Recent Pharmacological Advances in the Treatment of Acute Lymphoblastic Leukaemia

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Abstract: Acute lymphoblastic leukaemia (ALL) is the most common leukaemia in children and third most common in adults. Although the majority of children and adults with ALL achieve a complete remission with intensive chemotherapy, relapse will occur in 20% and 50% respectively. As further intensification risks greater toxicity and may not diminish the risk of relapse, new targeted therapies with less overall toxicity are urgently needed. There have been a number of new agents recently developed directed at specific cellular pathways involved in leukaemia genesis and are beginning to make their way into early phase clinical trials. This review will highlight a number of these novel chemotherapy agents and the pathways they target in relapse ALL.

Keywords: acute lymphoblastic leukaemia, ALL, chemotherapy agents, relapse
**Introduction**

Acute lymphoblastic leukaemia (ALL) is the most common leukaemia in children and the third most common in adults, with more than 2,400 children and 5,400 adults diagnosed each year in the US. The complete remission rate for newly diagnosed ALL in children and adults is between 96%–99% and 78%–93% respectively, however 15%–20% of children and >50% of adults will later relapse with their disease. Thus leukaemia free survival (LFS) at 5-years subsequently drops to 75%–85% in children and 30–40% for adults. The treatment of children and adults with relapsed or refractory ALL has historically been very poor. Although the majority (45%–90%) of patients in first relapse may be successfully re-induced into a second complete remission (CR2), most will eventually die of progressive disease. Therefore, there is an urgent need for new agents to be developed and quickly incorporated into both upfront and salvage therapy to hopefully improve these high rates of treatment failure.

There have been a number of novel agents that have recently worked their way into the treatment of relapsed leukaemia. Such therapies span a broad range of therapeutics from newer anti-metabolites (e.g. clofarabine) and monoclonal antibodies (e.g. epratuzumab) to epigenetic agents (e.g. demethylators, HDAC inhibitors) and kinase inhibitors (e.g. imatinib) many with very promising pre-clinical/clinical results. This review will highlight some of these more recent pharmacologic advances in ALL therapy.

**Purine nucleoside analogs**

The single largest class of cancer therapeutics consist of the nucleoside and nucleobase anti-metabolites, of which clofarabine, forodesine and nelarabine are three of the more recent additions to leukaemia therapy (Fig. 1). Clofarabine (2-chloro-20-fluorodeoxy-9-b-D-arabinofuranosyladenine) (Clolar, Evoltra; Genzyme Corporation, Cambridge, Massachusetts, USA), an analog of deoxyadenosine, is one of the most recent drugs to receive FDA approval as a single agent for the treatment of children with relapsed/refractory ALL. Clofarabine is similar in chemical structure to its two sister agents, fludarabine and cladribine, where it was synthesized to retain the 2-chloroadenine aglycone of cladribine and fluorinated in the arabinos configuration at the critical 2’-position of the carbohydrate to stabilize the glycosidic bond, thus making it highly resistant to both bacterial purine nucleoside phosphorolase and acid hydrolysis. Clofarabine’s primary mechanism of action is in disrupting DNA synthesis through inhibiting DNA polymerase and ribonucleotide reductase. It has been shown pre-clinically to disrupt the DNA repair by incorporating itself into the DNA during the repair process. Although mainly a cell cycle specific agent, clofarabine is able to cause cell death in non-cycling cells via disrupting mitochondrial function and releasing cytochrome C.

Clofarabine has been previously investigated in relapsed ALL as a single agent and most recently in combination therapy. In 2003, Kantarjian et al published their phase I trial results investigating single agent clofarabine in patients with solid tumors and acute leukaemia. There were 32 adult patients with acute leukaemia (13 patients with ALL) who received clofarabine (dose range 4 mg/m²–55 mg/m²) as a single agent administered intravenously over 1 hour daily for five consecutive days. The overall response rate for the 13 patients with ALL was 15% and a dose of 40 mg/m² was identified as the future phase II dose. There treatment overall was well tolerated with reversible hepatotoxicity being the only DLT reported at the highest dose level (55 mg/m²). The adult phase II trial that followed enrolled 12 patients with ALL who received single agent clofarabine at 40 mg/m² administered intravenously over 1 hour daily for five consecutive days every 3 to 6 weeks. A complete response (CR) or CR without platelet recovery to 100 × 10^3/L (CRp) was reported in 2/12 (17%) ALL patients.

