will be discussed in this article. Promising agents reported in early clinical trials since 2010 are herein highlighted, including antibody-drug and antibody-immunotoxins; blinatumomab (bispecific T-cell engaging antibody); second- and third-generation tyrosine kinase inhibitors; mTOR inhibitors; bortezomib (a proteasome inhibitor); liposomal vincristine (reformulated chemotherapy); and decitabine (a hypomethylating agent). Progress has been made over the last few years in the development of novel therapeutics in ALL and appears to be setting the stage for even greater progress over the next 5–10 years.

Keywords: acute lymphoblastic leukemia • allogeneic • blinatumomab • dasatinib • epratuzumab • imatinib • inotuzumab • nelarabine • Philadelphia chromosome • rituximab • sirolimus

Acute lymphoblastic leukemia (ALL) is an aggressive lymphoid malignancy with a bimodal age distribution, with peak incidences in children 2–5 years of age and in adults over the age of 50 years. It is the most common pediatric hematologic malignancy, while in adults ALL is a rare disorder. In addition, while complete hematologic remission rates are as high as 90–95% in adults and children, increased relapse rates have made the overall survival dramatically inferior in adults. There are three distinct subgroups of ALL, including T-cell ALL (T-ALL), Philadelphia chromosome-positive B-cell ALL (PhALL), and Philadelphia chromosome-negative B-cell ALL (B-ALL), each of which have different biologic features and thus different treatment considerations. Significant progress has been made over the last few decades increasing the overall survival of adult patients with ALL from approximately 25–30%, perhaps to as high as 50–55% in recent studies [1–3].

It could be argued that there have been five distinct and substantial advances in pharmacotherapy for ALL over the past 5–10 years:

- Reporting of the largest international trial in ALL (MRC UKALLXII/ECOG2993) demonstrating allogeneic hematopoietic stem cell transplantation (AlloSCT) may result in improvement in overall survival (OS) and, furthermore, demonstrating that such a large multicenter, international trial is possible in a rare disease such as adult ALL [4];
- The use of pediatric-intensive regimens in young adults appears to significantly
improve outcomes compared to traditional adult regimens.7–12

- The demonstration that monoclonal antibody treatment of B-ALL is safe and effective;5
- The incorporation of tyrosine kinase inhibitors (TKI) into the treatment of T-ALL;4
- The development of nelarabine for the treatment of relapsed/refractory T-ALL.

AlloSCT & the MRC UKALLXII/ECOG2993 trial

Only recently have comprehensive data been made available from the largest study ever performed for adult ALL. The study was a joint effort between the Medical Research Council in the UK and the Eastern Cooperative Oncology Group in the USA, and accrued patients with all subtypes of adult ALL from the early 1990s through the mid-2000s. Chemotherapy included two phases of induction, with phase one including daunorubicin, vincristine, l-asparaginase and prednisone; and phase two including cyclophosphamide, cytarabine, and 6-mercaptopurine. Intrafetal methotrexate was administered during induction. Further intensification was administered with three doses of methotrexate at 3 g/m² in combination with asparaginase. Assignment to allogeneic transplant (a sibling donor in 73% of patients and the patient was considered eligible) or randomization to autologous transplantation or maintenance chemotherapy was determined after intensification, respectively.4

In 2008, Goldstone and colleagues reported the final results of the UKALLXII/ECOG2993 study.4 A complete remission (CRi), for purposes of further discussion CRi will note cytologic remission rather than complete remission (CR1; for purposes of further discussion CR1 will note cytologic remission rather than chemically-induced remission) in CR1 when treated with conventional adult chemotherapy regimens, is considered standard risk (SR: 62 vs 52%; p = 0.02); survival was only statistically significant in those patients >35 years). However, the trend in HR appeared to favor patients <45 years of age [11]. A Spanish cooperative group demonstrated nearly identical results in 81 similar standard-risk patients [12]. The results of both observations noted above.

With the decreased expression of CD20 in B-ALL as noted above, evidence for the use of rituximab in this population has developed more slowly and has only recently been reported.16

The use of rituximab for B-ALL has largely been in combination with Hyper-CVAD. In a retrospective analysis at a single center, cohorts of patients with B-ALL with CD20 expression of ≥20% were assessed for response, complete remission duration and OS. CD20 expression was assessed by flow cytometry on bone marrow aspirates. While previous work by the same group demonstrated, CD20 expression was prognostic of OS. Within 10–15 years from initial Phase I studies, rituximab has become a standard of care for initial and subsequent therapy of indolent and aggressive B-cell lymphomas.17–19

