Venetoclax and BCR-ABL Tyrosine Kinase Inhibitor Combinations: Outcome in Patients with Philadelphia Chromosome-Positive Advanced Myeloid Leukemias

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Keywords

Venetoclax · Acute myeloid leukemia · BCR/ABL · Chronic myeloid leukemia · Decitabine · Ponatinib · Tyrosine kinase inhibitors · Myeloid blast phase · Philadelphia chromosome-positive acute myeloid leukemia

Abstract

Background: Philadelphia chromosome-positive (Ph+) advanced leukemias, including acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) in myeloid blast phase (MBP), have poor outcomes. Venetoclax has shown synergism with BCR-ABL1 tyrosine kinase inhibitors (TKI) in pre-clinical studies. However, clinical activity of venetoclax and TKI-based regimens is unknown. **Methods:** We conducted a retrospective study on patients with Ph+ AML ($n = 7$) and CML-MBP ($n = 9$) who received venetoclax combined with TKI-based regimens at our institution. **Results:** Median patient age was 42 years, and the median number of prior therapy cycles was 5 (range 2–8). Nine patients received

decitabine-based, and 7 received intensive chemotherapy-based regimens. Ten patients (63%) received ponatinib. The overall response rate (ORR) in 15 evaluable patients was 60% (1 complete remission [CR], 6 CR with incomplete hematologic recovery [CRi], 1 morphologic leukemia-free state, and 1 partial response). The ORR was 43% in Ph+ AML and 75% in CML-MBP. The median overall survival (OS) for all patients was 3.6 months, for AML OS was 2.0 months, and for CML-MBP OS was 10.9 months. The median relapse-free survival for AML and CML-MBP was 3.6 and 3.9 months, respectively. Compared to nonresponders, patients achieving CR/CRi had higher baseline Ph+ metaphases and BCR-ABL1 PCR. **Conclusions:** Combination therapy of venetoclax with TKI-based regimens shows encouraging activity in very heavily pretreated, advanced Ph+ leukemias, particularly CML-MBP.

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Introduction

Acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) in myeloid blast phase (MBP) are aggressive myeloid leukemias with overall poor outcomes [1, 2]. Both AML and CML-MBP are more frequently diagnosed in older patients, with a median age of >60 years at diagnosis [3, 4]. While AML is the most common acute leukemia in adults, CML is much less common, and only a minority of patients progress to the aggressive blast phase. t(9;22) leads to the formation of the Philadelphia chromosome (Ph), which is almost universally present in CML and leads to the development of the constitutively active BCR-ABL tyrosine kinase. However, in rare instances, Ph has been noted in AML [5–7]. Patients with newly diagnosed Ph+ AML have a poor outcome, with a reported median overall survival (OS) of 9 months, although there is a dearth of data on this entity given its rarity [5, 6]. Transformation to advanced-phase CML occurs in 1–5% patients in chronic phase (CP) CML per year, and CML-MBP has a median OS of 6–12 months despite the use of second- or third-generation tyrosine kinase inhibitors (TKI) [2, 8, 9]. These poor outcomes highlight the need for novel therapies for these patients.

The anti-apoptotic BCL2 family of proteins regulate the mitochondrial apoptotic response. BCL2 is highly and almost universally expressed in leukemia cells and leukemic stem cells in AML and CML, is upregulated by BCR-ABL1 signaling, and is overexpressed in CML blast phase [10–14]. Venetoclax, a selective BCL2 inhibitor, is approved for use with low-dose cytarabine or hypomethylating agents for older or “unfit” patients with newly diagnosed AML. Venetoclax has shown preclinical activity against TKI-resistant CML cells and has shown synergism with BCR-ABL TKI in eradicating leukemic stem cells in advanced CML [13, 15, 16]. However, clinical activity of venetoclax and BCR-ABL TKI-based combinations is unknown. Hence, we conducted a retrospective study to summarize the activity of such combination therapies in advanced Ph+ myeloid leukemias.

