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Venetoclax in combination with chemotherapy as treatment for pediatric advanced hematologic malignancies

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Abstract

Background: Venetoclax is frequently used as salvage treatment in pediatric, adolescent, and young adult (AYA) patients with advanced hematologic malignancies. However, more data are needed from real-world studies to guide the safe and appropriate use of venetoclax in this population.

Procedure: We retrospectively reviewed the medical records of all patients diagnosed with hematologic malignancies less than 30 years of age treated with venetoclax outside of clinical trials at the University of California San Francisco (UCSF) Benioff Children's Hospitals from 2016 to 2022.

Results: We identified 13 patients (AML, *n= 8*, B-ALL, *n= 3*, MDS, *n= 2)* aged 4 months to 27 years. A median of 3 prior lines of therapy were given (range 0 to 5). All patients received venetoclax in combination with either a hypomethylating agent or conventional chemotherapy. Three (23%) patients achieved a complete remission (CR); 2 (15%) achieved a partial remission (PR); 3 (23%) had stable disease (SD), and 5 (42%) had progressive disease. Median survival and time to progression from venetoclax initiation was 9 months (range 2.5 to 52 months), and 3 months (range 2 weeks to 7.5 months), respectively. Six patients (46%) developed grade 3 or higher infections while receiving venetoclax, including bacteremia due to atypical organisms, invasive pulmonary infections with Aspergillus, cytomegalovirus (CMV) viremia, skin infections, and encephalitis with bacterial brain abscesses.

Conclusions: Venetoclax in combination with hypomethylating agents or cytotoxic chemotherapy was effective in a subset of pediatric/AYA patients with advanced hematologic malignancies, but multiple severe infections were observed, particularly among patients who received venetoclax in combination with chemotherapy. Prospective studies will be required to determine the optimal dose and duration of venetoclax in this population.

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Conflicts of Interest Statement

The authors do not have any conflicts of interests to declare.

Keywords

Venetoclax; pediatric; adolescent and young adults; leukemia; infection

Introduction

Therapeutic options for pediatric, adolescent and young adult (AYA) patients with relapsed/refractory acute myeloid leukemia (AML) are limited, and outcomes remain dismal; two-year relapse-free rates for these patients, even with current chemotherapeutic regimens and hematopoietic stem cell transplant (HSCT), are only 25%−30%.[1–3] Relapsed/refractory acute lymphoblastic leukemia (ALL) has also remained challenging to treat in children and AYA, with survival rates lagging significantly behind those observed at initial diagnosis. Although there have been improvements in outcomes over the past several decades, only ~50% of children and AYA with first relapse of ALL experience long term survival, and outcomes are even worse with second or later relapses.[4] Novel therapeutic strategies are thus needed to improve outcomes in pediatric/AYA patients with relapsed/refractory (advanced) hematologic malignancies.

Venetoclax, a potent, highly selective, orally available inhibitor of the anti-apoptotic protein B-cell lymphoma-2 (BCL-2), has emerged as one such promising agent. Venetoclax in combination with low-dose cytarabine or hypomethylating agents is Food and Drug Administration-approved for adults with newly diagnosed chronic lymphocytic leukemia and AML, based on results supporting its safety and efficacy in elderly adults deemed unfit for cytotoxic chemotherapy.[5–7] Several studies also suggest these combinations may be effective salvage regimens for adults with relapsed or refractory AML, even in heavily pre-treated populations.[8–10]

Venetoclax is currently the subject of several ongoing phase I/II clinical trials evaluating its safety and efficacy in pediatric/AYA patients with relapsed or refractory AML (NCT03194932) and in other malignancies (NCT03236857). A phase I dose-escalation study of venetoclax in combination with cytarabine with or without idarubicin in pediatric patients with relapsed/refractory AML or ambiguous lineage leukemia supported the safety and efficacy of venetoclax and conventional chemotherapy in this population.[11] Another phase I dose-escalation study demonstrated venetoclax with chemotherapy and low-dose navitoclax, a BCL-X_L/BCL-2 inhibitor, is a safe and promising combination in pediatric and adult patients with advanced ALL and lymphoblastic lymphoma.[12]

