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ORIGINAL ARTICLE

Venetoclax in patients with acute myeloid leukemia refractory to hypomethylating agents—a multicenter historical prospective study

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Abstract

Patients with acute myeloid leukemia (AML) who progress after exposure to hypomethylating agents (HMA) have a dismal prognosis. We hypothesized that the addition of venetoclax, a BCL-2 inhibitor, to AML patients who previously failed HMA might overcome resistance. Adult patients (≥ 18 years) with AML were eligible if leukemia relapsed after, or was refractory to HMA. In general, in addition to venetoclax, patients continued HMA or other low-intensity therapies. Patients who previously underwent allogeneic hematopoietic cell transplantation (HCT) were also eligible. Data were analyzed in November 2018. Twenty-three patients were treated between October 2016 and October 2018 and were eligible for this study. Median age was 76 years and 6 patients had leukemia that relapsed post allogeneic HCT. None of the patients experienced tumor lysis syndrome and toxicities were as expected and manageable. Febrile neutropenia was the most common toxicity (78% of patients). Median hospitalization time was 13 days. Forty-three percent of the patients achieved CR/CRi. Overall survival (OS) was 74% at 6 months and median OS in patients who achieved remission was 10.8 months. Higher number of blasts in both bone marrow and peripheral blood was associated with lower chances of CR, while higher WBC, LDH, and bone marrow or peripheral blasts were associated with increased mortality rate. The addition of venetoclax to patients with HMA-refractory AML may result in a substantial anti-leukemic activity, specifically in those achieving complete remission. This should be further tested in a well-designed prospective trial.

Keywords Venetoclax · Acute myeloid leukemia · Refractory · Hypomethylating agents

Introduction

Acute myeloid leukemia (AML) is primarily a disease of the elderly for which prognosis remains poor [1, 2]. In those patients who are not eligible for induction chemotherapy, hypomethylating agents (HMA), i.e., decitabine or azacytidine, have been shown to be beneficial [1, 3, 4]. While objective response to HMA occurs in only 30–40% of the patients, the median time of response is approximately 12 months [5]. In those patients who are primary refractory to or have progressed after given HMA, and are not eligible to hematopoietic cell transplantation, the prognosis is dismal [6].

Venetoclax is a BCL-2 inhibitor that has shown a remarkable activity in patients with AML and has been recently approved by the regulatory authorities in the USA and in some European countries as first-line treatment when combined with either low-dose cytarabine or HMA [7]. However, a significant portion of patients with AML have already been exposed to HMA at the time of their leukemia occurrence, either as part of the first-line treatment for AML or when progressing from an antecedent hematologic disease.

In this national historical prospective study, we focused on this group of patients, with HMA-refractory AML, and hypothesized that the addition of venetoclax may be beneficial.

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Methods

Patients

The electronic charts of AML patients diagnosed between January 2016 and January 2018 in 3 centers were systematically reviewed.

Eligibility criteria for this analysis included patients with de novo or secondary leukemia (except for acute promyelocytic leukemia) who received HMA (either decitabine or azacytidine) at any time during their course of therapy and either failed to achieve remission within 4 cycles, had a response and later progressed while still receiving HMA, or had a refractory disease during HMA therapy after at least 2 cycles of HMA. Patients who received HMA for progression after allogeneic hematopoietic cell transplantation (HCT) and did not respond were also included. All patients were given venetoclax.

Baseline cytogenetic analysis and molecular data were collected at diagnosis. AML type was classified according to the WHO 2016 classification and disease risk was scored according to the European leukemia network (ELN) 2017 criteria [8].

The protocol was approved by the Institutional Review Board in accordance with the Declaration of Helsinki.

Treatment schedules and supportive care

Prior HMA included either I.V decitabine at a dose of 20 mg/msq for 5 consecutive days every 28 days, or S.C azacytidine at a dose ranging between 37.5 and 75 mg/msq given for 5–7 consecutive days every 28 days.