Materials and Methods

In this retrospective chart review study, we included patients with Ph+ AML and CML-MBP treated at our institution with venetoclax and BCR-ABL1 TKI-based combinations.

Treatment Regimens

Dosing of agents was performed per institutional guidelines and practice. Venetoclax was dosed at 400 mg daily with dose reductions in conjunction with CYP3A4 inhibitors, e.g., azole antifungals

for infection prophylaxis or treatment. Reduction in the venetoclax treatment period from continuous to <2 weeks was allowed in cases of myelosuppression. TKI was administered concomitantly with venetoclax. Dasatinib was dosed at 100 mg daily ($n = 2$) or 50 mg daily ($n = 2$), bosutinib was dosed at 400 mg daily, nilotinib was dosed at 200 mg daily, and ponatinib was dosed daily at 30 mg ($n = 7$), 15 mg ($n = 2$), or 45 mg ($n = 1$). Two patients with concomitant *FLT3*-ITD received gilteritinib 80 and 120 mg daily, respectively. Decitabine (20 mg/m²) was administered for 5–10 days. The CLIA2 regimen consisted of cladribine 5 mg/m² on days 1–5, cytarabine 2,000 mg/m² i.v. on days 1–5, and idarubicin 10 mg/m² i.v. on days 1–3. The CIA regimen consisted of clofarabine 22.5 mg/m² i.v. on days 1–5, idarubicin 6 mg/m² i.v. on days 1–3, and cytarabine 0.75 g/m² i.v. on days 1–5. The FIA regimen consisted of fludarabine 30 mg/m² i.v. on days 1–5, idarubicin 6 mg/m² i.v. on days 1–3, and cytarabine 0.75 g/m² i.v. on days 1–5. Cladribine with HiDAC regimen consisted of cladribine 5 mg/m² and cytarabine 1,000 mg/m² i.v. daily for days 1–3. CPX-351 was administered at 44 U/m² on days 1, 3, and 5. Patients could proceed to allogeneic stem cell transplantation (allo-SCT) after achievement of a response if they were deemed fit for allo-SCT and a donor was available.

Response Assessment

The AML European LeukemiaNet 2017 criteria were used to determine response [17]. The BCR-ABL1 kinase domain mutation analysis done on cDNA with a nested polymerase chain reaction (PCR) method covered codons 221–500 [18]. Flow cytometry for minimal residual disease (MRD) testing had a sensitivity of 0.1% or higher [19]. Karyotype or fluorescence in situ hybridization were used to determine the proportion of Ph+ metaphases in bone marrow aspiration samples prior to starting therapy. Conventional karyotype was used to assess cytogenetic response after therapy.

Data Sharing

At this time, we will not be able to share individual patient level data outside of our institution.

Statistical Analysis

OS was determined from the date of therapy start to the date of death or censoring at the last follow-up. Relapse-free survival (RFS) was determined from the date of achievement of response to relapse, or death, or censoring at the last follow-up. OS and RFS were calculated using the Kaplan-Meier method. Student's *t* test was used to determine the association between continuous variables and response. GraphPad Prism v7.0 (GraphPad Software, San Diego, CA, USA) was used for statistical analyses.

Results

Patients and Treatment

Between July 2017 and May 2019, 16 patients with Ph+ AML and CML-MBP were treated with venetoclax and BCR-ABL1 TKI-based regimens. A summary of baseline patient characteristics and prior therapies is shown in Table 1. Seven patients had Ph+ AML, and 9 patients had CML-MBP. The median age of the patients was 42 years

Table 1. Baseline characteristics of patients with Ph+ AML and CML in myeloid blast phase (MBP)

