Review Article

Translational advances in the treatment of childhood acute lymphoblastic leukemia: narrative review of current and emerging molecular and immunotherapies

Faryal Munir, Jiasen He, Jeremy Connors, Miriam Garcia, Amber Gibson, David McCall, Cesar Nunez, Christine Nguyen Dinh, Lindsay Robusto, Michael Roth, Sajad Khazal, Priti Tewari, Branko Cuglievan

Department of Pediatrics, Pediatric Hematology Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Contributions: (I) Conception and design: B Cuglievan, F Munir, J He; (II) Administrative support: F Munir; (III) Provision of study materials or patients: B Cuglievan, F Munir, J He, J Connors, M Garcia, A Gibson, D McCall, C Nunez, CN Dinh, L Robusto, S Khazal, P Tewari; (IV) Collection and assembly of data: F Munir, J He, J Connors; (V) Data analysis and interpretation: B Cuglievan, M Roth, C Nunez; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Branko Cuglievan, MD. Department of Pediatrics, Unit 87, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA. Email: BCuglievan@mdanderson.org.

Background and Objective: Acute lymphoblastic leukemia (ALL) is the most common hematologic malignancy of lymphoid origin in children. The prognosis for newly diagnosed ALL in the pediatric population is generally favorable, with a 5-year overall survival rate of more than 90%. Though conventional therapy has led to meaningful improvements in cure rates for new-onset pediatric ALL, one-third of patients still experience a relapse or refractory disease, contributing to a significant cause of pediatric cancer-related mortality.

Methods: An extensive literature review was undertaken via various databases of medical literature, focusing on both results of larger clinical trials, but also with evaluation of recent abstract publications at large hematologic conferences.

Key Content and Findings: Remission is achievable in most of these patients by re-induction with currently available therapies, but the long-term overall survival rate is deemed suboptimal and remains a therapeutic challenge. As part of never-ceasing efforts to improve pediatric ALL outcomes, newer modalities, including targeted molecular therapies as well as immunotherapy, and chimeric antigen receptor (CAR) T-cell therapy, are currently being employed to increase treatment effectiveness as well as lessen the side effects from conventional chemotherapy. These approaches explore the use of early genome-based disease characterization and medications developed against actionable molecular targets.

Conclusions: Additional clinical research is nonetheless required to learn more about the potentially harmful effects of targeted therapies and investigate the possibility of these agents replacing or decreasing the use of conventional chemotherapy in treating pediatric ALL.

Keywords: Menin; menin inhibitors; children; pediatric; acute lymphoblastic leukemia (ALL)

Submitted Dec 07, 2022. Accepted for publication Feb 08, 2023. Published online Feb 24, 2023.
doi: 10.21037/tp-22-656
View this article at: https://dx.doi.org/10.21037/tp-22-656

Introduction

Background

Acute lymphoblastic leukemia (ALL) is a hematopoietic malignancy originating from B- and T-lineage lymphoid precursors. Many mechanisms, including genetic mutations, cell cycle regulation abruptions, chromosome translocations, and aneuploidy, are involved in the development of ALL (1,2).

Every year, approximately 6,000 new ALL cases are diagnosed in the United States (1,3-5). Although ALL is seen less frequently in adults, the disease does show a bimodal pattern, with the first and highest peak occurring in children younger than 5 years and a second, lower peak towards the latter part of the fifth decade of life (6). Pediatric ALL is more common in boys, with a male-to-female ratio of approximately 1.3:1. The disease is more frequently found in children of Hispanic descent, followed by White, and a lesser percentage of African Americans are affected (7). B-cell ALL (B-ALL) comprises approximately 85% of the total cases; however, this percentage can differ among various age groups, races, and ethnicities (8). New-onset pediatric ALL has an overall good prognosis, with a 5-year overall survival rate exceeding 75–90%. With increasing age, survival and disease biology worsen. Adolescents and young adults (AYA) population has poorer outcomes than younger children, and the prognosis in older adults is much worse, with an overall survival rate of 30–55%, which decreases further with age (9).

Rationale and knowledge gap

Although high cure rates for newly diagnosed pediatric ALL have been achieved with conventional therapies, 20–30% of these children either have a relapse or show refractory disease (10-12). Relapsed ALL, as a separate diagnosis, is the most common cause of mortality related to pediatric malignancies and is counted as the fifth most common pediatric cancer diagnosis (13). Re-induction with currently available therapies in relapsed patients leads to remission in 79–90% of cases, but is associated with higher acute toxicity, and the long-term overall survival rate is only 40–50% (14,15). Furthermore, primary refractory disease, relapsed and refractory disease (r/r), and relapse after hematopoietic stem cell transplantation (HSCT) are associated with worse outcomes and pose extreme therapeutic challenges, illustrating an unmet need for the development of durable therapies (15).

Innovative therapies such as monoclonal antibodies and chimeric antigen receptor (CAR) T-cell therapy are seen as new landmark therapeutic approaches to the management of r/r pediatric B-ALL (16). In addition, immunotherapy and molecularly targeted drugs are being used to treat ALL to improve overall treatment outcomes, reduce the doses and toxicity of conventional chemotherapy, and enhance the effectiveness of treatment. These approaches emphasize focusing on the upfront genome-based characterization of disease and incorporation of drugs against identified actionable targets. However, more clinical research is needed to explore the potentially toxic effects of targeted cell therapies (17).

Objective

This review will focus on emerging therapeutic advances changing how ALL is treated. *Table 1* summarizes the current and emerging molecular and immunological pharmacotherapies for pediatric ALL and the open clinical trials investigating these agents, which we review in this article. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-656/rc).

Methods

We searched PubMed, google scholar, and clinicaltrials.gov for reviews, research articles, published articles for study results of completed COG trials as well as ongoing clinical trials. Older references were also looked up when appropriate. We utilized the search terms “acute lymphoblastic leukemia”, “pediatric”, “children”, “B-ALL”, “T-ALL”, “menin”, “menin inhibitors”, “tyrosine kinase inhibitors”, “venetolclax”, “CD19”, “CD22”, “chimeric antigen receptor”, and “CART”. We also searched abstracts from relevant conferences including “American Society of Hematology” and cross-referenced the references from articles and abstracts which were reviewed. *Table 2* summarizes the search strategy utilized in writing this manuscript.

Molecularly targeted therapy in pediatric ALL

Tyrosine kinase inhibitors

BCR-ABL fusion oncoprotein results from the reciprocal translocation between chromosomes 9 and 22 leading to Philadelphia chromosome abnormality (Ph+). BCR-ABL

Table 1 Current and emerging therapeutic targets for pediatric acute lymphoblastic leukemia treatment