Aside from these early-phase trials, the published literature to date concerning venetoclax in pediatric/AYA patients with hematologic malignancies consists of a few single-institution reports that support the safety and efficacy of venetoclax in combination with cytotoxic chemotherapy in pediatric patients with ALL[13] and AML[14] and in combination therapy with azacitidine in pediatric patients with MDS or AML unfit for standard chemotherapy.[15]

While these reports are encouraging, more data are needed to guide clinicians in the safe and efficacious use of venetoclax combination therapy across a range of pediatric hematologic malignancies. We therefore retrospectively reviewed our institutional

experience of venetoclax use in pediatric/AYA patients at the University of California San Francisco (UCSF) Benioff Children's Hospitals and report on 13 pediatric and AYA patients with hematologic malignancies who received venetoclax combination therapy outside of a clinical trial between 2016 and 2022.

Methods

After IRB approval, a retrospective chart review identified patients diagnosed with acute leukemia or MDS at age 30 years or younger who received venetoclax combination therapy at UCSF Benioff Children's Hospitals. Eligible diagnoses included AML, MDS, and ALL. Patients who were treated on a clinical trial were excluded from this study.

Venetoclax was administered orally as a tablet, if tolerated, once daily with food. For younger patients unable to swallow pills, venetoclax was compounded in the oral hazardous compounding hood by crushing the appropriate number of tablets and dissolving in sterile water to a final volume of 5 mg/mL. Each dose was dispensed in an oral syringe and administered via NG tube with food. Each oral syringe was then rinsed with an additional 5–10mL sterile water and administered via NG tube to ensure the entire dose is given. The compounded dose was considered stable for one hour once dissolved.

Complete remission (CR) was defined as disappearance of all clinical and/or radiologic evidence of disease, plus absolute neutrophil count (ANC) $\geq 1.0 \times 10^3$/L, platelet count $\geq 100 \times 10^3$/L, and bone marrow differential with <5% blasts by morphology or flow cytometry of bone marrow. Partial response (PR) was defined as no peripheral blasts or peripheral blood absolute blast count decreased by ≥ 50% from baseline, bone marrow with 5 – 25% blasts and at least a 50% decrease in bone marrow blast percent from baseline, and no evidence of extramedullary disease. Progressive disease (PD) was defined as > 50% increase in absolute peripheral or bone marrow blasts by morphology or flow cytometry. Stable disease (SD) was defined as the conditions under which criteria for CR, PR, or PD were not met.

Minimal residual disease (MRD) was defined as multiparameter flow cytometry of bone marrow with less than 0.01% blasts. Venetoclax toxicities were graded per the Common Terminology Criteria for Adverse Events version 5.0. Overall survival (OS) defined as the time in months from the start of venetoclax therapy to death, and progression-free survival (PFS) was defined as the time from the start of venetoclax administration until disease progression or relapse. Patients alive without relapse or progression were censored at their date of last follow-up. Kaplan–Meier curves of OS and PFS were generated.

Next-Generation Sequencing

Next generation sequencing was available for 12 patients (14 leukemia samples, 12 germline samples). An institutional DNA sequencing panel assaying 479 cancer-related genes was used.[16] Genomic DNA was extracted from peripheral blood and tumor tissue microdissected from fresh frozen paraffin embedded blocks, as previously described.[16] Germline DNA was isolated from buccal specimens and sequenced with the same panel. Capture-based next-generation sequencing (NGS) was performed at the UCSF Clinical Cancer Genomics Laboratory, using an assay targeting the coding regions of these genes, *TERT* promoter,

select introns from 40 genes (for detection of gene fusions and other structural variants), and intergenic regions at regular intervals along each chromosome (for chromosomal copy number assessment), altogether with a total sequencing footprint of 2.8 Mb Sequencing libraries were prepared from genomic DNA with target enrichment performed by hybrid capture using a custom oligonucleotide library. Sequencing was performed on an Illumina HiSEquation 2500. Duplicate sequencing reads were removed computationally to allow for accurate allele frequency determination and copy number estimates. The analysis was based on the human reference sequence UCSC build hg19 (NCBI build 37). Single nucleotide variants and small insertions/deletions (indels) were visualized and verified using Integrated Genome Viewer.