Patient characteristics	Ph+ AML (<i>n</i> = 7)	CML-MBP (<i>n</i> = 9)
Age, years	47 [21–73]	38 [26–75]
ECOG performance status 0–2	6 (86)	7 (78)
WBC count, $\times 10^9/L$	9.7 [1.1–25.7]	6.9 [0.1–131.5]
Peripheral blasts, %	52 [1–73]	14 [2–88]
Bone marrow blasts, %	52 [10–78]	64 [2–79]
Ph+ metaphases, %	5 [0–100]	100 [86–100]
BCR-ABL1 PCR, %	7.05 [0.03–17.01]	71.74 [0.58–100]
Complex cytogenetics	5 (71)	3/6 (50)
Prior therapies	5 [2–6]	4 [2–8]
Prior TKI	3 (43)	9 (100)
Prior venetoclax	1 (14)	0 (0)
BCR-ABL1 kinase domain mutation	0/4 (0)	3/8 (38)
Response to prior therapy		
Refractory	6 (86)	4 (44)
Relapse	1 (14)	2 (22)
Transformation from CML-CP	0 (0)	3 (33)

Results are expressed as *n* (%) or medians [ranges]; CP, chronic phase; BCR-ABL1 RT-PCR reported as the percentage of BCR-ABL1 to ABL1 transcripts. See text for other abbreviations.

Table 2. Venetoclax-based regimens in patients with Ph+ AML and CML in myeloid blast phase (MBP)

Regimen	Ph+ AML (<i>n</i> = 7)	CML-MBP (<i>n</i> = 9)
Decitabine based	4 (57)	5 (56)
Intensive chemotherapy based	3 (43)	4 (44)
BCR-ABL TKI		
Ponatinib	6 (86)	4 (44)
Dasatinib	1 (14)	3 (33)
Bosutinib	0 (0)	1 (11)
Nilotinib	0 (0)	1 (11)

Results are expressed as *n* (%). See text for other abbreviations.

(range 21–73), and 13 patients (81%) had ECOG performance status ≤ 2 . Eight of 13 patients (62%) with evaluable karyotype had complex cytogenetics, and 7 of 11 patients (64%) with next-generation sequencing results had ≥ 1 adverse risk mutation as defined by AML ELN 2017 criteria. Three out of 11 tested patients (27%) had a *TP53* mutation. Nine patients were refractory to prior therapy, 3 patients had relapsed, and 4 patients had transformed from CML CP while on TKI therapy. Three of 12 patients tested prior to starting venetoclax plus the TKI combination harbored an *ABL1* kinase domain mutation including 1 mutation each of T315I, E255K, and E355G. Patients had re-

ceived a median of 5 prior lines of therapies (range 2–8), and CML-MBP patients had received a median of 2 prior TKI (range 1–3). Four of the 7 AML patients had received prior BCR-ABL1 TKI, including dasatinib (*n* = 3) and ponatinib (*n* = 1). One patient with Ph+ acute lymphoblastic leukemia had received prior venetoclax. A summary of treatment regimens is shown in Table 2. Nine patients (57%) received decitabine-based regimens, and the others received intensive chemotherapy-based regimens. Ten patients (63%) received ponatinib while the other patients received second-generation TKI.

Efficacy

Characteristics, treatment regimens, and outcomes of individual patients are shown in Table 3. Fifteen of the 16 patients were evaluable for response as 1 patient had early death due to pneumonia. The overall response rate (ORR) in 15 evaluable patients was 60%. One patient (7%) achieved complete response (CR), 6 (40%) achieved CR with incomplete hematologic recovery (CRi), 1 patient (7%) achieved a morphologic leukemia-free state (MLFS), and 1 patient (7%) had a partial response of extramedullary disease on positron emission tomography (PET)/computed tomography (CT). Another patient had hypoplastic bone marrow but did not meet the formal response criterion. The ORR in 7 Ph+ AML patients was 43% (3/7), and in 8 evaluable CML-MBP patients ORR

Table 3. Characteristics and outcomes of individual patients with advanced Philadelphia chromosome-positive (Ph+) myeloid leukemia treated with venetoclax and tyrosine kinase inhibitor (TKI)-based regimens