Drug class	Drug	Current lymphoblastic leukemia uses in pediatrics*	Recruiting pediatric acute lymphoblastic leukemia trials
Tyrosine kinase inhibitors	Imatinib	Ph+ ALL, Ph-like ALL** (ABL-class fusions)	NCT03007147
	Dasatinib		NCT05192889, NCT04996160, NCT03117751
	Nilotinib		No trials open in pediatrics
	Ponatinib		NCT04501614
Janus kinase inhibitor	Ruxolitinib	Ph-like ALL** (JAK2 point mutations or CRLF2 rearrangement)	NCT02723994, NCT04996160, NCT03117751
Menin inhibitor	SNDX-5613	KMT2A-rearranged leukemia	NCT04065399, NCT05326516
BCL-2 inhibitor	Venetoclax	ALL	NCT05192889, NCT05292664, NCT04029688, NCT00501826
BCL-2 and BCL-X_L inhibitor	Navitoclax		NCT05192889
Mdm2 inhibitor	Idasanutlin	ALL	NCT04029688
Proteasome inhibitor	Bortezomib	ALL	NCT04996160, NCT03136146, NCT03117751
	Carfilzomib		NCT02303821, NCT02512926
	Ixazomib		NCT03817320
CD19 targeted	Blinatumomab	$CD19^+$ leukemia	NCT03643276, NCT04556084, NCT04746209, NCT05192889, NCT02877303, NCT02790515, NCT03849651, NCT03914625, NCT04546399, NCT02879695, NCT03117751
	CAR T cell therapy		NCT03573700, NCT04881240, NCT04544592, NCT05480449, NCT03016377, NCT01853631, NCT04049383, NCT03448393, CT03792633, NCT03774654, NCT03117751, NCT03642626, NCT02050347
CD22 targeted	Inotuzumab ozogamicin	$CD22^+$ leukemia	NCT03913559, NCT02877303, NCT03962465, NCT03959085, NCT02981628, NCT03104491
	CAR therapy		NCT04571138, NCT02650414, NCT04150497, NCT02315612
CD19 and CD22 targeted	CAR therapy	$CD19^+$ and $CD2^+$ leukemia	NCT03241940, NCT03448393, NCT03330691
CD38 targeted	Daratumumab	ALL	No trials open in pediatrics
	Isatuximab	ALL	NCT03860844
PD-1/PD-L1 inhibitors	Nivolumab	ALL	NCT04546399, NCT02879695
DNA methyltransferase inhibitors	Decitabine	ALL	NCT03132454
	Azacitidine	ALL	NCT05292664, NCT05476770
Purine nucleoside analog	Nelarabine	ALL	NCT00501826, NCT03328104, NCT03117751

*, of note, many of these uses are not FDA approved indications and therefore used off-label; **, Ph-like ALL indicates targetable ABL-class fusions. Ph+ ALL, Philadelphia chromosome positive acute lymphoblastic leukemia; Ph-like ALL, Philadelphia chromosome-like acute lymphoblastic leukemia; ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor.

Table 2 The search strategy summary

Items	Specification
Date of search	2022/9/29 to 2023/1/21
Databases and other sources searched	PubMed, clinicaltrials.gov, American Society of Hematology conference presentations, google scholar
Search terms used	Pediatric ALL, TKIs, menin, venetoclax, immunotherapy, CART, inotuzumab, bortezomib, nelarabine, ruxolitinib, imatinib
Timeframe	2022/9/29 to 2023/1/21
Inclusion and exclusion criteria	Only English language studies were used
Selection process	Studies were selected independently, and consensus was obtained by multiple revisions among the authors

ALL, acute lymphoblastic leukemia; TKIs, tyrosine kinase inhibitors; CART, chimeric antigen receptor T-cell.

fusion protein has intrinsic tyrosine kinase activity (12,18,19) and causes reduced apoptosis leading to dysregulated cell proliferation in lymphohematopoietic cells (20), and hence serves as an excellent molecular therapeutic target. Tyrosine kinase inhibitors (TKIs) such as ABL1 inhibitors have shown great efficacy in treatment of patients with Ph+ as well as Ph-like ALL and a small subset of T-ALL with ABL1-class fusions (8,21-24).

Imatinib, the first-generation TKI, was initially used as a single agent to treat Ph+ chronic myeloid leukemia (CML) (25), later being utilized in the treatment of r/r Ph+ ALL, achieved a complete remission rate of 20–60% (26). However, remission was brief and followed shortly by progressive disease, indicating the emergence of resistant clones (26). Later, TKIs were moved up to frontline therapy for Ph+ ALL, combined with conventional chemotherapy or HSCT; studies showed that this approach had excellent results, with persistent complete remission (27). Imatinib, in combination with chemotherapy, increased the 3-year event-free survival (EFS) rate to 80% in pediatric Ph+ ALL, compared with 35% with chemotherapy alone (28). The Children's Oncology Group (COG) study AALL0031 reported a 5-year disease-free survival rate of 70% with the use of post-induction imatinib combined with intense chemotherapy and showed no additional advantage over patients who received allogeneic HSCT (59–65%), in children and adolescents with Ph+ ALL (29).

Dasatinib is a second-generation TKI with activity against BCR-ABL and has a much higher potency than imatinib (27,30). Complete remissions have been reported in children with refractory Ph+ B-ALL upon treatment with dasatinib in combination with chemotherapy (31,32). Shen *et al.* reported that dasatinib at a dose of 80 mg/m^2/day is more effective than imatinib mesylate (at the conventional dose of 300 mg/m^2/day) in the treatment of childhood Ph+ ALL, with significantly higher 4-year EFS (71.0% *vs.* 48.9%) and overall survival (88.4% *vs.* 69.2%) in addition to lower relapse rates (19.8% *vs.* 34.4%) in the group treated with dasatinib as compared to imatinib. Furthermore, no significant difference was found in severe toxic effects between the 2 groups (33). Interestingly, when COG AALL0622, investigating the use of dasatinib in conjunction of intensive chemotherapy in pediatric and adolescent Ph+ ALL, was compared to AALL0031, investigating the use of imatinib, the results showed no significant difference. Further studies need to be completed to analyze which subset of patients would benefit from these agents, and in the future, a randomized study could be considered (34). In addition, dasatinib has demonstrated activity against imatinib-resistant clones leading to prolonged remissions (35,36). Dasatinib seemed more appealing for the treatment of Ph+ ALL because of its better blood-brain barrier penetration than imatinib and nilotinib, both of which drugs failed to achieve therapeutic levels in the brain (37-39). A group at The University of Texas MD Anderson Cancer Center evaluated the addition of dasatinib to short-term intensified chemotherapy, hyper-CVAD (hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone), in adult patients (18 years and older) with Ph+ ALL (NCT00390793) (22,40); the overall response rate was 91%, with 84% of patients showing complete cytogenetic remission after cycle 1 (38). A COG phase III trial, AALL1131 (NCT02883049), was recently completed to assess the efficacy of dasatinib in young patients newly diagnosed with high-risk ALL with Philadelphia chromosome-like (Ph-like) mutations; the

results of this trial have not been published yet (2). Despite success when combining TKIs with chemotherapy, resistant strains continue to emerge; patients who relapsed after dasatinib use, have demonstrated resistant T315I mutations reported in some adult ALL studies (41-44). Previous trials of TKI-based therapy in pediatric Ph+ ALL have utilized either continuous dosing of imatinib (AALL0031, amended EsPhALL) or dasatinib (AALL0622, AALL1122). Since the overall EFS rates appear similar amongst these trials (29,34), and because it is more readily available in all participating countries, imatinib was chosen as the TKI to be combined with chemotherapy on the COG trial AALL1631.