The promise of ‘targeted’ treatments for hematologic malignancies seemed to be within reach. The most promising agent during this period was a B-ALL directed chimeric monoclonal antibody named rituximab. CD20 was felt to be an appropriate target antigen for the targeting of B-ALL (given the lesser expression in B-ALL) in malignancies of mature B cells. Phase I and II studies in the mid-to-late 1990s confirmed single agent activity as well as additive/synergistic activity in combination with chemotherapy.26–28 Within 10–15 years from initial Phase I studies, rituximab has become a standard of care for initial and subsequent therapy of indolent and aggressive B-cell lymphomas.17–19

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Phase of two-weekly etoposumab. Chemotherapy was then initiated with a typical block 1 induction regimen consisting of vincristine, prednisone, and PEG-asparaginase, doxorubicin and dexamethasone. Etoposumab was administered once weekly for 4 weeks during chemotherapy.

After the chemotherapy phase, 11 out of 15 patients had stable disease, one patient had a partial response (PR) and three patients progressive disease. All but one patient had a significant reduction in peripheral blood blasts, suggesting continued drug activity. The saturation of the CD22 target was nearly 100%. Nine out of 15 patients achieved a CR after induction block I. Seven out of nine CRs were molCRs after block I. One additional patient became a moCR after block II. Toxicity was limited, but notable for a first dose infusion reaction similar to that commonly encountered with a first dose of rituximab [30].

A Phase II component of this etoposumab/chemotherapy study has recently been reported after accrual of 116 children, adolescents and young adults (aged 2–30 years) at first relapse, treated at the maximum tolerated dose (MTD). Survival data have not yet been reported. When compared to historical controls, pooled patients treated with etoposumab and chemotherapy had CR rates similar to patients treated with chemotherapy alone [31]. In patients with a CR, however, molCR appeared improved with etoposumab/chemotherapy (42 vs 25%; *p = 0.01*). Further follow-up and Phase II or III trials in the relapsed/refractory setting will be necessary to draw further conclusions.

In addition to monoclonal antibodies such as rituximab and epratuzumab, antibody–drug conjugates and antibody–immunotoxins conjugates have been developed with varying degrees of success in other hematologic malignancies. Notably, brentuximab vedotin recently became the first antibody–drug conjugate to receive US FDA approval for the treatment of Hodgkin lymphoma. While preclinical data suggested adequate binding to CD30 (universal expression in Hodgkin’s lymphoma and anaplastic large-cell lymphoma) with a naked antibody, clinical activity (66% response rate) was disappointing. The naked antibody was then conjugated to an antitubulin agent, monomethyl auristatin E and renamed brentuximab vedotin. The first trial of this agent was reported in 2010 with 56% of heavily pretreated patients treated at the MTD experiencing early death in close proximity to treatment; three patients a CR and 6 patients experienced ≥50% reduction in leukemic blasts. Several patients experienced early death in close proximity to treatment; however, causality appeared more likely to be disease related [34].

While Combiotix was initially reported in pediatric B-ALL, it was not until recently that a Phase I study in adult B-ALL has been reported. The study enrolled 17 heavily pretreated relapsed/refractory patients with CD19 or CD22 expression ≥50%. All patients experienced a decrease in peripheral blasts with one patient experiencing a PR. The pharmacokinetic studies of the brentuximab vedotin drug levels not only correlated with the dose, but also correlated just as closely with the number of circulating blasts, with a much shorter half-life in patients with the most blasts. This led the authors to speculate that in states of disease flare, without the ‘antigen sink’ of the bone marrow and peripheral circulating blasts, this agent could

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### Table 1. Chemotherapy and allogeneic transplantation.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Setting</th>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Response/survival data</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fielding et al. (2007)</td>
<td>Relapsed</td>
<td>Outcomes after relapse</td>
<td>N/A</td>
<td>609 of 1372 CR1 patients relapsed: 5-year OS: 23% AllolSCT with matched related donor; 16% AllolSCT with matched unrelated donor; 4% chemotherapy alone</td>
<td>(a)</td>
</tr>
<tr>
<td>Goldstone et al. (2008)</td>
<td>Upfront</td>
<td>AllolSCT vs autologous transplantation vs maintenance chemotherapy</td>
<td>Graft vs leukemia effect</td>
<td>1913 patients; 1051 with HLA typing AllolSCT eligible, achieving CR1–5-year OS: 53%; 45% for no PH vs AllolSCT</td>
<td>(b)</td>
</tr>
<tr>
<td>Stock et al. (2008)</td>
<td>Upfront, AYA only</td>
<td>Chemotherapy only vs Chemotherapy, cytotoxicity</td>
<td>N/A</td>
<td>Child (CCG) vs adult (CALGB) for AYA; 7-year OS: C67% vs CALGB 46%</td>
<td>(c)</td>
</tr>
<tr>
<td>Gokbuget et al. (2011)</td>
<td>Relapsed/refractory, T cell only</td>
<td>Nabrelan vs Placebo</td>
<td>T cell only</td>
<td>Cell 36 and 10% CR</td>
<td>(d)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AllolSCT: Allogeneic hematopoietic stem cell transplantation; AYA: Adolescents and young adults; CALGB: Cancer and Leukemia Group B; CCG: Children’s Cancer Group; CR1: Cytologic remission; HLA: Human leukocyte antigen; OS: Overall survival; PH: AllolSCT. Philadelphia-negative acute lymphoblastic leukemia.
Review: Clinical Trial Outcomes  Burnette, Patrik & Litowitz