Paediatric studies investigating clofarabine have reported similar anti-leukaemia activity. A single center trial by Jeha et al enrolled 17 patients with ALL
who received clofarabine as a single agent (dose range 11.25 mg/m² to 70 mg/m²) administered intravenously over 1 hour for 5 consecutive days. The pediatric MTD identified was 52 mg/m² with reversible hepatotoxicity as the only DLT and a CR rate of 24% (4/17).17 A subsequent multi-center paediatric phase II trial of clofarabine given at the identified MTD of 52 mg/m² daily for 5 consecutive days was recently reported by Jeha et al.18 This trial enrolled 61 patients with ALL, many of which were heavily pretreated and 30% having failed a prior haematopoietic stem cell transplant, reporting an overall response rate of 20% (CR/CRp).

The relatively encouraging results of clofarabine used as a single agent in both adult and paediatric relapsed/refractory ALL as well as the overall tolerable toxicity profile observed in these early trials, provided rationale to begin incorporating clofarabine into combination regimens. Based on the primary mechanism of action in inhibiting DNA synthesis and disrupting DNA repair, combination trials have paired clofarabine with agents that cause DNA damage (e.g. alkylators). In an adult phase I dose escalation trial for relapsed/refractory leukaemia patients treated with cyclophosphamide (Cy) and clofarabine (Clo) (days 1–3 and 8–10), 18 patients were enrolled with 6 patients (3 ALL) treated at dose level 1 (Clo 20 mg/m²/Cy 400 mg/m²) and the remaining 12 patients (3 ALL) de-escalated down to dose level 0 (Clo 10 mg/m²/Cy 400 mg/m²) due to increased toxicities seen at the higher clofarabine dose.19 Of the 6 ALL patients, 4 achieved either a CR (n = 3) or PR (n = 1) for an overall response rate of 67% in a very high-risk population. Paediatric combination trials investigating clofarabine have been performed and shown similar encouraging efficacy in relapsed leukaemia. Hijiya et al reported the combination of clofarabine (initial dose 20 mg/m²), etoposide (initial dose 75 mg/m²) and cyclophosphamide (initial dose 340 mg/m²) in a dose escalation study of 25 relapsed/refractory acute leukaemia paediatric patients.20 The combination therapy was well tolerated with no MTD identified, and 9/20 (55%) ALL patients achieved a CR/CRp.

Based on the very encouraging results of clofarabine in the adult and paediatric population of relapsed/refractory ALL, both as a single agent and in combination therapy, the Children’s Oncology Group (COG) will be investigating clofarabine in an upcoming Phase III trial for very high-risk ALL.

The next purine antimetabolite that has had equal excitement to clofarabine in the treatment of ALL is nelarabine. Nelarabine is a soluble pro-drug of 9-β-D-arabinofuranosylguanine (ara-G) that preferentially accumulates in T-cells and received FDA approval for the treatment of relapsed T-ALL and T-Cell lymphoblastic lymphoma in 2005. Nelarabine, like clofarabine, is able to incorporate itself into the DNA and disrupt DNA synthesis as well as replication and leading ultimately to cell death.21 A phase I single agent dose escalation study of nelarabine (days 1–5) in relapsed/refractory heme malignancies was reported by Kurtzberg et al which included adults (n = 59) and children (n = 34).22 The MTD identified was 60 mg/kg for the paediatric cohort and 40 mg/kg in the adult with a single DLT (grade 4 neurotoxicity) reported at dose level 75 mg/kg. The overall response for the 39 patients with either T-ALL or T-cell lymphoma was a CR in 9 (23%) and PR in 12 (31%). The most common toxicity reported in this trial was neurotoxicity (72%) which included malaise/fatigue (63%), somnolence (49%) and confusion (22%), occurring early after initial exposure to nelarabine and typically reversible. In a larger paediatric phase II trial investigating nelarabine in relapsed T-ALL of 106 patients assessable for response, 18/33 (55%) patients after first marrow relapse achieved a CR/PR and 8/30 (27%) in second or greater relapse achieved CR/PR.23 Neurotoxicity was again the most common toxicity identified requiring 2 dose de-escalations with overall 18% of the patients reporting grade 3 or greater neurotoxicity.