Results

Patient and Disease Characteristics

Thirteen patients were identified, 8 (62%) with AML, 3 (23%) with B-ALL, and 2 (15%) with MDS. The median age upon initiation of venetoclax was 14 years (range: 4 months to 27 years). Six (46%) patients were male. Three patients had a history of a prior malignancy: one patient with T-ALL, one with AML, and one with neuroblastoma. The median number of lines of therapy was 3 (range 0 to 5). Five (38%) patients had received a hematopoietic stem cell transplant prior to receiving venetoclax therapy. Two patients had a defined predisposition to developing malignancy: one patient had Schwachman-Diamond Syndrome (SDS) who developed AML, and one had a germline *GATA2* mutation who developed MDS. There were no patients with a known underlying primary immunodeficiency, aside from Patient 8 with the germline *GATA2* deficiency. Patient and disease characteristics are summarized in Table 1.

Treatment and Response

All patients received venetoclax in combination with either a hypomethylating agent or conventional chemotherapy. Median follow-up time was 8 months from venetoclax initiation (range 2 to 52 months). Treatment regimens and responses for each patient are summarized in Table 2 and in Figure 1. The standard adult AML dosing of 400 mg daily (or adult equivalent weight-based dosing), with a bioequivalent dose for patients receiving a concurrent CYP3A4 inhibitor, was given.[17,18] Three of 8 patients with AML received venetoclax in combination with decitabine (20 mg/m^2 daily for 5 days). In two of these three cases, the patient was a poor candidate for conventional chemotherapy due to morbidities from prior therapy, and venetoclax was administered with palliative intent; in one case, the patient with SDS and newly-diagnosed AML was deemed ineligible for standard chemotherapy due to the risk of toxicity.[19] The remaining 5 patients with AML received venetoclax in combination with cytarabine (1000 mg/m^2/dose every 12 hours for 8 total doses). One patient with an intracranial myeloid sarcoma received venetoclax and cytarabine with concomitant focal radiation therapy. Both patients with MDS received venetoclax in combination with a hypomethylating agent (decitabine in one case and azacitidine in the other).

Two of the three patients with relapsed B-ALL received venetoclax in combination with vincristine, dexamethasone, and PEG-asparaginase. One patient with relapsed B-ALL received venetoclax in combination with fludarabine, high-dose cytarabine, and G-CSF (FLAG).

The median number of cycles of venetoclax combination therapy patients received was 1 (range <1 to 3). The most common reason for discontinuation of venetoclax was disease progression in 6 patients (46%), and in 2 cases it was discontinued due to infections.

Three (23%) patients achieved a CR; 2 (15%) achieved a PR; 3 (23%) had stable disease, and 5 (42%) had PD. Of the 3 patients who achieved a CR, two had a diagnosis of relapsed B-ALL, and one had a diagnosis of SDS-associated AML. Two of these patients became MRD negative after one cycle of venetoclax combination therapy. All 3 patients who achieved a CR remain alive with no evidence of disease with a median follow-up time of 48 months. All patients with durable responses were transplanted after achieving a CR.

Nine patients (69%) experienced disease progression following venetoclax therapy. Median survival was 9 months from venetoclax initiation (range 2.5 to 52 months), and median time to progression was 3 months (range 2 weeks to 7.5 months). (Fig. 2).

Toxicities

All patients experienced hematologic toxicity with grade 3–4 thrombocytopenia, anemia, and neutropenia. Non-hematologic Grade 3–4 adverse events (AEs) and infections of any grade are summarized for each patient in Table 3. The antimicrobial prophylaxis regimens for each patient initiated at the time of venetoclax initiation are also included in Table 3. Infections of any grade occurred in 8 patients (62%) while receiving venetoclax. Six patients (46%) developed grade 3 or higher infections while receiving venetoclax. Four patients (23%) developed bacteremia, one of whom developed four distinct episodes of bacteremia in addition to multiple other infectious complications (Patient 10). Patient 12 developed a grade 4 infection with multiple rim-enhancing brain lesions thought to be bacterial abscesses. Two patients developed invasive pulmonary infections with Aspergillus. Patient 9 developed an orbital cellulitis. Two patients developed grade 2 skin infections (Patients 7 and 8). Patient 6, an infant, developed grade 3 nausea, which prompted discontinuation of venetoclax. No deaths occurred within 30 days of the start of venetoclax combination therapy, and no grade 5 AEs were reported as associated with venetoclax. No clinically significant tumor lysis syndrome was seen.