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Table 2. Immunotherapy/antibody-directed therapy for Philadelphia chromosome-negative B-lineage adult acute lymphoblastic leukemia.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Setting</th>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Response/survival data</th>
</tr>
</thead>
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<tr>
<td>Thomas et al. (2010)</td>
<td>Uprfront</td>
<td>Rituimusab/ hyper-CVAD</td>
<td>Anti-CD20 antibody with chemotherapy</td>
<td>5-year OS: R-chemotherapy 71%; chemotherapy 57%</td>
</tr>
<tr>
<td>Raetz et al. (2011)</td>
<td>Relapsed/ refractory</td>
<td>Eptuzumab</td>
<td>Anti-CD20 antibody</td>
<td>MOE: R-chemotherapy 42%; chemotherapy 25%</td>
</tr>
<tr>
<td>O’Brien et al. (2011)</td>
<td>Relapsed/ refractory</td>
<td>Comirnaty</td>
<td>Anti-CD20 antibody</td>
<td>Response rate: 57%</td>
</tr>
<tr>
<td>Schindler et al. (2011)</td>
<td>Relapsed/ refractory</td>
<td>Comibiox</td>
<td>Anti-CD20 antibody conjugated to immunotoxin</td>
<td>All 17 patients decrease blasts, one PR</td>
</tr>
<tr>
<td>Wayne et al. (2011)</td>
<td>Relapsed/ refractory</td>
<td>Moxetumomab</td>
<td>Anti-CD20 antibody conjugated to immunotoxin</td>
<td>CR: 29%; PR: 7%</td>
</tr>
<tr>
<td>Topp et al. (2011)</td>
<td>Relapsed/ refractory</td>
<td>Blinatumomab</td>
<td>Bispecific T-cell engaging antibody (CD3/CD19)</td>
<td>67% rapid/durable CR and moiCR</td>
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**TKi in PhALL**

One of the most important advances in hematology over the past several decades was the reporting of the early studies of the TKI, imatinib in chronic myelogen- eous leukemia (CML), in chronic phase as well as blastic phase or PhALL. In chronic phase CML, an unprecedented 98% response rate for doses >300 mg daily was reported (with an exceptional tolerability with this agent). In blastic phase CML or relapsed/refractory PhALL, a remarkable 70% response rate was demonstrated. While the median duration of response was 58 days, the results were no less remarkable in such an aggressive, therapy refractory disease.

Soon after the initial Phase I trials, a number of Phase I and II trials, which combined imatinib with chemotherapy, were completed and reported. Importantly, GMLA compared the safety and effi- cacy of sequential versus concurrent imatinib with a standard intensive ALL regimen. With a somewhat limited follow-up, no difference in OS or RFS was noted. Concurrent therapy, however, was tolerated similarly and was associated with superior moiCR after consolidation of 52 versus 19 in the sequential group.

One group from Japan also reported results of a Phase II trial investigating conventional chemother- apy with concurrent imatinib in 80 adult patients with PhALL. The imatinib was initiated at day 0 of induction therapy, excluded from consolidation one, and then continued from the start of consolidation two through 2 years of maintenance (maintenance also including monthly vincristine and pulse corticosteroids). CR1 was achieved with this strategy in 96% of patients with 50% achieving molecular CR1 on day 63. Notably, death during induction therapy occurred in only 2.5% of patients. AlloSCT was recommended for patients with an identified HLA-identical sibling donor if the patient had achieved CR1. Event-free survival (EFS) and OS at 1 year were 60 and 76%, respectively. Both EFS and OS appeared superior to historical controls. At 1 year, outcomes appear similar in the 49 patients undergoing AlloSCT versus those that did not. With results reported of 1-year EFS and OS rates, results between patients undergoing AlloSCT and those not undergoing AlloSCT should be interpreted with caution.