With the very promising results seen in the single agent trials for T-ALL using nelarabine, further combination studies and upfront (phase III) trials are forthcoming. A phase I trial investigating the combination of nelarabine, etoposide and cyclophosphamide in relapsed paediatric T-ALL is currently open through the TAACL (Therapeutic Advances in Childhood Leukaemia) consortium as well as nelarabine having been incorporated into the frontline therapy in a COG phase III trial for children and young adults with newly diagnosed T-ALL. The last of the more recent anti-metabolites to enter into ALL therapy is forodesine. Forodesine is a purine nucleoside
phosphorylase (PNP) inhibitor that causes apoptosis in cells (primarily T-cells) that accumulate deox-
yguanosine triphosphate in the absence of PNP. Single agent studies using forodesine in hema-
tologic malignancies have been performed with some encouraging results.24–26 Furman et al reported results of a dose escalation phase I/II trial of forodesine (days 1–5) in 15 patients with heme malignan-
cies. There were no DLTs reported and 7/15 (47%) patients (2 T-cell and 5 B-cell) had a decrease in their
malignancy burden.26 A phase II trial followed investigating single agent forodesine (40 mg/m² iv days 1–5)
in 34 relapsed/refractory T-ALL patients (median age, 31 yr; range, 3–76 yr).24 A CR was achieved in
7 patients (20.6%) and PR in 4 (11.8%) for an OR of 32.4%. The therapy was overall very well toler-
ated with no non-haematologic drug related grade
3–4 toxicities reported. Although there have yet to
be combination trials reported incorporating forode-
sine into ALL therapy, the single agent activity and
overall low toxicity of this agent warrant pursuit of
such studies in the future.

Monoclonal antibodies
The development of targeted therapies which have
the potential to dramatically decrease toxicity while
increasing efficacy has been a driving force behind
the design of monoclonal antibodies which can tar-
get leukaemia surface antigens. Although some of
the earlier monoclonal antibodies developed [e.g.
alemtuzumab (anti-CD52), rituximab (anti-CD20)]
have shown both tolerability and efficacy in ALL treatment,27–30 some of the more recently designed
therapies have shown considerable promise.

Epratuzumab is one such therapy that recently
has gained much excitement for the treatment of
B-precursor ALL. Epratuzumab is a humanized
monoclonal anti-CD22 antibody targeting the B-cell
restricted, developmentally regulated receptor CD22
that appears to modulate both B-cell activation and sig-
nalizing, with in vitro studies reporting several mecha-
nisms of action including antibody-dependent cellular
cytotoxicity, CD22 phosphorylation, and prolifera-
tion inhibition with cross linking.31 The Children’s
Oncology Group (COG) recently completed a phase
I/II study investigating epratuzumab in paediatric B-
precursor ALL with encouraging results.32 In this
report Raetz et al described 12 patients on the
phase 1 portion of the study with a median age of 10
(range 3–18) years that completed both the upfront
epratuzumab window phase and first re-induction
chemotherapy block with epratuzumab and were
evaluable for toxicities. There were 3 additional
patients not fully assessable for toxicity, 2 of which
did not complete the block 1 therapy because of infec-
tion not attributed to epratuzumab and 1 patient who
was removed by the treating physician during the
window phase prior to the block 1 therapy. Overall,
epratuzumab was very well tolerated with the most
common toxicities identified as grade 1–2 infusion
reactions. Two dose limiting toxicities were reported;
a grade 4 seizure occurring at the end of the first re-
induction block and one grade 3 ALT elevation. The
response attributed to epratuzumab alone as assessed
after the window phase of the trial reported 11
patients with stable disease, 1 with partial response
and 3 with progressive disease. The median blast
count at study entry was 384/µl (range 0–9,400/µl)
compared to 17/µl (range, 0–55,088/µl) after the 2
week window period. For the 12 patients who com-
pleted both the upfront arm and the block 1 therapy,
nine patients (60%) achieved a complete remission
with seven (47%) having no evidence of MRD at the
end of the first re-induction block. A larger phase II
trial for early marrow relapse B-precursor ALL is
currently ongoing through the COG.