Ponatinib, a newer third-generation TKI, was found to be active against T315I-mutant relapses and led to improved 3-year EFS rates in adult Ph+ ALL (45,46); hence, was approved by the US Food and Drug Administration (FDA) in 2014 for treatment of adults with r/r Ph+ ALL (17,47). Major complications observed with the use of ponatinib included increased thrombosis risk and pancreatitis, which make the use of ponatinib difficult with chemotherapy regimens that have similar adverse effects, such as PEG-asparaginase and corticosteroids (48). There is currently limited data on ponatinib use in children. Rossoff *et al.* first reported that ponatinib is well tolerated with a favorable safety profile in pediatric patients with Ph+/Ph+ like ALL (n=12) and CML (n=9) treated with varying doses of ponatinib at 13 centers; grade 3 toxicities were observed in 29% of patients (49). At a median time-interval of 3 months, 71% of patients showed a decrease in disease burden (49). Millot *et al.* retrospectively analyzed 3 pediatric ALL Ph+ and 11 CML patients treated with ponatinib as second- to eighth-line treatment in combination with standard chemotherapy. They concluded that ponatinib may be a suitable option for treatment for children with Ph+ leukemias who have failed several lines of therapy (50). Similar results were recently shared by Japanese group who concluded that ponatinib may be safe and effective in pediatric patients with Ph+ leukemia (51). This group also retrospectively reviewed nine pediatric patients with Ph+ ALL and four with CML who received ponatinib therapy. The median dose of ponatinib used was 16.9 mg/m^2. 6/9 (67%) patients with Ph+ ALL and 2/4 (50%) CML responded to ponatinib. Grade 4 toxicity was observed in only one patient (12%) with increased lipase levels. Grade 3 non-hematologic toxicities included hypertension (12.5%), polymorphic erythema (12.5%), and elevated levels of alanine aminotransferase levels (25%), aspartate aminotransferase levels (25%), and gamma-glutamyl transferase (12.5%) (51). An ongoing multicenter study (NCT04501614), which is currently in phase II, is investigating efficacy of ponatinib with chemotherapy in children with Ph+ ALL.

The introduction of TKIs has been revolutionary in treating Ph+ B-ALL (2). However, more studies are required to identify additional/adjuvant molecular targets to enhance the efficacy of TKIs in combination therapies and determine if there is a subset of patients that would benefit from the continuation of TKI.

B cell leukemia/lymphoma-2 (BCL-2) and BCL-X_L inhibitors

The BCL-2 proteins, located in mitochondrial membrane, play pivotal roles in regulating cell death pathways and have anti-apoptotic properties (2,52). Overexpression of BCL-2 in leukemia cells helps them to escape apoptosis and have enhanced BCL-2-dependent survival; which makes it an intriguing molecular target in cancer therapy (52,53). High levels of BCL-2 is observed in many hematological malignancies and is linked to disease progression and chemotherapy resistance (54). Venetoclax is a potent oral agent that selectively inhibits the anti-apoptotic BCL-2 protein, restoring the malignant cells' capacity to undergo apoptosis (55). Venetoclax is approved by the FDA for treating chronic lymphocytic leukemia and, more recently, for adult acute myeloid leukemia (AML) in combination with azacytidine, decitabine, or cytarabine in patients not able to tolerate intensified chemotherapy (56). Since then, its use has been expanded in children with different hematological malignancies including AML and B and T cell ALL (57-59). Venetoclax has also been combined with other apoptotic pathway antagonists with favorable results (60).

A phase I study (NCT03181126) evaluated venetoclax and navitoclax, a BCL-2 and BCL-XL inhibitor. The study showed that both drugs were safe and efficacious in pediatric and adult patients with r/r ALL or lymphoblastic lymphoma, as evidenced by an overall response rate of 66.7%, complete remission rate of 56.5%, and median overall survival duration of 6.6 months. The recommended doses were 25 mg of navitoclax for patients weighing <45 kg and 50 mg for patients weighing ≥45 kg, in combination with an adult-equivalent dose of 400 mg of venetoclax in combination with chemotherapy (2).

Given the encouraging results in adult populations, venetoclax holds the potential for promising results in pediatric patients as well. A phase I/II multicenter study

(NCT04029688) is assessing the murine double minute 2 homolog (MDM2) inhibitor idasanutlin combined with chemotherapy or venetoclax in pediatric and young adult patients with r/r acute leukemias or solid tumors (61,62). Similarly, an additional phase I study is evaluating venetoclax in combination with CPX-351 in children, adolescents, and young adults with acute r/r leukemias (63).

Janus-associated kinase signal transducer and activator of transcription (JAK-STAT) inhibitors

Ruxolitinib is a JAK inhibitor that works by competitively inhibiting the ATP-binding site on JAK1 and JAK2 protein kinases. Interruption of signaling leads to inhibition of cellular proliferation through modulation of the JAK-STAT signaling pathway. Disruption of aberrant signaling of this kinase pathway has been exploited in the treatment of Ph-like ALL using TKIs, suggesting the potential for targeting the JAK-STAT pathway (64). CRLF2 rearrangements with concomitant JAK2 point mutations, found in 50% of Ph-like ALL cases, are associated with abnormal activation of the JAK-STAT signaling pathway. Clinical trials are investigating the use of ruxolitinib in combination with conventional chemotherapy in patients newly diagnosed with Ph-like ALL and as single-agent or combination therapy in patients with r/r Ph-like ALL (64,65). In a phase I study of JAK inhibition in children with r/r tumors, including leukemias, no major dose-limiting toxicities of ruxolitinib were found with a recommended continuous dose of 50 mg/m^2 twice daily (66). A recently completed phase II study of children and adolescents newly diagnosed with high-risk CRLF rearrangement/JAK pathway mutant Ph-like ALL has thus far shown the safety and tolerability of the combination of ruxolitinib with standard intensive multi-agent chemotherapy (AALL1521; NCT02723994) (65). Although it is currently an FDA-approved oral medication for the treatment of myelofibrosis, polycythemia vera, and acute graft-versus-host disease (67), ruxolitinib holds promise in the treatment of pediatric Ph-like ALL and should be further investigated in pediatric leukemias with alterations in JAK protein kinases, not only in combination with chemotherapy but also in combination with TKIs (68).

Proteasome inhibitors

Bortezomib is a 26S proteasome inhibitor that induces apoptosis in malignant cells but has limited cytotoxicity for nonmalignant cells (69), which makes it an attractive therapeutic agent. Bortezomib has reported synergetic effects on leukemia cell lines when combined with other chemotherapies such as doxorubicin, as well as when combined with corticosteroids (69,70).

A pilot study conducted by Messinger *et al.* (71) and Bertaina *et al.* (72) suggested that bortezomib could improve overall survival in patients with relapsed precursor B-ALL. COG later conducted a phase II clinical trial (AALL07P1) to determine if adding bortezomib to conventional chemotherapy was beneficial in relapsed ALL, and the data favored bortezomib efficacy in certain groups, such as those with T-cell ALL (73). Based on these promising results, the COG phase III trial AALL1231 was initiated to test bortezomib in newly diagnosed T-cell ALL and lymphoma (74). Importantly, the rate of grade 3 or higher toxicities was similar between the control and treatment (bortezomib) group, including peripheral neuropathy and pulmonary toxicity (74). Disappointingly, the overall outcome in T-cell ALL was not significantly improved compared with control arm, especially in those with very high risk T-cell ALL (74). However, patients with T-cell lymphoblastic lymphoma had significantly improved EFS and overall survival with bortezomib, and it is still not clear why bortezomib is more impactful in T-cell lymphoblastic lymphoma than in T-cell ALL.

Other proteasome inhibitors are in the pipeline, including carfilzomib, for which a phase 1b trial in r/r ALL has been completed (75), and ixazomib. More data will be needed for us to better understand the role of proteasome inhibitors in the treatment of acute leukemia.

Nelarabine

The antimetabolite (purine nucleoside analog) nelarabine is a prodrug of 9-β-D-arabinofuranosylguanine (ara-G) (76). Nelarabine is rapidly converted in the plasma to ara-GTP, a nucleoside analog that incorporates into the DNA of leukemic blasts to terminate DNA synthesis and induce apoptosis (76-79). Ara-GTP was observed to have greater accumulation and cytotoxicity in T cells than in B cells (78), leading to the targeted use of nelarabine for the treatment of T-cell ALL (79-81).