Pt	Age, years	Diagnoses	Prior chemo., n	Prior TKI, n	ABL mut.	Ph+ meta., % [†]	BCR-ABL PCR, % [‡]	Regimen	TKI	Response MRD by FCM	CyR	MRD (PCR), % [‡]	FU, mo	Relapse	Status
<i>Ph+-AML</i>															
1	21	Refractory AML	5	0	Neg	100	11.20	DEC 10 d	PON	CRi	CCyR	5.34	8.2	Y	SCT > Dead
2	47	Refractory AML	6	0	ND	5	7.05	CPX-351+ Gilteritinib	PON	MRD+ Hypocellular marrow	IS	2.5	2.7	N	SCT > Dead
3	73	Relapsed AML	3	2	Neg	0	0.03	DEC 5 d	PON	MLFS		0.02	1.4	NA	Dead
4	29	Refractory AML	5	0	ND	0	0.06	DEC 10 d	DAS	NR	NA	NA	1.8	NA	Dead
5	50	Refractory AML	6	1	Neg	20	8.20	CIA	PON	NR	NA	NA	2.4	NA	Dead
6	24	Refractory AML	4	0	ND	0	0.49	FIA	PON	NR	NA	NA	2.0	NA	Dead
7	70	Refractory AML	2	1	Neg	30	17.01	DEC 10 d + gilteritinib	PON	CR	IS	7.12	9.2	N	SCT > Alive
<i>CML-MBP</i>															
1	42	Refractory MBP	4	1	Neg	100	100	DEC 10 d	DAS	CRi	IS	100	5.9	N	Dead
2	60	Transformed CP	2	1	E355G	100	100	DEC 5 d	BOS	MRD+ CRi	PCyR	23.7	2.7	Unk	Dead
3	34	Transformed CP	4	2	T315I	100	100	CLIA2	PON	MRD- CRi	CCyR	0.23	2.8	Y	Alive
4	26	Relapsed MBP	5	2	Neg	100	8.00	DEC 10 d	PON	MRD- CRi	CCyR	0	12.3	Y	SCT > Dead
5	65	Relapsed MBP	6	3	Neg	86	100	DEC 5 d	NIL	ED	NA	NA	0.2	NA	Dead
6	30	Refractory MBP	8	3	ND	100	0.58	Cladribine + HiDAC	DAS	NR	NA	NA	13.7	NA	Dead
7	26	Refractory MBP	5	3	E255K	100	71.74	CIA	PON	NR	NA	NA	1.5	NA	Dead
8	61	Transformed CP	3	3	Neg	IS	9.42	CLIA2	PON	PR	NA	0	10.2	N	SCT > Alive
9	75	Transformed CP	2	2	Neg	93	48.16	DEC 10 d	DAS	MRD- CRi	CCyR	0.01	6.6	N	Alive

CML, chronic myeloid leukemia; MBP, myeloid blast phase; CP, chronic phase; DEC, decitabine; CLIA2, cladribine, idarubicin, cytarabine; HiDAC, high-dose cytarabine; CIA, clofarabine, idarubicin, cytarabine; PON, ponatinib; DAS, dasatinib; BOS, bosutinib; NIL, nilotinib; CR, complete remission; CRi, CR with incomplete hematologic recovery; PR, partial response of extramedullary disease on PET/CT; MRD, minimal residual disease; FCM, flow cytometry; ED, early death; NR, no response; NA, not applicable; Neg, negative; Unk, unknown, lost to follow-up; Y, yes; SCT, stem cell transplantation; FU, follow-up; mo, months; IS, insufficient sample; ND, not done; CyR, cytogenetic response; CCyR, complete CyR = 0% Ph+ metaphases; PCyR, partial CyR = 1–35% Ph+ metaphases.

[†] Metaphases harboring t(9;21), reported as a percentage of karyotyped metaphases.

[‡] BCR-ABL1 RT-PCR reported as the percentage of BCR-ABL1 to ABL1 transcripts.

was 75% (6/8). Median time to response in these 9 responding patients was 2.1 months (range 0.8–4.2) with a median of 2 cycles of therapy to best response (range 1–4). Four patients proceeded to subsequent allo-SCT.