Discussion

We report on our real-world experience using venetoclax in pediatric and AYA patients with hematologic malignancies. Our experience builds on emerging data demonstrating the efficacy of venetoclax across a range of diagnoses. We also report on a number of infections observed during treatment with venetoclax-based regimens in this cohort.

Our experience adds to the growing evidence[11,13–15] that venetoclax may be effective in combination with multiple regimens across a range of hematologic malignancies, even in

the relapsed/refractory setting. We found a subset of responders, even among those who received multiple lines of prior therapy. Three patients achieved a CR: one patient with SDS-associated AML who received venetoclax and decitabine and achieved a CR after 1 cycle, and two patients with relapsed B-ALL who received venetoclax with a 3-drug induction chemotherapy backbone (vincristine, dexamethasone, and PEG-asparaginase) each achieved a CR after receiving one cycle of therapy. Both patients with B-ALL were subsequently treated with bispecific T-cell engagers as bridging therapy to HSCT. Two patients who had received 3 or more prior lines of chemotherapy achieved a PR: one patient with treatment related-AML who received venetoclax and decitabine and one patient with refractory AML who received venetoclax with cytarabine; neither patient had significant venetoclax-related toxicities. Most patients received maximal benefit within 1–2 cycles of venetoclax-based therapy and all durable responses were followed by HSCT, indicating venetoclax-based regimens are unlikely to be curative as definitive therapy.

Our experience is also in agreement with prior studies suggesting patients unfit for conventional chemotherapy may benefit from venetoclax in combination with a hypomethylating agent.[6,14] This combination was generally well-tolerated, and in two cases of patients with refractory AML, it afforded excellent quality of life in the palliative setting.

Venetoclax was not effective in our two cases of infant AML, both with GLIS fusions, which are associated with a highly refractory phenotype across pediatric AML subtypes.[20,21] Recent preclinical data using murine models of CBFA2T3-GLIS2 pediatric acute megakaryoblastic leukemia demonstrate resistance to venetoclax but sensitivity to BCL-X_L inhibition with navitoclax, suggesting a potential path toward clinical translation for this high-risk infant leukemia.[22]

To date, published reports have reported venetoclax is well-tolerated in combination with a variety of cytotoxic agents in pediatric/AYA patients with hematologic malignancies.[11–14] Our experience calls attention to the severity and range of infections patients experienced during treatment with venetoclax. Eight patients (62%) experienced at least one infection, including bacteremia caused by multiple uncommon organisms, invasive pulmonary fungal disease, CMV viremia, and a grade 4 infection with bacterial brain abscesses in one case. (Table 3). Infections occurred in an equal proportion of patients who received venetoclax combined with a hypomethylating agent and with cytotoxic chemotherapy, but they were generally more severe and prolonged with the latter combination (Table 3). All patients who experienced serious infections received prophylactic antibiotics and antifungals at the start of venetoclax treatment with dose adjustments for concomitant azole use.[18] Patients were treated with a broad range of antimicrobial prophylaxis regimens, reflecting the lack of consensus regarding the optimal approach to infection prophylaxis while using venetoclax.

The reported incidence of grade 3 or higher infectious complications in children and AYA with hematologic malignancies vary widely across previous studies, ranging from 19–70% in prior relapsed/refractory AML trials[3,23,24] and 15–90% in relapsed/refractory ALL trials.[25–27] This broad range of historical outcomes and the heterogeneous nature of our cohort makes comparison with historical groups difficult to interpret. Prospective

randomized clinical trials are required to determine whether venetoclax increases the risk of infection.

This study has several limitations, including the small sample size, heterogeneous cohort, and lack of a control group, thereby precluding any conclusions regarding responses among specific subgroups or a causal link between venetoclax and infectious risk. Our cohort was predominantly comprised of patients with relapsed and refractory disease, 70% of whom had received 3 or more prior lines of therapy; thus, our findings may not be relevant to other populations, including those receiving upfront therapy for newly diagnosed hematologic malignancies.