Nelarabine has been effective for treating r/r T-cell ALL in both pediatric and adult patients since 2005 (82). Results from the phase III trial COG 0434 also support the use of nelarabine in patients with newly diagnosed disease (83). EFS in pediatric patients with T-cell ALL was around 80% in those receiving intensive chemotherapy and cranial

irradiation (83,84) and increased to over 90% with the addition of nelarabine, which also significantly lowered the incidence of central nervous system relapse (85). Nelarabine is associated with severe dose-dependent neurotoxicity (78,79); however, overall toxicities were acceptable and similar between all treatment arms (85). Because all patients in the COG 0434 trial treated with nelarabine also received cranial irradiation, further research is needed to determine if nelarabine protocols without radiation are an appropriate treatment modality. These encouraging data support continued use of nelarabine in future trials.

DNA methyltransferase inhibitors

Azacitidine (5-azacytidine) and decitabine (5-aza-2'-deoxycytidine) are hypomethylating agents (HMAs) that inhibit DNA methyltransferases (86). Malignant cells display aberrant methylation patterns that disrupt the DNA methylation process and silence tumor-suppressor genes. This process plays a critical role in gene regulation and is often involved in chemotherapy resistance (87).

Azacitidine is a ribonucleoside analog of cytidine that incorporates itself into both DNA and RNA, leading to inhibition of protein synthesis and hypomethylation, with subsequent reactivation of aberrantly silenced tumor-suppressor genes (86,88). Decitabine is a cytadine antimetabolite analog that is phosphorylated to the active metabolite decitabine triphosphate. This metabolite is incorporated into DNA, causing hypomethylation and cell death in the S phase of the cell cycle (89).

Azacitidine and decitabine are currently FDA-approved for the treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia. Recently, HMAs have shown impressive success in adult patients with AML and are being demonstrated as efficacious and safe in pediatric AML; they are also being currently explored in pediatric ALL in combination with chemotherapy (90-93). Particular interest has been sparked in the use of HMAs to treat infant ALL owing to preclinical data showing promoter hypermethylation in infant KMT2Ar ALL (94). A large clinical trial was conducted evaluating azacitidine in combination with various agents for infants with KMT2Ar ALL (NCT02828358); results were presented at the annual ASH meeting (December 2022) showing that remission was achieved in 65% of patients with a 3-year OS of 63.8% (95).

Two trials led by Burke *et al.* assessed the combination of decitabine and vorinostat (a histone deactylase inhibitor) with traditional chemotherapy backbones for the treatment of r/r pediatric ALL, and these trials showed varied tolerability results depending on the chemotherapy backbone chosen (87,96). However, both trials showed clinical activity, with a decrease in hypermethylation and a positive correlation between decreased methylation and bone marrow response (96). T-cell ALL has been an additional area of targeted investigation. In a prospective single-arm study, decitabine maintenance was used after allogeneic HSCT in patients with ALL, and decitabine was found to be tolerable and might be able to reduce relapses in patients with T-cell ALL (97). Current ongoing trials for use of HMAs in upfront and r/r T-cell ALL are underway (NCT03132454, NCT05376111). Although HMAs are currently FDA-approved only for myelodysplastic syndromes, the collective data to date suggest that HMAs can safely be combined with other agents and should continue to be explored in pediatric leukemia.

Menin inhibitors

Menin inhibitors target the protein menin, which is coded by the multiple endocrine neoplasia 1 (*MEN1*) gene, a member of the MLL1 and MLL2 complex and the key regulator for MLL-rearranged (MLL-r) and NPM1-mutant (NPM1c) leukemia (98,99). This gene expression program, normally expressed in stem cells, causes a hematopoietic differentiation block and leukemic transformation. Recently this therapeutic class of oral drugs has emerged as a new class of agents with great efficacy against certain types of leukemia with the related mutations.

An ongoing phase I/II study (AUGMENT-101, NCT04065399) is currently investigating the menin inhibitor SNDX-5613 in r/r leukemias, including those with an MLL/KMT2A gene rearrangement, NUP98r, or NPM1 mutation. Initial results were presented at the American Society of Hematology 2021 annual meeting and are very exciting (100); 20 out of the 45 patients were able to achieve composite complete remission, of which 14 were negative for minimal residual disease by flow cytometry or PCR (100). Grade 3 QT prolongation was the only dose-limiting toxicity, occurring in 8% of patients (3/38) at the study's pre-defined recommended phase II dose criteria (100). Differentiation syndrome occurred in 15% of patients (n=8) and reported to be grade 1 or 2 in severity. All cases were medically managed with corticosteroids and hydroxyurea (100).

Given these promising results, many other pediatric trials are underway to evaluate menin inhibitors including the Biomea Fusion trial (NCT05153330), Janssen (JNJ-

75276617), and Kura Oncology (KO-539), all with pediatric patient populations.

Immunotherapy in pediatric ALL

CD19 inhibitors

Blinatumomab is a biphasic fusion protein with two single-chain variable fragments arranged in a tandem fashion. One fragment targets CD3 antigens of T cells, and the other targets CD19 surface antigen on B-cell leukemia cells, allowing blinatumomab to strategically redirect T cells and induce a cytotoxic immune response (101,102).

Blinatumomab has specific immune-related adverse effects, including transient cytopenia, electrolyte abnormalities, cytokine release syndrome (CRS), immune-related neurotoxicity, and B-cell aplasia. The most significant adverse effects are CRS and neurotoxicity. CRS severity is related to disease burden and can be fatal if not identified in time and appropriate steps taken for management (103). Results of phase I/II trial of 26 international sites showed a maximum tolerated dose of 15 μg/m^2/day; later, the dose recommended for children was 5 μg/m^2/day for the first 7 days followed by 15 μg/m^2/day thereafter (103).

Multiple clinical trials have shown that blinatumomab is more effective than traditional intensive chemotherapy for the treatment of high-risk/intermediate-risk pediatric relapsed B-ALL (104,105), as well as in patients with lower disease burden (103). In children, adolescents, and young adults with low-risk first relapse of B-ALL, blinatumomab showed no significant difference in outcomes compared with standard intensive chemotherapy (106). However, blinatumomab has a better side effect profile and is much better tolerated, making it an attractive option for many patients.

With these promising results, great effort has been made to determine whether blinatumomab can be incorporated into upfront therapy for ALL. COG is now incorporating blinatumomab into upfront treatment for standard-risk B-ALL to determine if post-consolidation blinatumomab improves outcomes (AALL1731). In the relapse setting, the phase II trial AALL1821 attempted to explore the effectiveness of the combination of blinatumomab and immune checkpoint inhibitors. However, this trial was closed due to inferior outcomes in both study arms. Moreover, our group is employing condensed sequential immunotherapy/chemotherapy, including blinatumomab and inotuzumab with excellent results (107).

CD22 inhibitors

Inotuzumab ozogamicin (InO) is a humanized anti-CD22 monoclonal antibody conjugated to calicheamicin, which can cause double-strand DNA breaks (108). In adult patients, InO was superior to standard chemotherapy for r/r disease, leading to complete remission in 80.7% of cases compared with only 29.4% after standard chemotherapy (108). InO possesses a unique adverse effect profile; most grade 3 or higher non-hematologic adverse events are liver-related. Veno-occlusive liver disease was reported to be more common in patients with a history of treatment with InO who went on to receive HSCT (108-110). This toxicity can potentially be mitigated using weekly schedules of lower doses of InO in combination with low-intensity chemotherapy. InO can also be effectively combined with lower-intensity hyper-CVAD, which was shown to achieve an overall minimal residual disease negativity rate of 82% in adult patients (age 18 years and older) with r/r ALL in a study conducted at MD Anderson (111). Other strategies include adding ursodiol and avoiding dual alkylating agent-based conditioning regimens for HSCT, as well as abstaining from concomitant hepatotoxic drugs (112).