With such remarkable results in two Phase II studies incorporating concurrent imatinib with conventional chemotherapy, concurrent therapy thus became the standard for ongoing clinical trials. While TKIs have been rapidly accepted as the stan- dard of care with concurrent chemotherapy, data sup- porting this approach have not been optimal. It was not until 2010 that high-level evidence was presented from UKALLXII/ECOG2993 clearly demonstrating the benefit of the addition of a TKI to chemotherapy in untreated PhALL. The trial was not originally designed to include imatinib, as the study was designed in the pre-imatinib era, but enrollment opened in 1993. With the introduction of imatinib and the exciting activity of this agent, in March 2003 patients enrolled with PhALL were initiated on imatinib during the second phase of the first induction cycle (week 5) or the start of the first consolidation cycle (week 9). Patients not proceeding to AlloSCT continued with daily imatinib (600 mg once daily) for 2 years with maintenance therapy. In patients undergoing AlloSCT, imatinib was initiated and continued for 2 years after AlloSCT, if tolerated. Long-term results of 441 patients with PhALL were presented in late 2010. Despite a greater median age (not reported) due to an increase in the maximum allowable

demonstrate efficacy, eradicate molecular disease and possibly cure patients. Additionally, it was speculated that there may be therapeutic potential if administered after chemotherapy had ‘debunked’ the leukemia and decreased the ‘antigen sink’ [41]. Moxetumomab is an additional antibody-immuno- toximab targeting CD22. The agent is an anti-CD22 anti- body, linked to pseudomones exotoxin A. A Phase I study in pediatric CD22 expressing B-ALL enrolled 21 patients with relapsed/refractory disease. Capillary leak syndrome was the dose limiting toxicity and was experienced in two patients. Subsequently, corticoste- roids were randomly administered, with no further capillary leak syndrome. Otherwise, toxicity was mild and reversible. Hematologic response occurred in five out of 17 evaluable patients (29%), with four CRs and one PR. A decrease of >50% in circulating blasts was observed in seven (41%) patients. The tolerability and response was felt to be impressive enough for the investigators to pursue further Phase II studies [41].

Despite the fact that it has been over 10 years since the first reports of dramatic B-cell cytotoxicity in cell lines from a new class of novel therapeutic agents called bispecific T-cell engagers, data in humans were not presented until recently. Binatumomab is a single-chain bispecific antibody targeting cytotoxic T cells and B-cells. Upon attachment to T-cells, the other arm of the bispecific antibody binds to CD19 on B cells. The activated cytotoxic T cells then induce perforin-mediated lysis of B cells. CD19 is one of the cell surface markers expressed earliest in B-cell maturation and its expression in B-ALL blast has been found to be universal, suggesting that CD19 would be a very attractive target.

The first report of binatumomab was a Phase I trial in B-cell lymphoma patients reported in 2008. Of 38 evaluable patients, 11 obtained a major response, with the agent demonstrating some degree of cytotoxicity in all patients. At the maximum achieved dose (dose escalation was ongoing at the time of publication), all seven patients demonstrated an objective response. Responses were durable and the agent was well tol- erated with common toxicities including lymphopenia, leukopenia, pyrexia and chills. No anaphylactic reactions to the initial infusion were noted, a feature common with chimeric monoclonal antibody adminis- tration [41].

The potential efficacy of this agent in ALL was described in a recent Phase II trial from Germany. The trial enrolled 16 B-ALL and five PhALL patients who had a CR1 to initial therapy, but had either MRD or minimal residual disease. Binatumomab was administered as a continuous infusion for 4 weeks followed by 2 weeks free from treatment. Patients responding could receive three additional cycles. Patients with a matched donor were permitted to pursue AlloSCT at any time after cycle 1. Currently, 10 patient experienced grade 3 seizures during the first cycle and discontinued treatment (seizures resolved within 24 h). Toxicity was mostly limited to cytopen- a (leucopenia and lymphopenia) with four documented grade 3/4 infections, mild pyrexia and mild chills.

Out of 20 evaluable patients, 16 achieved durable molecular remission (CR1) with a CR1 rate of 75% at the end of 3 cycles. This response rate and depth of response with this agent, in March 2003 patients enrolled with PhALL were initiated on imatinib during the second phase of the first induction cycle (week 5) or the start of the first consolidation cycle (week 9). Patients not proceeding to AlloSCT continued with daily imatinib (600 mg once daily) for 2 years with maintenance therapy. In patients undergoing AlloSCT, imatinib was initiated and continued for 2 years after AlloSCT, if tolerated. Long-term results of 441 patients with PhALL were presented in late 2010. Despite a greater median age (not reported) due to an increase in the maximum allowable...
imatinib. In patients undergoing alloSCT, 3-year OS was superior to both imatinib (72% vs 64%) and chemotherapy/nilotinib (55% vs 43%). In patients undergoing alloSCT, 3-year EFS was superior to both imatinib (59% vs 49%) and chemotherapy/nilotinib (40% vs 34%). The authors concluded that dasatinib is a promising alternative to imatinib in patients with imatinib-resistant disease, with equivalent or superior outcomes compared to chemotherapeutic regimens. The study also demonstrated the feasibility and safety of combining dasatinib with other treatments, such as allogeneic transplantation and cytokine therapy.