Nevertheless, our experience highlights the potential promise and risks associated with venetoclax across a diverse set of pediatric and AYA patients with hematologic malignancies, providing real-world evidence complementary to randomized clinical trial data for guiding decision-making in routine clinical practice. Our experience provides a rationale for conducting randomized controlled trials to query a potential association between venetoclax and infection risk. Future studies should also focus on identifying subgroups of patients most likely to benefit from venetoclax and strategies to mitigate adverse events.

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Abbreviations key:

AEs	adverse events
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
AYA	adolescent and young adult
BCL-2	B-cell lymphoma-2
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
HSCT	hematopoietic stem cell transplant
MDS	myelodysplastic syndrome
MRD	minimal residual disease
OS	overall survival

PD	progressive disease
PFS	progression-free survival
PR	partial response
SD	stable disease
SDS	Schwachman Diamond Syndrome

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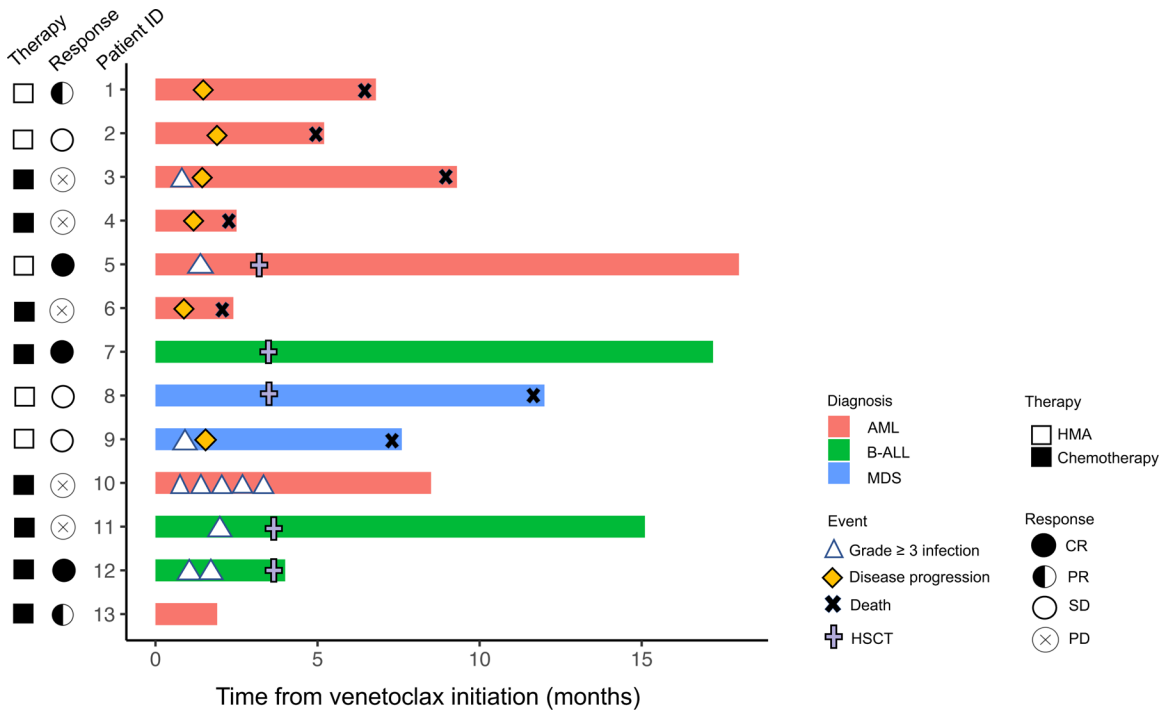

Figure 1.

Swimmer plot showing the clinical course of each patient over time. Each bar represents one patient color-coded based on diagnosis treated with venetoclax (AML, pink; B-ALL, green; MDS, blue) Dates of severe infection, hematopoietic stem cell transplantation (HSCT), disease progression, or death are depicted by symbols. Therapy combined with venetoclax are shown on the left with a white box (hypomethylating agent, HMA) or black box (chemotherapy). Response to therapy is depicted to the left: circles are filled (complete response, CR), partially filled (partial response, PR), empty (stable disease, SD), or contain an “x” (PD, progressive disease.