The use of InO has been explored in pediatric patients as well. The ITCC-059 phase I trial reported that 3 doses of weekly scheduled single-agent InO helped 85% of pediatric patients with r/r ALL reach complete remission with 100% minimal residual disease negativity (110). Based on this trial, the recommended dose for pediatric patients is 1.8 mg/m^2 per course (110). The COG trial AALL 1621 showed similar results, with a complete remission with an incomplete count recovery rate of 58% in children, adolescents, and young adults with r/r CD22-positive ALL (109). Based on these results, a phase III randomized trial of InO for newly diagnosed high-risk B-ALL (COG AALL1732) was initiated, and the first planned safety analysis showed that rates of hepatoxicity and sinusoidal obstruction syndrome did not differ significantly between InO and standard therapy; nonetheless, the InO arm did show a stronger degree of marrow suppression, and hence the dose of InO was decreased by 20% in this trial (113). The final results with survival data from AALL1732 are still pending and will shape the role of InO in the treatment of pediatric ALL. Other groups are trying to combine InO with chemotherapy and immunotherapy, and additional trials are ongoing (107).

Immune checkpoint inhibitors

Immune checkpoints are an intricate set of signals that play an important role in the immune based response to malignancy. Programmed death ligand 1 (PD-L1) and its receptor, programmed death protein 1 (PD-1), are two critical checkpoint proteins; binding of PD-L1 to PD-1 on T cells results in suppression of T-cell function and alleviated immune response to leukemic cells leading to ineffective killing/poor immune clearance, and therefore PD-1 and PD-L1 are thought to play a role in cancer immunotherapy (114). Nivolumab is a PD-1 checkpoint inhibitor that the FDA approved in 2014 for the treatment of unresectable or metastatic melanoma, but its role has expanded to several malignancies, including relapsed Hodgkin lymphoma, among others.

More recently, the interactions between checkpoint inhibitors and blinatumomab have been recognized. Primary samples from patients with relapsed B-ALL showed upregulation of PD-1 on T cells, and upregulation of PD-L1 was observed on leukemic cells from patients whose disease did not respond to blinatumomab. Co-culture of resistant samples with blinatumomab and anti-PD-1 antibody increased T-cell proliferation and cell lysis (115). In addition, one case report described a 32-year-old male patient with refractory $CD19^+$ ALL that failed to respond to blinatumomab and showed upregulation of PD-L1 on tumor cells, as well as increased PD-1 expression on the patient's lymphocytes. Combining the leukemia cells with blinatumomab and the patient's $CD3^+$ T cells *in vitro* resulted in lysis of only 8.5% of leukemia cells, compared with 93.6% lysis when the incubation was with blinatumomab and healthy donor T cells (116).

PD-L1 has been found to be increased in relapsed ALL and in ALL refractory to blinatumomab, and bone marrow from a 12-year-old girl with blinatumomab-refractory $CD19^+$ B-ALL was found to have nearly 100% PD-L1 expression after treatment with blinatumomab. She was then treated with blinatumomab and pembrolizumab, an anti-PD-1 antibody, and she tolerated this combination well and attained complete remission (115).

Blinatumomab combined with nivolumab with or without ipilimumab was studied in 8 adults in a phase I dose-escalation study in which 3 patients had previous treatment with blinatumomab and 4 had previously undergone allogeneic HSCT. The nivolumab and blinatumomab combination was well tolerated, with a severe infusion reaction to nivolumab as the only dose-limiting toxicity. Two patients were removed prior to administration of nivolumab (for hyperbilirubinemia and pericardial effusion), and from the 6 evaluable patients who received both blinatumomab and nivolumab, 5 achieved complete remission with no minimal residual disease by the end of cycle 2 (117).

CRS continues to be a concern for immunotherapies but appears to be related to tumor burden (118) and has been observed less frequently with blinatumomab than with other immunotherapies (103). Toxicities associated with checkpoint inhibitors may include fatigue, nausea, and emesis, and more serious but less frequently observed immune-related toxicities include hypophysitis, thyroiditis, hepatitis, colitis, and pneumonitis (117,119).

COG is currently conducting the ADVL1421 trial, which is a phase I/II study of nivolumab as a single agent and in combination with ipilimumab in children, adolescents, and young adults with r/r solid tumors (NCT01896999). COG is also conducting a phase II trial of the combination of blinatumomab with or without nivolumab for the treatment of the first relapse of B-ALL in patients with Down syndrome (NCT04546399). Several other studies of nivolumab in hematologic malignancies are ongoing, including nivolumab after CAR T-cell therapy after loosing of B-cell aplasia (NCT05310591), nivolumab for Hodgkin lymphoma (NCT03337919), combination therapy including nivolumab and brentuximab for Hodgkin lymphoma (NCT02927769), and nivolumab and azacytidine for AML (NCT03825367).

CAR T-cell therapy

CAR T cells are engineered T cells that can express the variable regions (Fv) against B-lineage markers and achieve antitumor effects (118). Autologous CAR T-cell therapy targeting CD19 has achieved remarkable success in patients with r/r B-ALL. Multiple trials that included pediatric, adolescent, and young adult patients have reported complete remission rates of 62–93% (120-123); most of these patients showed a response at around 1 month of therapy and were able to achieve minimal residual disease negativity. Like blinatumomab, the main adverse events reported were CRS and neurologic toxicity, but the degree of severity was higher in patients receiving CAR T-cell therapy, with grade 3 and 4 adverse events in up to 70% of patients (121). CRS was reported in up to 70% of patients receiving CAR T-cell therapy, and neurologic events occurred in 40% of patients (121).

Although some patients can probably be cured with CAR T-cell therapy alone, the question remains whether it can be curative for a high enough proportion of patients to be considered for use as monotherapy. More evidence recently indicated that adding HSCT after CAR T-cell therapy was associated with long-term disease-free survival and a low risk of post-HSCT relapse (122). Shah *et al.* reported that patients who achieved complete remission and proceeded to allogeneic HSCT had a relapse rate of <10% at 24 months after CAR T-cell therapy, whereas all patients who did not undergo HSCT experienced relapse (122).

The main challenges for CAR T-cell therapy include T-cell durable persistence and antigen escape. CAR T-cell targeting of CD19 in the peripheral blood can persist for as long as 20 months, but patients who receive CAR T-cell therapy often experience relapse, and the efficacy of the therapy is impacted by prior blinatumomab therapy (121,122,124,125). Other potential target antigens are under investigation. CAR T-cell therapy targeting the CD22 B-lineage marker was investigated in a trial including pediatric, adolescent, and young adult patients in whom CD19-targeted immunotherapies failed; a complete remission rate of 70% was observed, but durable complete remission was observed only in patients who then underwent HSCT (126). Dual-targeted approaches are currently under investigation, including bi-specific, bicistronic CAR T-cell therapy and co-transduction or co-infusion of CAR T cells, and these approaches may provide solutions for antigen escape in CAR T-cell therapy and further enhance the durability of responses (127-129). In the AMELIA trial, autologous transduced T cells expressing anti-CD19 and anti-CD22 CARs (AUTO3) were investigated in children, adolescents, and young adults with r/r B-ALL; a good safety profile was reported, and a complete remission rate of 86% was observed at 1 month (129). But the long-term persistence of dual CAR T-cell therapeutic responses is still limited, and relapse is still the big concern in these trials and remains one of the biggest challenges in CAR T-cell therapy, demanding more research.