In another study, the combination of dasatinib with hematopoietic stem cell transplantation as consolidation therapy after induction chemotherapy was investigated in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia. The study included 36 patients who achieved a complete remission after induction therapy with a combination of vincristine, dexamethasone, and high-dose cytarabine. Dasatinib was administered after the completion of induction therapy, and the median follow-up was 12 months. The study reported a complete remission rate of 94%, with 86% of patients achieving complete remission and 80% of patients achieving complete remission with minimal residual disease. The study concluded that the combination of dasatinib with hematopoietic stem cell transplantation as consolidation therapy after induction chemotherapy is a promising approach for patients with Philadelphia chromosome-negative acute lymphoblastic leukemia.
mutations were 39% and 37%, respectively, while CR and major cytogenetic responses in patients with minimally informative pre 17 and 24%, respectively. Of note, it was not reported in this group of blast/accelerated phase CML and PhALL the number of imatinib resistant versus nilotinib intolerant, nor has it been reported how many patients had previously received a second-generation TKI. Both issues would greatly impact the interpretation of data [61].

Another new TKI, ponatinib, has demonstrated promising preclinical activity in cell lines with dasatinib and nilotinib resistance, and in T315I-mutant cell lines. In addition, ponatinib appears to differ from earlier TKIs with significant inhibition in vitro (FGFR-1–4), which have been implicated in a number of malignancies. With >80% of expected enrollment, an interim analysis of a Phase II trial of ponatinib in dasatinib/nilotinib intolerant/refractory CML or PhALL, or patients with CML or PhALL with T315I mutation (rendering currently available TKIs ineffective) was recently reported. A high percentage of patients (88%) were resistant to dasatinib/nilotinib rather than intolerant. In this interim analysis, 30 patients with blast phase CML or PhALL with resistance/intolerance and 22 patients with T315I mutations were evaluable. A major cytogenetic response was experienced in 27% of patients with resistant/intolerant disease and T315I mutations, respectively. Treatment appeared to be well tolerated. Given the heavily pretreated population – most of whom had failure of both imatinib and a second generation TKI – this agent appears promising for future development [62]. A brief summary of articles we find to be of particular importance regarding TKI targeting of BCR/ABL in PhALL is included in Table 3.

Nelarabine for T-ALL
Nelarabine is a purine nucleoside and a pro-drug of deoxyguanosine analogue ara-G. It is demethylated and phosphorylated intracellularly to form the active compound ara-GTP. Ara-GTP’s mechanism of action is as a substrate for GTP in a number of biologic processes including, most importantly for our purposes, DNA replication. With the substitution of ara-GTP for GTP in DNA replication, DNA synthesis is inhibited ultimately leading to cell death. Preclinical studies nelarabine acetate were conducted to much greater concentrations in T cells lymphocytes, due to a more rapid phosphorylation in T cells and a more rapid catabolism of deoxyguanosine triphosphate in B lymphocytes; ultimately leading to a greater selectivity and toxicity for T lymphocytes [63]. An initial Phase I trial established a MTD and demonstrated evidence for T-cell accumulation of ara-G. However, it was not until a number of years later that the entire dataset was reported [64]. The full Phase I trial enrolled 93 patients with refractory hematologic malignancies, of which 66% had T-cell malignancies. Dose limiting toxicity was neurotoxicity, but was otherwise well tolerated. In this heavily pretreated pediatric and adult population, nine (23%) CRs and 12 (31%) PRs were demonstrated in T-cell lymphoblastic lymphoma and T-ALL. It was felt that this agent warranted further investigation for T-cell malignancies [65]. A German Phase II trial has recently reported the results of single-agent nelarabine for relapsed/refractory T-ALL and T-cell lymphoblastic lymphoma. Of 126 heavily pretreated adult patients, 36% achieved a CR and 10% a PR. Of patients achieving a CR, 80% proceeded to AlloSCT. Median OS was 6 months, with a 24% 1-year OS and a 12% 3-year OS. In patients who proceeded to AlloSCT, 3-year OS was estimated at 31%. Treatment was well tolerated with toxicity similar to that in the Phase I [64]. A US group demonstrated similar findings in a US-based Phase II trial of 39 adults with either T-ALL (26 patients) and T lymphoblastic lymphoma (13 patients) with a 1-year OS of 28% and response rate of 41% [66]. Recently, nelarabine has also been combined with upfront chemotherapy for pediatric T-ALL. A novel design randomized patients with >/=1 MRD in the bone marrow or >/=5% blasts at day 29 of an induction chemotherapy including this approach for patients with an unfavorable response to induction. The protocol was randomized to chemotherapy with or without 5 days of nelarabine in consolidation, delayed intensification and at the start of each maintenance cycle. In total, 477 patients were identified to much greater concentrations in T lymphocytes, due to a more rapid phosphorylation in T cells and a more rapid catabolism of deoxyguanosine triphosphate in B lymphocytes; ultimately leading to a greater selectivity and toxicity for T lymphocytes [63]. Other therapeutic agents for all undergoing active investigation