Venetoclax was started at a daily dose of 100 mg and ramped up every 2 days to a maximal dose of 400 mg. Cycle 1 of venetocolax was always given in addition to HMA (azacitidine, $n = 16$ or decitabine, $n = 4$) or low-dose cytarabine ($n = 3$). Dose reduction of either HMA/low-dose cytarabine or venetecolax was optional in subsequent cycles.

Hospitalization was not required and most patients were given the protocol as outpatients, with daily assessment of blood count, electrolytes, and renal function.

Supportive care was given according to the physician's discretion and included ciprofloxacin (500 mg twice daily), fluconazole (400 mg daily), and G-CSF (5 μg/kg/day). In patients that were given azoles, the maximal dose of venetoclax was reduced to 200 mg daily.

Patients treated for a relapse post allogeneic HCT were basically off immune-suppression prior to the initiation of the protocol. All patients were given in addition to venetoclax, donor lymphocyte infusion every 4–6 weeks. Dose of infusion was escalated from 5×10^7 CD3-positive cells/kg to 10^8 CD3-positive cells/kg in cases of a sibling donor, and from 10^7 CD3-positive cells/kg to 5×10^7 CD3-positive cells/kg in cases of unrelated donors. In patients who developed persistent neutropenia (neutrophil count below 500/μL), the HMA dose was either reduced or completely eliminated.

Toxicity assessment

Patients were evaluated for tumor lysis syndrome and hematologic toxicity at least once a week. In addition, patients were also evaluated for the incidence of significant major bleeding (any gastrointestinal or life-threatening bleeding), the number of clinical and microbiology documented infections (CDI, MDI, respectively), and the number and the total days of hospitalization. Toxicity profile was graded according to CTCAE v4.0. Acute and chronic GVHD were assessed according to the MAGIC and the NIH criteria, respectively.

Efficacy assessment

The primary endpoint of this study was overall survival (OS), defined as the time from initiation of first course of venetoclax to last follow-up or death. Refractory disease was defined as a stable or an increase in the number of marrow blast cells after completion of second course of treatment, and relapse as the reappearance of blasts after the achievement of remission. Secondary end points were the rate of CR and CRi and toxicity profile of the regimen. CR/CRi rates were evaluated according to the standard criteria for hematological CR [8]. Bone marrow aspiration was performed according to physician's discretion and center's policy, but in general was performed between the 2nd and the 4th cycles of treatment. Only patients that underwent at least one bone marrow aspiration for the evaluation of response were included in the analysis of response assessment.

Statistical analysis

Data were analyzed as of November 2018. Overall survival was estimated using the Kaplan-Meier method. Death was treated as a competing risk in the analyses of relapse/progression. Cox regression was used for univariate analyses of risk factors for all time-to-event end points. For each analysis, hazard ratios (HR) and 95% confidence intervals (95% CI) are given together with p values for comparisons with the reference category. All p values are derived from likelihood ratio statistics and are two sided. Data were analyzed using the SPSS version 24.0.

Results

Patients

Between October 2016 and October 2018, we treated 23 patients with AML who were refractory to HMA (azacitidine,

$n = 21$; decitabine, $n = 2$). Table 1 depicts patients' characteristics. Ten patients (44%) had myelodysplasia-related changes and 5 patients (22%) had therapy-related AML. Majority of patients had intermediate-risk ($n = 11$, 48%) or high-risk ($n = 10$, 43%) ELN score. The median number of HMA courses prior to venetoclax was 6 (range, 2–25). In 18 patients, HMA were the last line of therapy given before venetoclax was added while in 5 patients, HMA were given as part of a more distant line of therapy and were reused with venetoclax as part of a salvage attempt. Median age was 76 (range, 41–92) years and median follow-up was 5.3 (range, 2.3–16.1) months. Six patients (26%) underwent allogeneic HCT with documented disease progression prior to venetoclax. In addition to venetoclax, patients were treated with low-dose cytarabine ($n = 4$), azacytidine ($n = 13$), azacytidine and DLI ($n = 5$), and only DLI ($n = 1$).