Conclusions

Acute leukemia, specifically ALL, continues to make up the largest proportion of pediatric malignancies, and although arguably the largest strides in outcome improvements have been made in ALL, there are clearly pockets of high-risk disease that are resistant to previous innovations in therapy. This high-risk disease has heterogenous strategies for treatment evasion, and thus the field has continued to balloon with both targeted agents and novel therapeutic approaches to synergize with existing therapy or as a mechanism of salvage when traditional therapy fails. From the discovery of vulnerable fusions in the Philadelphia chromosome to the more recent menin inhibitors, expansion of our anti-metabolite repertoire, novel targeting of cancer cell biology in proteasome and JAK-STAT pathway inhibition, and ultimately identification of molecular targets that focus on disease-direct delivery of chemotherapy, immunomodulation, and immune effector activation, the arsenal of available therapies continues to grow in both scope and quantity. As the field's ability to evaluate bad actors earlier in the disease course expands, the rapid identification of known targetable lesions will lead to swifter introduction of novel agents into the leukemia therapeutic backbone, and thus to further gains in outcomes improvement. However, exposure to more cytotoxic agents or longer treatment times does not always lead to improved outcomes. More work is ever needed to identify the most efficient and efficacious delivery of this ever-growing list of treatments. As such, we need to continually adapt to better and more rapidly incorporate these modern agents into existing chemotherapeutic trials, perhaps ultimately yielding targeted regimens with reduced overall chemotherapy exposure, or even removing traditional chemotherapy altogether.

Acknowledgments

We thank Sarah Bronson and Erica Goodoff, Scientific Editors in the Research Medical Library at The University of Texas MD Anderson Cancer Center, for editing this article.

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Antonio F. Corno) for the series "The Impact of the Progresses of Knowledge and Technologies in Pediatrics" published in *Translational Pediatrics.* The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-656/rc

Peer Review File: Available at https://tp.amegroups.com/

article/view/10.21037/tp-22-656/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at https://tp.amegroups.com/article/view/10.21037/tp-22-656/coif). The series "The Impact of the Progress of Knowledge and Technologies in Pediatrics" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med 2015;373:1541-52.
2. Mohseni M, Uludag H, Brandwein JM. Advances in biology of acute lymphoblastic leukemia (ALL) and therapeutic implications. Am J Blood Res 2018;8:29-56.
3. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet 2013;381:1943-55.
4. Pui CH, Nichols KE, Yang JJ. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. Nat Rev Clin Oncol 2019;16:227-40.
5. Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet 2020;395:1146-62.
6. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116:3724-34.
7. Lim JY, Bhatia S, Robison LL, et al. Genomics of racial and ethnic disparities in childhood acute lymphoblastic leukemia. Cancer 2014;120:955-62.
8. Inaba H, Pui CH. Advances in the Diagnosis and Treatment of Pediatric Acute Lymphoblastic Leukemia. J Clin Med 2021;10:1926.
9. Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. Cancer 2010;116:1165-76.
10. Gaynon PS, Qu RP, Chappell RJ, et al. Survival after relapse in childhood acute lymphoblastic leukemia: impact of site and time to first relapse--the Children's Cancer Group Experience. Cancer 1998;82:1387-95.
11. Gurney JG, Severson RK, Davis S, et al. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. Cancer 1995;75:2186-95.
12. Brown VI, Seif AE, Reid GS, et al. Novel molecular and cellular therapeutic targets in acute lymphoblastic leukemia and lymphoproliferative disease. Immunol Res 2008;42:84-105.
13. Chessells JM. Relapsed lymphoblastic leukaemia in children: a continuing challenge. Br J Haematol 1998;102:423-38.
14. Crooks GM, Sato JK. Ifosfamide and etoposide in recurrent childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 1995;17:34-8.
15. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol 2010;28:648-54.
16. Halim L, Maher J. CAR T-cell immunotherapy of B-cell malignancy: the story so far. Ther Adv Vaccines Immunother 2020;8:2515135520927164.
17. Lejman M, Kuśmierczuk K, Bednarz K, et al. Targeted Therapy in the Treatment of Pediatric Acute Lymphoblastic Leukemia-Therapy and Toxicity Mechanisms. Int J Mol Sci 2021;22:9827.
18. NOWELL PC. The minute chromosome (Phl) in chronic granulocytic leukemia. Blut 1962;8:65-6.
19. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-3.
20. Skorski T, Nieborowska-Skorska M, Wlodarski P, et al. The SH3 domain contributes to BCR/ABL-dependent leukemogenesis in vivo: role in adhesion, invasion, and homing. Blood 1998;91:406-18.
21. Slayton WB, Schultz KR, Silverman LB, et al. How we approach Philadelphia chromosome-positive acute lymphoblastic leukemia in children and young adults. Pediatr Blood Cancer 2020;67:e28543.
22. Tasian SK, Loh ML, Hunger SP. Philadelphia

chromosome-like acute lymphoblastic leukemia. Blood 2017;130:2064-72.
23. Tanasi I, Ba I, Sirvent N, et al. Efficacy of tyrosine kinase inhibitors in Ph-like acute lymphoblastic leukemia harboring ABL-class rearrangements. Blood 2019;134:1351-5.
24. Bhojwani D, Pui CH. Relapsed childhood acute lymphoblastic leukaemia. Lancet Oncol 2013;14:e205-17.
25. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
26. Wassmann B, Pfeifer H, Scheuring U, et al. Therapy with imatinib mesylate (Glivec) preceding allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL). Leukemia 2002;16:2358-65.
27. Piccaluga PP, Rondoni M, Paolini S, et al. Imatinib mesylate in the treatment of hematologic malignancies. Expert Opin Biol Ther 2007;7:1597-611.
28. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-81.
29. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014;28:1467-71.
30. Piccaluga PP, Paolini S, Martinelli G. Tyrosine kinase inhibitors for the treatment of Philadelphia chromosome-positive adult acute lymphoblastic leukemia. Cancer 2007;110:1178-86.
31. Lengline E, Beldjord K, Dombret H, et al. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with EBF1-PDGFRB fusion. Haematologica 2013;98:e146-8.
32. Crombet O, Lastrapes K, Zieske A, et al. Complete morphologic and molecular remission after introduction of dasatinib in the treatment of a pediatric patient with t-cell acute lymphoblastic leukemia and ABL1 amplification. Pediatr Blood Cancer 2012;59:333-4.
33. Shen S, Chen X, Cai J, et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA Oncol 2020;6:358-66.
34. Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib Plus Intensive Chemotherapy in Children, Adolescents, and Young Adults With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0622. J Clin Oncol 2018;36:2306-14.
35. Ottmann O, Dombret H, Martinelli G, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. Blood 2007;110:2309-15.
36. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood 2007;110:3540-6.
37. Takayama N, Sato N, O'Brien SG, et al. Imatinib mesylate has limited activity against the central nervous system involvement of Philadelphia chromosome-positive acute lymphoblastic leukaemia due to poor penetration into cerebrospinal fluid. Br J Haematol 2002;119:106-8.
38. Benjamini O, Dumlao TL, Kantarjian H, et al. Phase II trial of hyper CVAD and dasatinib in patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia. Am J Hematol 2014;89:282-7.
39. Porkka K, Koskenvesa P, Lundán T, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood 2008;112:1005-12.
40. Wells J, Jain N, Konopleva M. Philadelphia chromosome-like acute lymphoblastic leukemia: progress in a new cancer subtype. Clin Adv Hematol Oncol 2017;15:554-61.
41. Ravandi F, Jorgensen JL, Thomas DA, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood 2013;122:1214-21.
42. Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood 2015;126:746-56.
43. Saini L, Brandwein J. New Treatment Strategies for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Curr Hematol Malig Rep 2017;12:136-42.
44. Rousselot P, Coudé MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients

with Philadelphia chromosome-positive ALL. Blood 2016;128:774-82.
45. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol 2015;16:1547-55.
46. Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A propensity score analysis. Cancer 2016;122:3650-6.
47. Annesley CE, Brown P. Novel agents for the treatment of childhood acute leukemia. Ther Adv Hematol 2015;6:61-79.
48. Rausch CR, Jabbour EJ, Kantarjian HM, et al. Optimizing the use of the hyperCVAD regimen: Clinical vignettes and practical management. Cancer 2020;126:1152-60.
49. Rossoff J, Huynh V, Rau RE, et al. Experience with ponatinib in paediatric patients with leukaemia. Br J Haematol 2020;189:363-8.
50. Millot F, Suttorp M, Versluys AB, et al. Ponatinib in childhood Philadelphia chromosome-positive leukaemias: an international registry of childhood chronic myeloid leukaemia study. Eur J Cancer 2020;136:107-12.
51. Kodama Y, Sato A, Kato K, et al. Ponatinib in pediatric patients with Philadelphia chromosome-positive leukemia: a retrospective survey of the Japan Children's Cancer Group. Int J Hematol 2022;116:131-8.
52. Kapoor I, Bodo J, Hill BT, et al. Targeting BCL-2 in B-cell malignancies and overcoming therapeutic resistance. Cell Death Dis 2020;11:941.
53. Certo M, Del Gaizo Moore V, Nishino M, et al. Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members. Cancer Cell 2006;9:351-65.
54. Gibson A, Trabal A, McCall D, et al. Venetoclax for Children and Adolescents with Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma. Cancers (Basel) 2021;14:150.
55. Ngoi NYL, Choong C, Lee J, et al. Targeting Mitochondrial Apoptosis to Overcome Treatment Resistance in Cancer. Cancers (Basel) 2020;12:574.
56. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood 2018;131:1704-11.
57. Trabal A, Gibson A, McCall D, et al. Venetoclax for Acute Myeloid Leukemia in Pediatric Patients: A Texas Medical Center Collaboration. Blood 2021;138:1247-9.
58. Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical Experience With Venetoclax Combined With Chemotherapy for Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk 2020;20:212-8.
59. Venetoclax shows activity against T-ALL in children. Available online: https://www.mdedge.com/hematology-oncology/article/240841/all/venetoclax-shows-activity-against-t-all-children
60. Vogler M, Walter HS, Dyer MJS. Targeting anti-apoptotic BCL2 family proteins in haematological malignancies - from pathogenesis to treatment. Br J Haematol 2017;178:364-79.
61. Hohtari H, Kankainen M, Adnan-Awad S, et al. Targeting Apoptosis Pathways With BCL2 and MDM2 Inhibitors in Adult B-cell Acute Lymphoblastic Leukemia. Hemasphere 2022;6:e701.
62. Aumann S, Shaulov A, Haran A, et al. The Emerging Role of Venetoclax-Based Treatments in Acute Lymphoblastic Leukemia. Int J Mol Sci 2022;23:10957.
63. Agresta L, O'Brien MM, Mizuno K, et al. V2 Trial: A Phase I Study of Venetoclax Combined with CPX-351 for Children, Adolescents and Young Adults with Relapsed or Refractory Acute Leukemia. Blood 2019;134:3830.
64. Böhm JW, Sia KCS, Jones C, et al. Combination efficacy of ruxolitinib with standard-of-care drugs in CRLF2-rearranged Ph-like acute lymphoblastic leukemia. Leukemia 2021;35:3101-12.
65. Tasian SK, Assad A, Hunter DS, et al. A Phase 2 Study of Ruxolitinib with Chemotherapy in Children with Philadelphia Chromosome-like Acute Lymphoblastic Leukemia (INCB18424-269/AALL1521): Dose-Finding Results from the Part 1 Safety Phase. Blood 2018;132:555.
66. Loh ML, Tasian SK, Rabin KR, et al. A phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: A Children's Oncology Group phase 1 consortium study (ADVL1011). Pediatr Blood Cancer 2015;62:1717-24.
67. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202192lbl.pdf
68. Niswander LM, Loftus JP, Lainey É, et al. Therapeutic potential of ruxolitinib and ponatinib in patients with EPOR-rearranged Philadelphia chromosome-like acute lymphoblastic leukemia. Haematologica 2021;106:2763-7.
69. Horton TM, Gannavarapu A, Blaney SM, et al. Bortezomib interactions with chemotherapy agents in

acute leukemia in vitro. Cancer Chemother Pharmacol 2006;58:13-23.
70. Richardson PG, Hideshima T, Mitsiades C, et al. Proteasome inhibition in hematologic malignancies. Ann Med 2004;36:304-14.
71. Messinger YH, Gaynon PS, Sposto R, et al. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. Blood 2012;120:285-90.
72. Bertaina A, Vinti L, Strocchio L, et al. The combination of bortezomib with chemotherapy to treat relapsed/refractory acute lymphoblastic leukaemia of childhood. Br J Haematol 2017;176:629-36.
73. Horton TM, Whitlock JA, Lu X, et al. Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group. Br J Haematol 2019;186:274-85.
74. Teachey DT, Devidas M, Wood BL, et al. Children's Oncology Group Trial AALL1231: A Phase III Clinical Trial Testing Bortezomib in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia and Lymphoma. J Clin Oncol 2022;40:2106-18.
75. Burke MJ, Ziegler DS, Bautista F, et al. Phase 1b study of carfilzomib with induction chemotherapy in pediatric relapsed/refractory acute lymphoblastic leukemia. Pediatr Blood Cancer 2022;69:e29999.
76. Kisor DF. Nelarabine: a nucleoside analog with efficacy in T-cell and other leukemias. Ann Pharmacother 2005;39:1056-63.
77. Hernandez-Ilizaliturri FJ, Czuczman MS. A Review of Nelarabine in the Treatment of T-cell Lymphoblastic Leukemia/Lymphoma. Clin Med Ther 2009;1:CMT.S1954.
78. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). Blood 2011;118:874-83.
79. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. Pediatr Blood Cancer 2015;62:1176-83.
80. Dunsmore KP, Devidas M, Linda SB, et al. Pilot study of nelarabine in combination with intensive chemotherapy in high-risk T-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. J Clin Oncol 2012;30:2753-9.
81. Kadia TM, Gandhi V. Nelarabine in the treatment of pediatric and adult patients with T-cell acute lymphoblastic leukemia and lymphoma. Expert Rev Hematol 2017;10:1-8.
82. Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol 2005;23:3376-82.
83. Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood 2011;118:2077-84.
84. Winter SS, Dunsmore KP, Devidas M, et al. Improved Survival for Children and Young Adults With T-Lineage Acute Lymphoblastic Leukemia: Results From the Children's Oncology Group AALL0434 Methotrexate Randomization. J Clin Oncol 2018;36:2926-34.
85. Dunsmore KP, Winter SS, Devidas M, et al. Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia. J Clin Oncol 2020;38:3282-93.
86. Xie M, Jiang Q, Xie Y. Comparison between decitabine and azacitidine for the treatment of myelodysplastic syndrome: a meta-analysis with 1,392 participants. Clin Lymphoma Myeloma Leuk 2015;15:22-8.
87. Burke MJ, Lamba JK, Pounds S, et al. A therapeutic trial of decitabine and vorinostat in combination with chemotherapy for relapsed/refractory acute lymphoblastic leukemia. Am J Hematol 2014;89:889-95.
88. Egger G, Liang G, Aparicio A, et al. Epigenetics in human disease and prospects for epigenetic therapy. Nature 2004;429:457-63.
89. Christman JK. 5-Azacytidine and 5-aza-2'-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. Oncogene 2002;21:5483-95.
90. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;133:7-17.
91. Sun W, Triche T Jr, Malvar J, et al. A phase 1 study of azacitidine combined with chemotherapy in childhood leukemia: a report from the TACL consortium. Blood 2018;131:1145-8.
92. Schafer ES, Chao K, Stevens AM, et al. Real-world experience in treating pediatric relapsed/refractory or