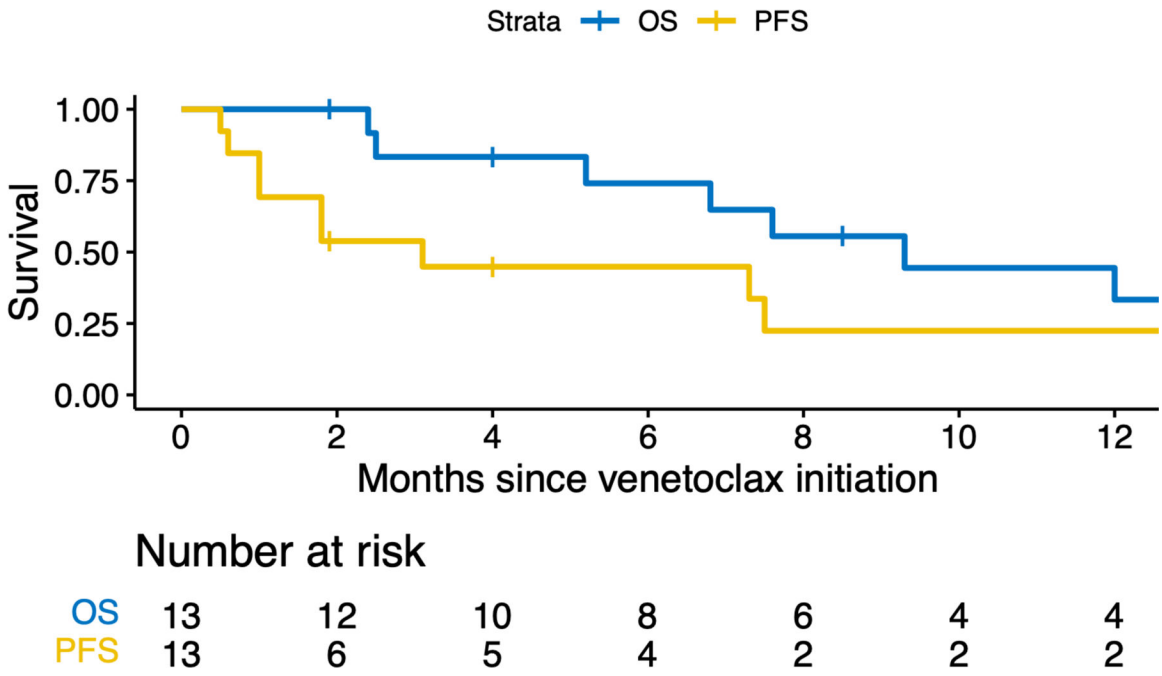

Figure 2.
Overall survival (OS) and progression-free survival (PFS) of 13 patients who received venetoclax combination therapy.

TABLE 1

Patient and Disease Characteristics

Patient number	Sex/Age received venetoclax (years)	Prior cancer diagnosis or predisposition	Diagnosis	Lines of prior therapy	CNS status	Cytogenetics/t FISH findings	Genes with Somatic P/LP variants or RNA-seq findings
1	F/17	T-ALL	t-AML	3	1	Monosomy 7; 46, XXder(7)t(7;11)(q22;q13)	*PTPN11, SETD2, RUNX1, BCOR*
2	M/10		refractory AML	4	1	45, XY,inv(3)(q21q26),−7[17]; MECOM (EVI1) rearrangement at 3q26.2	
3	M/8		relapsed AML	5	3	44–46, XY, t(6;11)(q27;q23); KMT2Ar	*NRAS*
4	F/1		refractory AML	4	1	46, XX,add(17)(q25),der(19)t(1;19) (q?21; p13.3)[2]/46,XX[20]	*GLIS3* fusion
5	M/14	SDS	AML	0	1	46, XY	*IDH1, KMT2A*
6	F/0.7		refractory AML	4	2	46, XX	*CBFA2T3-GLIS2* fusion
7	F/20	AML	relapsed B-ALL	3	1	45, XX,−9,add(12)(p13)[9]/46,XX	*ETV6-NTRK* fusion*; IKZF1; CDNK2B*
8	F/17	Germline *GATA2* mutation	MDS	1	1	49, XX,+8,+11,+19[1]//46,XY[29]	*GATA2* (germline)
9	F/5	Neuroblastoma	t-MDS	0	1	46, XX	*PTPN11*
10	M/29		AML	5	3	46, XY	*AXLS1; ATM1*
11	M/27		relapsed B-ALL	3	3	46, XY,dup(1)(q21q?43),t(9;12)(p12;p13) [2]/46,XY[16]; CRLF2 rearrangement	CRLF2r Ph-like ALL; *IKZF1*
12	F/15		relapsed B-ALL	1	2	iAMP21	*KRAS*
13	M/13		AML	4	3	46, XY	*MLL-MLLT10*; C*BL-MLL, NOTCH4, NOTCH3, KRAS, SETD2*