The second generation of monoclonal antibodies,
coupled to toxins (immunotoxins), has been devel-
oped with the idea of enhancing cell kill compared
to the typical “naked” antibodies (e.g. rituximab
and epratuzumab). Combotox is an example of an
immunotoxin created by combining 2 monoclonal
mouse IgG1 antibodies [anti-CD19 (HD37-dgA)
and anti-CD22 (RFB4-dgA)] and linking a degly-
cosylated ricin-A chain (dgRTA). A phase I dose
escalation trial investigating combotox (3 doses
administered iv over 4 hours alternating days) in
paediatric relapsed/refractory B-precursor ALL was
reported by Herrera et al.33 There were 17 patients
enrolled (ages 1–16 years) with a median number of
2 prior relapses and 9 patients (53%) having received
a prior allogeneic haematopoietic cell transplantation
(allo-HCT). Overall the therapy was well tolerated
with 3/17 (18%) reporting grade 3–4 toxicities (grade
3 pancreatitis/abd pain; grade 3 anaphylaxis; grade 4
GVHD) and 3 patients achieving a CR.
Another novel immunotoxin that has begun clinical investigation is blinatumomab. Blinatumomab is a single-chain bispecific antibody with specificity for CD19 and CD3 that belongs to the class of bispecific T cell engagers or BiTE® antibodies which have the ability to activate host T-cells against the targeted leukemia cells, resulting in cell lysis. Topp et al recently reported results of a phase II trial for patients with minimal residual disease (MRD) positive ALL investigating blinatumomab as a single agent. Patients with B-precursor ALL who had completed induction/consolidation chemotherapy with the persistence of MRD disease were eligible. Blinatumomab was given as a continuous 4 week infusion with responses assessed after 1 cycle. Sixteen patients were evaluable with 13/16 (81%) achieving molecular remission and the remaining 3 having stable MRD by quantitative PCR. The most common toxicities reported were lymphopenia, leukopenia, fever and hypoimmunoglobulinemia. Overall this therapy was well tolerated and effective in patients with persistent MRD positive B-precursor ALL and warrants future investigation in combination with both upfront and salvage therapies.

Other immunotoxins that have been recently investigated include HA22/CAT-8015 (anti-CD22 linked to pseudomonas exotoxin-A), inotuzumab ozogamicin (CMC-544) (anti-CD22 linked to calicheamicin) and DT2219 (anti-CD19/anti-CD22 linked to diphtheria toxin) all of which have shown exciting preclinical efficacy in B-precursor ALL and currently are in phase I trials for relapsed/refractory leukaemia. If results for these novel immunotoxins are similar to what has been previously reported in prior monoclonal antibody trials with rituximab and epratuzumab, then moving these agents forward into combination therapies and eventually upfront for treatment of B-precursor ALL should be a pursued.

Epigenetic agents

Epigenetics can be described as the study of chromatin modifications that impact gene expression without altering the primary DNA sequence. Most often these chromatin changes initiate gene silencing, which can alter normal cellular pathways and lead to tumorgenesis. Two of the most prevalent epigenetic alterations identified in oncogenesis are aberrant DNA methylation and histone modification, both of which have been identified in ALL (Fig. 2). These changes are believed to be reversible and that certain epigenetic chemotherapy agents (demethylating agents and histone deacetylase (HDAC) inhibitors) can act by reversing the chromatin changes which in turn can revert the leukaemia cell back to physiologic gene expression. Recently both demethylating agents (e.g. decitabine) and HDAC inhibitors (e.g. vorinostat) have made their way into the treatment of ALL. Garcia-Manero et al reported the results of a Phase I study using 5-aza-2’-Deoxycytidine (decitabine) alone or in combination with Hyper-CVAD therapy in relapsed or refractory ALL, at the American Society of Haematology (ASH) meeting in 2007. There were no dose limiting toxicities reported and a complete marrow response was observed in 4/12 (30%) patients who received decitabine as a single agent and in 3/9 (30%) patients who received decitabine concurrently with Hyper-CVAD therapy.