• mTOR inhibitors

The mTOR pathway has been implicated as a pathway dysregulated and leading to increased proliferation and decreased apoptosis in a number of malignancies. The potential of mTOR inhibitors has led to the evaluation of mTOR inhibitors in both pediatric and adult patients with leukemia. Mature in human studies have not progressed sufficiently at this point in time to assess efficacy of mTOR inhibitors, such as everolimus, sirolimus, temsirolimus or rapamycin. As sirolimus has immunosuppressive properties and is regularly used in this manner for solid organ transplantation, its use has been increasingly investigated as an immunosuppressive agent in AlloSCT. With the potential for specific antitumor activity in ALL, there may be a dual role for sirolimus in patients undergoing AlloSCT. This role was recently investigated in pediatric ALL patients in a Phase II study. The study included 35 patients in second CR and 12 patients in third CR or greater. Conditioning was myeloablative with total body irradiation, cyclophosphamide and thiopeta. Besides sirolimus, graft versus host disease (GVHD) prophylaxis included tacrolimus and methylprednisolone administered and tapered per routine clinical practice. Sirolimus was continued for 6 months, and then tapered to discontinue within 4 weeks. In total, 26 patients received a matched sibling graft, five received a matched unrelated donor graft and 30 received an unrelated cord blood stem cell transplant. A total of 35 patients had acute and chronic GVHD, toxicity and transplant related mortality all appeared similar to historical cohorts. Sirolimus was well tolerated. RFS and OS at 2 years were 64 and 73%, respectively [67]. For multiple reasons, this trial was not able to demonstrate a benefit for patients with relapsed disease. A Phase III study in pediatric ALL is ongoing, hopefully with results to be anticipated within the next 3–5 years.

• Proteasome inhibitors

Bortezomib is a proteasome inhibitor with evidence of benefit in hematologic malignancies, most notably multiple myeloma and indolent lymphomas. It has also been studied as a chemotherapy sensitizer. In pediatric ALL, there may be a dual role for sirolimus in ALL [75]. As sirolimus has immunosuppressive properties and is regularly used in this manner for solid organ transplantation, its use has been increasingly investigated as an immunosuppressive agent in AlloSCT. With the potential for specific antitumor activity in ALL, there may be a dual role for sirolimus in patients undergoing AlloSCT. This role was recently investigated in pediatric ALL patients in a Phase II study. The study included 35 patients in second CR and 12 patients in third CR or greater. Conditioning was myeloablative with total body irradiation, cyclophosphamide and thiopeta. Besides sirolimus, graft versus host disease (GVHD) prophylaxis included tacrolimus and methylprednisolone administered and tapered per routine clinical practice. Sirolimus was continued for 6 months, and then tapered to discontinue within 4 weeks. In total, 26 patients received a matched sibling graft, five received a matched unrelated donor graft and 30 received an unrelated cord blood stem cell transplant. A total of 35 patients had acute and chronic GVHD, toxicity and transplant related mortality all appeared similar to historical cohorts. Sirolimus was well tolerated. RFS and OS at 2 years were 64 and 73%, respectively [67]. For multiple reasons, this trial was not able to demonstrate a benefit for patients with relapsed disease. A Phase III study in pediatric ALL is ongoing, hopefully with results to be anticipated within the next 3–5 years.

Potentially, when combined with chemotherapy in relapsed/refractory ALL was pursued. Ten pediatric patients with relapsed/refractory ALL were administered bortezomib, which was dose escalated to 1.3 mg/m² on days 1, 4, 8 and 11 in combination with typical induction chemotherapy. The combination was well tolerated, with hematologic toxicity being the most prominent and not differing significantly from that historically experienced. Nine patients were evaluable (one death during induction due to invasive zygomycosis), of which six patients experienced a CR [67]. With dose escalation complete, the same group proceeded to a Phase II trial in 22 pediatric ALL patients with relapsed/refractory disease after two or three previous regimens. The toxicity was similar to that experienced in adult patients undergoing induction. Nine patients, 14 experienced a CR and two patients experienced a CR. All responders were B-ALL. Results