Abbreviations: M, male; F, female; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome, SDS, Schwachman Diamond Syndrome

TABLE 2

Summary of treatment and outcomes

Patient number	Diagnosis	Treatment combined with venetoclax	Best response	MRD (flow cytometry, morphology)	Number of cycles prior to best response	HSCT following venetoclax	Vital Status	Survival (months from venetoclax initiation)	Time to progression (months from venetoclax initiation)	
1	AML	Decitabine	PR	2.9%; 28%	2	No		Dead	6.8	1.8
2	AML	Decitabine	SD		3	No		Dead	5.2	3.1
3	AML	Cytarabine	PD		1	No		Dead	9.3	1
4	AML	Cytarabine	PD		1	No		Dead	2.5	0.6
5	AML	Decitabine	CR	0%, <5%	1	Yes		Alive, NED	52	N/A
6	AML	Cytarabine	PD		<1	No		Dead	2.4	0.5
7	B-ALL	VCR/PEG/DEX	CR	0%, <5%	1	Yes		Alive, NED	17.2	N/A
8	MDS	Azacitidine	PD		2	Yes		Dead	12	1.8
9	MDS	Decitabine	SD		2	No		Dead	7.6	7.5
10	AML	Cytarabine (+ 24Gy focal RT)	SD		2	No		Alive with disease	8.5	7.3
11	B-ALL	FLAG	PD		1	Yes		Alive, NED	15.1	1
12	B-ALL	VCR/PEG/DEX	CR	0.26%, <5%	1	Yes		Alive, NED	4	N/A
13	AML	Cytarabine	PR		1	No		Alive with disease	1.9	N/A

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; N/A, not applicable; NED, no evidence of disease; VCR, vincristine; PEG, pegaspargase; DEX, dexamethasone; RT, radiation therapy; FLAG, fludarabine, cytarabine, Granulocyte-Colony Stimulating Factor

Table 3:

Summary of non-hematologic adverse events during treatment with venetoclax

Patient number	Treatment combined with venetoclax	Infection prophylaxis	Relevant prior infection history informing prophylaxis regimen	Non-hematologic AE*	Grade*	Description
1	HMA	amoxicillin/clavulanate, isavuconazole	Actinomyces, fungal sinusitis	None		
2	HMA	levofloxacin, fluconazole		None		
3	Chemo	levofloxacin, fluconazole		Salivary duct inflammation	3	Parotiditis secondary to Influenza A
4	Chemo	cefepime, micafungin	Strep mitis bacteremia	None		
5	HMA	levofloxacin, caspofungin		None		
6	Chemo	levofloxacin, fluconazole		Nausea	3	Prompted discontinuation of therapy
7	Chemo	levofloxacin, micafungin		Paronychia	2	Paronychia associated with febrile neutropenia
8	HMA	none		Skin infection	2	Cellulitis of the buttocks
9	HMA	none		Eye infection	3	Orbital cellulitis
10	Chemo	levofloxacin, micafungin		Lung infection Sepsis Cytomegalovirus infection reactivation Soft tissue infection Appendicitis	3 3 3 3 3	Aspergillus; 4 distinct episodes of sepsis due to the following organisms: *Klebsiella, Morganella, Staphylococcus epidermidis*, and *Actinomyces*; Pilonidal abscess
11	Chemo	levofloxacin, caspofungin		Sepsis	3	Streptococcus sanguinis
12	Chemo	cefepime, isavuconazole	Steptoccocus Group G bacteremia, Cryptococcus fungemia	Sepsis Infections and infestations - Other	3 4	*Enterococcus faecalis* and *Streptococcal* bacteremia Brain abscesses
13	Chemo	levofloxacin, micafungin		None		

Abbreviations: AE, adverse event; HMA, hypomethylating agent; CMV, cytomegalovirus

*Based on CTCAE v. 5

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