Although HDAC inhibitors, as single agents, have not been reported for the treatment of patients with relapsed ALL, pre-clinical studies have provided background rationale for these agents to be integrated into early phase clinical trials for acute leukaemia. Yee et al recently reported early results of a phase I trial investigating two sequence-specific schedules of decitabine and vorinostat in patients with AML. Twenty-

Figure 2. DNA Methylation A) Methylation by DNA methyltransferases at CpG islands. B) DNA demethylation relaxes chromatin structure allowing histone acetylation and the binding of transcriptional complexes. C) Leukemia cells are characterised by hypermethylation of CpG islands and general DNA hypomethylation. (Figure reference: Taylor SM: p53 and deregulation of DNA methylation in cancer. Cellscience Reviews 2006; 2(3). www.cellscience.com/reviews7/Taylor1.jpg)
seven patients, median age of 67 (range, 32–82) years, received escalating doses of vorinostat (100 mg BID; 200 mg BID; 200 mg TID) either sequentially or concurrently with decitabine (20 mg/m²/d iv Days 1–5). There were no grade 3 or 4 toxicities reported. The most common toxicities being nausea (71%), fatigue (54%), diarrhea (54%), vomiting (42%), anorexia (25%), constipation (13%), abdominal pain (13%), dehydration (13%), and headache (13%). Of the 25 evaluable patients, one patient achieved an incomplete CR (without neutrophil recovery), one a morphologic remission (without blood count recovery), and three partial remissions. A second Phase I study by Ravandi et al investigated sequential therapy of decitabine (10, 15, 20 and 25 mg/m² iv daily × 5) followed by vorinostat (100 mg PO tid × 14 days in the first cohort and 200 mg PO tid × 14 days in all subsequent cohorts) in 31 refractory/relapsed leukaemia patients (3 ALL) with a median age of 62 (range, 22–82) years.46 Thirty patients were evaluable for toxicity. The toxicities reported included syncope, neutropenic fever, diarrhea, fatigue, renal failure, rash, nausea, thrombosis, and angioedema. Of the 30 evaluable pts, 1 patient achieved a CR lasting 5.5 weeks, 4 had significant reductions in the percentage of bone marrow blasts present, 4 had stable disease, 7 were too early for response evaluation, and 14 had no response/disease progression.

Based on the data by Yee45 and Ravandi46 reporting the feasibility of decitabine and vorinostat in combination for heavily pre-treated patients with relapsed leukaemia, we recently opened a phase II trial at the University of Minnesota investigating decitabine and vorinostat in combination with vincristine, prednisone, PEG-asparaginase and doxorubicin (VPLD) for relapsed/refractory ALL or Lymphoblastic Lymphoma (LL) (NCT00882206). On this trial patients (ages 2–60 years) receive decitabine (15 mg/m² iv QD) and vorinostat (230 mg/m² PO divided BID) for 4 consecutive days followed by VPLD chemotherapy. As of April 2010, 6 patients have been enrolled (ages 3–27 years) with 3 patients completing protocol therapy. All 3 patients had an isolated bone marrow relapse of B-Precursor ALL and achieved a second CR upon study completion with an M1 bone marrow (<5% blasts) and no evidence of disease as measured by flow cytometry (MRD negative). The toxicities reported associated with the study agents have included grade I diarrhea and fatigue with one patient having grade 4 hypertriglyceridermia attributed to PEG-asparaginase. Although this trial is in its early period of enrolment, the results so far are encouraging.