### Table 3. Tyrosine kinase inhibitors in Philadelphia chromosome-positive B-cell lineage acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Setting</th>
<th>Treatment</th>
<th>Mechanism of action</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fielding et al. (2010)</td>
<td>Upfront</td>
<td>Imatinib and chemotherapy</td>
<td>BCR/ABL inhibition and chemotherapeutic</td>
<td>3-year OS (n = 441): imatinib 42%; no imatinib 25%; AlloSCT 59%; no AlloSCT 29%</td>
<td>[61]</td>
</tr>
<tr>
<td>Ravandi et al. (2010)</td>
<td>Upfront</td>
<td>Hyper-CVAD with dasatinib</td>
<td>BCR/ABL inhibition and chemotherapeutic</td>
<td>2-year OS: 62%</td>
<td>[61]</td>
</tr>
<tr>
<td>Foa et al. (2011)</td>
<td>Upfront</td>
<td>Dasatinib and prednisone</td>
<td>BCR/ABL inhibition</td>
<td>2-year OS: 67%; median OS: 31 months</td>
<td>[61]</td>
</tr>
<tr>
<td>Cortes et al. (2011)</td>
<td>Relapsed/refractory</td>
<td>Ponatinib</td>
<td>BCR/ABL inhibition</td>
<td>CR: 37% TKI resistant; 27% T315I</td>
<td>[61]</td>
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</tbody>
</table>

Table 3. Tyrosine kinase inhibitors in Philadelphia chromosome-positive B-cell lineage acute lymphoblastic leukemia.
met predefined criteria for early discontinuation. Grade 3 or greater peripheral neuropathy developed in 9% of patients [77].
Given this heavily pretreated population, an 80% CR plus CRi (in B-ALL) appears remarkable in this pediatric population. While not reported, it appears highly likely that patients who received vincristine had received nearly identical chemotherapy in the past, but had relapsed despite it, suggesting benefit from bortezomib. To our knowledge, this combination has not been evaluated concurrently. It appears unlikely, however, that adults would tolerate a similar regimen. It should be noted that the administration of bortezomib intravenously on this schedule has been associated with peripheral neuropathy, most notably in the myeloma population. If administered with concurrent vincristine, as was done in this trial (also associated with significant neurotoxicity), it is our impression this would not be tolerated by adults. It is possible that the risk of neuropathy could be mitigated, as it has in multiple myeloma, by a change to once-weekly subcutaneous administration or with the use of an alternative proteasome inhibitor [74-76].

■ Liposomal vincristine

Vincristine has been an integral part of ALL inductions, intensifications and maintenance in the upfront and relapsed setting for decades. Vincristine’s mechanism of action involves the binding to microtubules, causing depolymerization, metaphase arrest and cell death. It remains one of the most active agents for ALL and lymphoid malignancies. Vincristine, however, is associated with significant dose-limiting neurotoxicity likely due to rapid binding to neurologic tissues. Outside of its neurotoxicity, vincristine is one of the most well-tolerated chemotherapies currently administered. It has been postulated that if neurotoxicity were diminished while maintaining drug activity, the administration of higher doses could be achieved. Such was the thinking in reformulating vincristine into a liposomal compound.

Liposomal vincristine sulfate is a nanoparticle formulation that is encapsulated in sphingomyelin and cholesterol liposomes. In preclinical models this encapsulated formula appeared to prolong the serum half-life and decrease drug absorption to normal tissue uptake while increasing bioavailability. In a Phase I trial in adults with relapsed/refractory ALL, liposomal vincristine sulfate was administered in a dose escalating manner. After concluding this phase, dose escalation was continued in a Phase II fashion for relapsed/refractory pediatric and adult ALL. In the initial phase, patients were administered decitabine for 5 days every 2 weeks in a dose escalating manner. After concluding this initial phase, decitabine was then administered for 5 consecutive days at the beginning of the 28-day hyper-CVAD regimen. This was alternated per the usual CVAD regimen. In total, 39 patients were enrolled, of whom the 24% responded to this combination. The median CR plus CRi lasted 12 months. Another 28% had a bone marrow response to treatment. Responses to therapy appeared to be durable. Of note, all patients were heavily pretreated and had been unsuccessfully treated in the upfront setting with Hyper-CVAD without decitabine alternating with high-dose methotrexate and cytarabine. Toxicity appeared similar to that experienced with Hyper-CVAD alone. Hypomethylation was confirmed in combining decitabine to Hyper-CVAD as investigators concluded that this regimen appears to have sufficient activity to warrant further clinical trials in a treatment naïve, or less heavily pretreated population [78].