MRD negativity tested by flow cytometry was achieved in 3 of 7 (43%) responding and evaluable patients. Median BCR-ABL1 PCR at response was 1.4% (range 0–23.7%) in 8 responding patients tested. Four patients achieved a complete cytogenetic response (CCyR) including 3 patients with CML-MBP and 1 patient with Ph+ AML. Among 3 patients with *TP53* mutation, 2 patients achieved a CRi and 1 patient achieved MLFS. Two patients with concomitant *FLT3*-ITD mutation treated with gilteritinib achieved CR with detectable MRD and hypocellular marrow, respectively.

Out of 10 patients who received ponatinib, 5 patients achieved CRi/MLFS, 1 patient achieved partial response on PET/CT, 1 patient had hypoplastic marrow with positive MRD, and 3 patients did not respond. Out of 6 patients who received second-generation TKI, 3 patients achieved CRi, 2 patients did not respond, and 1 patient had early death. Patients treated with ponatinib had a trend towards longer survival, with a median OS of 5.3 months compared to patients treated with second-generation TKI who had a median OS 3.6 months (hazard ratio 0.82, 95% confidence interval [CI] 0.25–2.68, $p = 0.11$). Compared to nonresponders, patients achieving CR/CRi had a higher number of baseline Ph+ metaphases (100 vs. 20%, $p = 0.06$) and baseline BCR-ABL1 PCR (48.16 vs. 0.58%, $p = 0.05$). The 2 patients in the AML cohort who

Fig. 1. Overall survival (OS) of patients with advanced Philadelphia chromosome-positive (Ph+) myeloid leukemias treated with venetoclax and BCR-ABL tyrosine kinase inhibitor-based regimens.

Fig. 2. Relapse-free survival (RFS) of patients with advanced Philadelphia chromosome-positive (Ph+) myeloid leukemias treated with venetoclax and BCR-ABL tyrosine kinase inhibitor-based regimens.

achieved CR/CRi were those who had the highest proportion of Ph+ metaphases and highest BCR-ABL1 level by PCR. Both of these responders had 30% of higher Ph+ metaphases on karyotype and had BCR-ABL1 PCR >10%.

Of patients who received decitabine-based regimens, 7 patients achieved CRi/MLFS, 1 patient did not respond, and 1 patient had early death. Out of 7 patients who received intensive chemotherapy-based regimens, 4 patients did not respond, 1 patient achieved CRi, 1 patient achieved partial response on PET/CT, and 1 patient had hypocellular marrow. Decitabine-based regimens yielded higher odds of achieving CRi/MLFS compared to intensive chemotherapy-based regimens (odds ratio 21.00, 95% CI 1.50–293.25, $p = 0.02$).

At a median follow-up of 14 months, 4 patients are alive, and 2 patients continue on therapy. Out of these 4

surviving patients, 3 patients received ponatinib, and 2 patients had undergone allo-SCT. There was 1 death within 30 days in a patient treated with a decitabine-based regimen due to pneumonia. There were no early deaths in patients treated with intensive chemotherapy-based regimens. Median OS for all patients was 3.6 months, for patients with CML-MBP it was 10.9 months, and for patients with Ph+ AML it was 2.0 months (Fig. 1). Median RFS for patients with CML-MBP was 3.9 months and for patients with Ph+ AML 3.6 months (Fig. 2). Patients treated with decitabine-based regimens had a median OS of 4.4 months, and for those receiving intensive chemotherapy-based regimens it was 2.4 months (hazard ratio 0.73, 95% CI 0.24–2.26, $p = 0.56$). Reasons for treatment discontinuation in 14 patients included no response in 5 patients, SCT in 4 patients, relapse in 2 patients, loss to follow-up in 1 patient, sepsis in 1 patient, and early death in 1 patient.