**Proteasome, BCL-2 and kinase inhibitors**

The understanding that proteasome inhibition sensitizes malignant but not normal cells to apoptosis has led to the investigation of this class of agents in the treatment of cancer. Bortezomib, a proteasome inhibitor, is one such agent that has recently received much attention in the treatment of haematologic malignancies and particularly acute leukaemia.47,48 As a dipetidyl boronic acid, bortezomib selectively inhibits the ubiquitin-proteasome pathway which is required for the degradation of most intracellular regulatory proteins in eukaryotic cells.49 More specifically, bortezomib inhibits the 26S proteasome, an ATP dependent multi subunit protein which degrades proteins involved in apoptosis, transcription factor activation, cell cycle regulation, peptide processing and cell trafficking (Fig. 3).50,51 Bortezomib has been used as a single agent in phase I adult trials for leukaemia/lymphoma with encouraging results.48,52,53 With reports of some efficacy and overall tolerability in adults with haematologic malignancies, the Children’s Oncology Group completed a phase I trial of bortezomib in relapsed/refractory leukaemia.51 In this trial bortezomib was administered twice weekly intravenously (1.3 mg/
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m² or 1.7 mg/m²) for 2 consecutive weeks. Twelve patients, median age of 11 (range, 1–18) years, with relapsed acute leukaemia (9 ALL and 3 AML) were enrolled. Although rapid disease progression led to 7/12 patients not completing protocol therapy and therefore were not fully assessable, the dose of 1.3 mg/m² was identified as the phase II dose as 2 patients experienced a grade 3 or 4 DLT at 1.7 mg/m² (grade 3 confusion (n = 1) and grade 4 fever/neutropenia, hypotension/grade 3 creatinine, hypokalemia (n = 1)).

Although little single agent activity was demonstrated in the COG phase I trial, combination therapies using proteasome inhibition with cytotoxic therapy was gaining interest in adult leukaemia. In a dose escalation phase I study, Attar et al reported the results of bortezomib (days 1, 4, 8 and 11 at doses 0.7, 1.0, 1.3 or 1.5 mg/m²) given intravenously in combination with idarubicin (12 mg/m² days 1–3) and cytarabine (100 mg/m² days 1–7) in 31 patients (median age 62 years) with either relapsed (n = 9) or de novo AML (age ≥60 years; n = 22). All dose levels were achieved and tolerable with reported non-haematologic grade 3 or greater toxicities including hypoxia (38%), hyperbilirubinemia (13%), and elevated aspartate aminotransferase (19%). A CR was achieved in 19 (61%) patients with 3 achieving a CRp for an overall response (CR/CRp) of 71%. In terms of combination trials using bortezomib in ALL, a phase 1 trial for relapsed ALL in children was recently reported by the TACL Consortium. Ten patients were enrolled with 1st marrow relapse (n = 5) or greater (n = 5) and received bortezomib (1 mg/m² or 1.3 mg/m² iv days 4, 8, 11 and 14) in combination with chemotherapy (vincristine, doxorubicin, dexamethasone, pegylated asparaginase). There were no DLTs observed with 8/10 (80%) patients reporting a CR.

The class of BCL-2 inhibitors have recently gained interest for the treatment of haematologic malignancies based on their preclinical evidence to induce apoptosis in leukaemia and potential synergy with chemotherapy (Fig. 4). Obatoclax, a pan anti-apoptotic BCL-2 inhibitor, has been shown to have activity in ALL cell lines and primary leukaemia samples, particularly those harbouring mixed lineage leukaemia (MLL) rearrangements. Zhang et al reported greater sensitivity of obatoclax inducing cell death in primary MLL+ ALL samples compared to AML and has shown drug synergy with chemotherapy.

Obatoclax was recently reported in an adult phase I study for refractory leukaemia and myelodysplasia syndrome (MDS). Forty-four patients were enrolled (ALL n = 1) (median age of 63 (range, 26–82) years) receiving obatoclax as a 24 hour infusion with a dose range of 7–28 mg/m² every 1–2 weeks (306 total infusions). There were no DLTs reported with the most common grade 1 or 2 toxicity related to study drug being central nervous system [somnolence (43%), dizziness (38%), fatigue (36%), euphoric mood (34%), and gait disturbance (34%)] which typically occurred within 2 hours of beginning the infusion and stopped shortly after the infusion ended. There was a single CR reported in a patient with AML who harbored a chromosome (9;11q23 MLL+) translocation and 3 patients with MDS reporting haematologic improvement. Overall obatoclax was well tolerated and showed some, although limited, haematologic efficacy in leukaemia/MDS.