Future perspective

One could argue that, over the past 2 years, more encouraging studies evaluating exciting new treatments for adults have been reported than had been reported in the previous 5–10 years. It is with great enthusiasm that we look toward a future with more efficacious and less toxic therapy for ALL, such that a cure may be achieved in an ever increasing number of patients. The new and evolving therapies and issues discussed in this review are in no way inclusive of each and every agent evaluated in clinical trials or in preclinical studies, but those that we feel have been evaluated in sufficient human studies to warrant discussion are included.

Executive summary

Allologic hematopoietic stem-cell transplantation for adult acute lymphoblastic leukemia

■ UKALLXII/ECOG2993: demonstrated benefit of allogeneic transplant in adult acute lymphoblastic leukemia (ALL) and the feasibility of performing feasible international multicenter trials for ALL.

■ Pediatric protocols for adolescents and young adults: adolescents and young adults fare better when treated on pediatric protocols, suggesting a lesser role for transplant in complete cytologic remission for such patients.

Antibody-directed therapy of B-cell ALL

■ Rituximab: a CD20-directed antibody that appears to confer a survival benefit in retrospective studies.

■ Epratuzumab: a CD22-directed antibody with activity in relapsed/refractory ALL.

■ Inotuzumab: a CD22-directed antibody–drug conjugate with activity in relapsed/refractory ALL.

■ Combitox: CD19 and CD22 antibodies conjugated to an immunotoxin with activity in relapsed/refractory ALL.

■ Moxetumomab: a CD22-directed antibody–immunotoxin conjugate with activity in relapsed/refractory ALL.

■ Blinatumomab: a CD3/CD19 first-in-class novel agent called a bispecific T-cell engager demonstrates activity in relapsed/refractory ALL.

Tyrosine kinase inhibitors for Philadelphia chromosome-positive B-cell ALL

■ Imatinib/chemotherapy: first-in-class tyrosine kinase inhibitors (TKIs) demonstrates survival benefit in UKALL XI/ECOG2993.

■ Dasatinib or nilotinib/chemotherapy: several studies demonstrating feasibility and possibly improved response rates and overall survival with second-generation TKIs.

■ TKIs with corticosteroids: feasibility, decreased toxicity and possible increased survival in Phase II studies with TKIs/corticosteroids alone, or TKI/corticosteroids/decreased chemotherapy.

■ Third-generation TKIs: ponatinib and bosutinib demonstrate significant activity in Philadelphia chromosome-positive ALL relapsed/refractory after imatinib/dasatinib/nilotinib.

■ Other therapeutic agents: mTOR inhibitors: early-phase studies on ramiprilan and sirolimus suggest tolerability and possible benefit.

■ Proteasome inhibitors: bortezomib in combination with traditional chemotherapy appears to increase response rate to previously administered chemotherapy agents.

■ Liposomal vincristine: reformulated vincristine appears to allow for an increase in delivered vincristine dose without increased toxicity.

■ Hypomethylating agents: decitabine with Hyper-CVAD very early-phase studies suggesting safety and possible signal for efficacy.

Future perspective

Over the next 5–10 years, we anticipate and expect significant progress through clinical trials in the understanding of novel therapies and their incorporation into the standard of care for the treatment of adults with ALL.
Will novel bispecific T-cell engaging agents, such as blinatumomab, translate the exciting results from early phase trials to actual clinical benefit for patients?

Can more patients with Ph+ALL survive induction therapy with less intensive chemotherapy (or without chemotherapy) and with less hematopoietic growth factor support to reduce the incidence and severity of GVHD as well as reduce the risk of recurrence?

Can nelanerib be substituted for cytotoxic agents or added to reduce therapy-related toxicities?

Can immunosuppressants with an mTOR inhibitor substitute for or add to reduce the incidence of early phase toxicity? Alternatively, can we also identify patients with residual/recurrent molecular disease who are at HR for relapse, and treat them more aggressively or with novel and investigational treatment strategies?

Can mTORC1/mTORC2 suppressants with an mTOR inhibitor substitute for or add to reduce the incidence of early phase toxicity? Alternatively, can we also identify patients with residual/recurrent molecular disease who are at HR for relapse, and treat them more aggressively or with novel and investigational treatment strategies?

In patients who have achieved a rapid and persistent mCR and have a good prognosis, can we reduce the intensity and/or duration of therapy? Alternately, can we also identify patients with residual/recurrent molecular disease who are at HR for relapse, and treat them more aggressively or with novel and investigational treatment strategies?

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In Philadelphia chromosome-positive ALL in the upfront setting, a 0.2% 2-year overall survival and a 3-1-month median overall survival is achieved with dasatinib and prednisolone induction alone for induction. In addition, in those patients eligible and who proceeded to allogeneic transplant, 16 of 18 patients appeared to be long-term disease-free survivors.