Discussion

In this retrospective study, we showed feasibility and activity of venetoclax and TKI-based regimens in relapsed/refractory Ph+ AML and CML-MBP patients. This is the first report of clinical activity of this rational combination in a retrospective cohort of patients. In this heavily pretreated adverse risk group of patients with advanced Ph+ myeloid leukemia, venetoclax and TKI-based regimens showed an ORR of 60% and median OS of 2 months in the Ph+ AML group and of 10.9 months in the CML-MBP group. The median OS of 10.9 months in this pretreated CML-MBP group was comparable to a previously reported median OS of 9–12 months in a cohort of patients with CML-MBP which included newly diagnosed and TKI-naïve patients, both of which confer better outcomes compared to treated CML-MBP [2]. In contrast, within our cohort of patients with CML-MBP, the median number of prior TKI was 2 (range 1–3).

Dasatinib has shown single-agent activity in CML-MBP; however, the venetoclax-TKI combination may be better than single-agent dasatinib. With necessary precautions for cross-study comparisons, this combination of venetoclax with TKI-based regimens offered a median OS of 10.9 months in patients with CML-MBP compared to 7.9 months with single-agent dasatinib in a more favorable risk population [25]. Patients with CML-MBP in our cohort were more heavily pretreated and had received a median of 2 prior TKI and included relapsed/refractory patients while, in comparison, the dasatinib START-B trial only included patients who were imatinib resistant or intolerant.

Ponatinib has shown favorable responses as single agent or in combination with nonchemotherapeutic agents in advanced Ph+ leukemias and relapsed/refractory pre-B acute lymphoblastic leukemia [20, 21]. In our current report, 3 of the 4 surviving patients received ponatinib. We had previously reported that ponatinib showed the highest major hematologic and major molecular response rates of 67 and 27%, respectively, compared to other TKI in patients with CML-BP [2]. Furthermore, preclinical studies have shown that ponatinib synergizes with venetoclax in Ph+ acute lymphoblastic leukemia samples through induction of LYN-mediated pro-apoptotic BIM and decreasing anti-apoptotic MCL1, and potentially abrogating venetoclax resistance [22]. Hence, taken together, these data provide a strong rationale for combining venetoclax with ponatinib in this population. Decitabine-based regimens showed significantly higher response rates than intensive chemotherapy-based regimens, but OS was comparable. Given how venetoclax synergizes with both decitabine and intensive chemotherapy, either of these backbones may be a reasonable option for such patients depending on older versus younger age, and “fitness” for intensive therapy.

Despite limited numbers, there was a trend towards higher clonal burden of Ph+ metaphases and higher baseline BCR-ABL1 PCR among patients who achieved CR/CRi compared to nonresponders. The only 2 patients in the AML cohort who achieved CR/CRi had 30% or higher Ph+ metaphases and BCR-ABL1 PCR of 10% or higher. Response rates also appeared higher in CML-MBP, which is more strongly driven by BCR-ABL1 signaling than is Ph+ AML, which often only contains a subclonal BCR-ABL1-driven population. This suggests that venetoclax and TKI-based combinations may be particularly useful in patients where the Ph+ clone is a dominant clone without other major coexisting drivers. We speculate that minor Ph subclones may develop in advanced leukemia due to chromosomal instability, and TKI addition may not offer additional benefit in such cases when BCR-ABL is not the main driver.

This was a retrospective study with all inherent limitations thereof. We could not assess the impact of venetoclax addition compared to TKI alone or with chemotherapy. The heterogeneous patient population and treatment regimens limit broad-reaching conclusions from these data. Given the retrospective nature of this study, we could not provide assessment of treatment-emergent adverse events. Hence, we have opened a clinical trial to prospectively evaluate this combination of decitabine, venetoclax, and ponatinib in Ph+ AML and CML-MBP (NCT04188405).

Conclusion

Venetoclax and TKI-based combination regimens are a feasible approach to treat advanced Ph+ myeloid leukemias. Patients with CML-MBP may stand to benefit particularly from this combination due to BCR-ABL1 being the predominant driver. Previously published preclinical data of synergy and clinical activity reported here warrant further evaluation of such combinations in these poor-risk populations.

Statement of Ethics

This work complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Patients signed a written informed consent before receiving the treatments described here, but requirement of informed consent for this study was waived due to the retrospective chart review nature of this study. This study was approved by the Institutional Review Board and received ethics committee clearance.

Disclosure Statement

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