Based on the particular activity of obatoclax in MLL+ leukemias, the COG recently opened a phase I study which will include 2 leukaemia stratum (MLL+ and MLL– leukaemia) investigating the combination of obatoclax with vincristine and doxorubicin.

Figure 4. BCL-2 Family Inhibition. Small molecule BCL-2 family inhibitors regulate cytochrome c release from the mitochondria which binds to Apaf-1 and induces recruitment of Caspase 9/apoptosome. This in turn leads to activation of Caspase and ultimately cell death. (Figure reference: Ashkenazi A. Nat Rev Cancer. 2002 Jun;2(6):420–30)
Perhaps one of the most landmark agents to ever be introduced into the treatment of leukaemia has been the tyrosine kinase inhibitor, imatinib. Imatinib mesylate (formerly STI571 and Gleevec; Novartis Pharma, Basel, Switzerland) is an oral tyrosine kinase inhibitor of ABL, of the fusion gene BCR-ABL1, which results from the chromosomal translocation involving chromosomes 9q34 and 22q11 (t9, 22[q34;q11]). Imatinib, which works by binding adenosine triphosphate (ATP) and catalyzing the transfer of a phosphate group to the hydroxy group of a tyrosine residue on a protein participating in a signal transduction cascade, received FDA approval in 2002 as first-line treatment in patients with chronic myelogenous leukaemia (CML) (Fig. 5). Shortly after its introduction into the treatment of CML, imatinib was investigated in relapsed/refractory Ph+ ALL with some encouraging single agent activity. Ottmann et al reported their phase II results of imatinib (dose 400 mg or 600 mg once daily) in 56 relapsed/refractory Ph+ leukaemia patients, 48 patients (median age 50 years) with Ph+ ALL. The most common non-haematologic toxicities included nausea (77%), vomiting (63%), edema (55%) and abdominal pain (25%) with very few reported as grade 3 or 4. Grade 4 haematologic toxicities included thrombocytopenia and neutropenia seen in 27% and 54% of patients respectively. A complete haematologic response was seen in 9 (19%) patients, complete marrow response in 5 (10%), and a partial marrow response in 15 (31%), with the median overall survival of 4.9 months.

Following this early single agent data on imatinib, combination studies of chemotherapy and imatinib began and showed dramatic improvement in induction remission (IR) rates in adult Ph+ ALL. With previously reported IR rates for adult Ph+ ALL ranging 50–80% prior to imatinib, Tovatari et al reported 96% IR once imatinib was combined with intensive chemotherapy. Imatinib has since become standard therapy in adult Ph+ ALL protocols and continues to show superiority when compared to earlier studies without the addition of this TKI therapy. Children with Ph+ ALL who once had reported outcomes <30% when treated with systemic chemotherapy alone and 40%–70% when allo-HCT was utilized, now have significantly increased survival reported with the introduction of imatinib. The Children’s Oncology Group recently reported excellent 3 year EFS rates (80% ± 11%) in 44 Ph+ ALL patients treated on the COG AALL0031 trial with intensive imatinib and combination chemotherapy (cohort 5), compared to historical controls (35% ± 4%; P < 0.0001). The addition of imatinib to pre or post allo-HCT therapy has presently not been shown to greatly improve outcomes in the allo-HCT setting compared to HCT alone for either adults or children with Ph+ ALL. Second generation TKIs (e.g. Dasatinib) are currently under investigation to see if improvements in survival to imatinib can be made for Ph+ ALL.

Summary
In summary, leukaemia recurrence continues to be the main barrier to a successful outcome for patients diagnosed with ALL and once relapse occurs; very few become long term survivors. Therefore new therapies to improve outcomes for the relapse patient as well as diminish relapse from occurring in the upfront setting are urgently needed. As more targeted therapies for the treatment of ALL are developed and incorporated into early phase clinical trials, with hopes of enhancing leukaemia cell kill while decreasing overall toxicity, we may begin to see a paradigm shift into how we approach and treat patients with ALL. For as crafty and resilient as the leukaemia blast is, our patients deserve equal innovation from the physicians and scientists that have devoted their lives to this terrible and hopefully one day completely curable disease, which is acute lymphoblastic leukaemia.
Disclosure
This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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