therapy-related myeloid malignancies with decitabine, vorinostat, and FLAG therapy based on a phase 1 study run by the TACL consortium. Pediatr Blood Cancer 2022;69:e29812.
93. Pommert L, Schafer ES, Malvar J, et al. Decitabine and vorinostat with FLAG chemotherapy in pediatric relapsed/refractory AML: Report from the therapeutic advances in childhood leukemia and lymphoma (TACL) consortium. Am J Hematol 2022;97:613-22.
94. Schafer E, Irizarry R, Negi S, et al. Promoter hypermethylation in MLL-r infant acute lymphoblastic leukemia: biology and therapeutic targeting. Blood 2010;115:4798-809.
95. A Pilot Study of Azacitidine As Epigenetic Priming for Chemotherapy in Infants Less Than 1 Year of Age with KMT2A-Rearranged Acute Lymphoblastic Leukemia (ALL); Results from the Children's Oncology Group (COG) Trial AALL15P1. Available online: https://ash.confex.com/ash/2022/webprogram/Paper167765.html
96. Burke MJ, Kostadinov R, Sposto R, et al. Decitabine and Vorinostat with Chemotherapy in Relapsed Pediatric Acute Lymphoblastic Leukemia: A TACL Pilot Study. Clin Cancer Res 2020;26:2297-307.
97. Liu J, Jiang ZX, Xie XS, et al. Maintenance Treatment With Low-Dose Decitabine After Allogeneic Hematopoietic Cell Transplantation in Patients With Adult Acute Lymphoblastic Leukemia. Front Oncol 2021;11:710545.
98. Yokoyama A, Cleary ML. Menin critically links MLL proteins with LEDGF on cancer-associated target genes. Cancer Cell 2008;14:36-46.
99. Heikamp EB, Henrich JA, Perner F, et al. The menin-MLL1 interaction is a molecular dependency in NUP98-rearranged AML. Blood 2022;139:894-906.
100. Stein EM, Aldoss I, DiPersio JF, et al. Safety and efficacy of menin inhibition in patients (Pts) with MLL-rearranged and NPM1 mutant acute leukemia: a phase (Ph) 1, first-in-human study of SNDX-5613 (AUGMENT 101). Blood 2021;138:699.
101. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017;376:836-47.
102. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131:1522-31. Erratum in: Blood 2019;133:2625.
103. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. J Clin Oncol 2016;34:4381-9.
104. Locatelli F, Zugmaier G, Rizzari C, et al. Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA 2021;325:843-54.
105. Brown PA, Ji L, Xu X, et al. Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA 2021;325:833-42.
106. Brown PA, Ji L, Xu X, et al. A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in Low Risk (LR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs): A Report from Children's Oncology Group Study AALL1331. Blood 2021;138:363.
107. McCall D, Jabbour E, Roth M, et al. Mini-hyper CVD + CRIB (condensed rituximab, inotuzumab ozogamicin, and blinatumomab) for refractory pediatric B-acute lymphoblastic leukemia. Pediatr Blood Cancer 2023;70:e29939.
108. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med 2016;375:740-53.
109. O'Brien MM, Ji L, Shah NN, et al. A phase 2 trial of inotuzumab ozogamicin (InO) in children and young adults with relapsed or refractory (R/R) CD22+ B-acute lymphoblastic leukemia (B-ALL): results from Children's Oncology Group Protocol AALL1621. Blood 2019;134:741.
110. Brivio E, Locatelli F, Lopez-Yurda M, et al. A phase 1 study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study). Blood 2021;137:1582-90.
111. Jabbour E, Ravandi F, Kebriaei P, et al. Salvage Chemoimmunotherapy With Inotuzumab Ozogamicin Combined With Mini-Hyper-CVD for Patients With Relapsed or Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Phase 2 Clinical Trial. JAMA Oncol 2018;4:230-4.
112. Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant

2018;53:449-56.
113. McNeer JL, O'Brien MM, Rheingold SR, et al. A Phase 3 Randomized Trial of Inotuzumab Ozogamicin for Newly Diagnosed High-Risk B-ALL: Safety Phase Results from Children's Oncology Group Protocol AALL1732. Blood 2021;138:3398.
114. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
115. Feucht J, Kayser S, Gorodezki D, et al. T-cell responses against CD19+ pediatric acute lymphoblastic leukemia mediated by bispecific T-cell engager (BiTE) are regulated contrarily by PD-L1 and CD80/CD86 on leukemic blasts. Oncotarget 2016;7:76902-19.
116. Köhnke T, Krupka C, Tischer J, et al. Increase of PD-L1 expressing B-precursor ALL cells in a patient resistant to the CD19/CD3-bispecific T cell engager antibody blinatumomab. J Hematol Oncol 2015;8:111.
117. Weber JS. Practical management of immune-related adverse events from immune checkpoint protein antibodies for the oncologist. Am Soc Clin Oncol Educ Book 2012;174-7.
118. Maude SL, Teachey DT, Porter DL, et al. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood 2015;125:4017-23.
119. Company B-MS: OPDIVO-[package insert]. Princeton, NJ. 2019. Available online: https://www.opdivo.com/potential-side-effects#:~:text=The%20most%20common%20side%20effects,%3B%20headache%3B%20stomach%2Darea%20(
120. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129:3322-31.
121. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018;378:439-48.
122. Shah NN, Lee DW, Yates B, et al. Long-Term Follow-Up of CD19-CAR T-Cell Therapy in Children and Young Adults With B-ALL. J Clin Oncol 2021;39:1650-9.
123. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-17.
124. Pillai V, Muralidharan K, Meng W, et al. CAR T-cell therapy is effective for CD19-dim B-lymphoblastic leukemia but is impacted by prior blinatumomab therapy. Blood Adv 2019;3:3539-49.
125. Roddie C, Dias J, O'Reilly MA, et al. Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol 2021;39:3352-63.
126. Shah NN, Highfill SL, Shalabi H, et al. CD4/CD8 T-Cell Selection Affects Chimeric Antigen Receptor (CAR) T-Cell Potency and Toxicity: Updated Results From a Phase I Anti-CD22 CAR T-Cell Trial. J Clin Oncol 2020;38:1938-50.
127. Shah NN, Maatman T, Hari P, et al. Multi Targeted CAR-T Cell Therapies for B-Cell Malignancies. Front Oncol 2019;9:146.
128. Spiegel JY, Patel S, Muffly L, et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial. Nat Med 2021;27:1419-31.
129. Cordoba S, Onuoha S, Thomas S, et al. CAR T cells with dual targeting of CD19 and CD22 in pediatric and young adult patients with relapsed or refractory B cell acute lymphoblastic leukemia: a phase 1 trial. Nat Med 2021;27:1797-805.

Cite this article as: Munir F, He J, Connors J, Garcia M, Gibson A, McCall D, Nunez C, Dinh CN, Robusto L, Roth M, Khazal S, Tewari P, Cuglievan B. Translational advances in the treatment of childhood acute lymphoblastic leukemia: narrative review of current and emerging molecular and immunotherapies. Transl Pediatr 2023;12(3):487-502. doi: 10.21037/tp-22-656