Administration of venetoclax and documented side effects

Most patients (21 of 23) were treated as outpatients with every other day visit at the outpatient clinic. Ramp-up protocol was mainly based on rapid doubling of the dose (every 1–2 days); thus, by day 6, all patients have been treated with the maximal dose. None of the patients experienced laboratory or clinical tumor lysis.

Patients were given different final doses of venetoclax (100 mg, $n = 3$; 200 mg, $n = 9$; 400 mg, $n = 11$). After

Table 1 Patient characteristics

Domain	All cohort ($n = 23$)
Sex (female, %)	9, 39%
Age in years (median, range)	76, 41–92
AML type (WHO 2016) (*n*, %)*	
AML with recurrent genetic abnormalities	Mutated NPM1 (1, 4%), inv(16) (1, 4%), t(9;11) (1, 4%)
AML with myelodysplasia-related changes	10, 44%
Therapy-related AML	5, 22%
AML, NOS	5, 22%
ELN 2017 risk group (*n*, %)*	
Favorable risk	2, 9%
Intermediate risk	11, 48%
High risk	10, 43%
Cytogenetics	
Normal karyotype	11, 48%
-7q	3, 13%
Inv 16	1, 0.04%
t(4:12)(q1.2, 12 p1.3)	1, 0.04%
t(11q23)	1, 0.04%
Complex karyotype	6, 26%
FLT3-ITD	3, 13%
Number of courses of HMA prior to venetocolax (median, range)	6, 2–25
Number lines of previous chemotherapy (median, range)	2, 1–5
Prior allogeneic HCT (*n*, %)	6, 26%
WBC at onset of venetoclax (median, range) $10^3/\mu L$	3.46, 1.7–25.2
Blasts in marrow at onset of venetoclax (%, range)	30%, 10%–80%
Patients with circulating blasts (*n*, %)	10, 44%
LDH at onset of venetoclax (median, range) U/L	454, 243–5343
Concomitant therapy	
Low-dose cytarabine	3, 13%
Azacitidine	16, 70%
Decitabine	4, 17%

*At diagnosis

AML, acute myeloid leukemia, *WHO*, World Health Organization, *ELN*, European Leukemia Net, *NOS*, not otherwise specified, *HMA*, hypomethylating agent, *HCT*, hematopoietic cell transplantation

adjustment for concomitant medications (mainly azoles), only 2 patients were given less than the recommended 400-mg dose (both received 200 mg). In the case of hematologic toxicity, the dose was decreased or withheld, or the HMA was discontinued. Of note, in 7 out of the 11 (64%) patients that survived more than 4 months after the initiation of venetoclax, the dose of venetoclax was reduced and maintained at the same dose thereafter.

Eighteen patients (78%) developed at least one infectious episode. None experienced a major bleeding episode. Sixteen patients (70%) were admitted at least once during treatment and median duration of hospitalization among all patients was 13 (range, 0–52) days throughout the study period.

Response to venetoclax

Ten patients (43%) achieved CR ($n = 5$)/CRi ($n = 5$). Median time to CR/CRi was 62 (range, 28–102) days. Among them, only 3 patients with a molecular marker were evaluated for minimal residual disease (MRD). Of those, 1 patient with an NPM1-mut AML achieved a negative MRD state.

For the subgroup of patients that relapsed after allogeneic HCT ($n = 6$), CR was achieved in 4 patients (67%) and the median OS was 12.4 months. Four patients were given DLI in addition to venetoclax. Of them, one patient developed overlap GVHD, 3 weeks after the infusion and continued venetoclax treatment for 6 additional months. One patient proceeded to a second allogeneic HCT. This patient is currently alive in continued CR, 16 months after the original relapse.

The following factors were evaluated as predictors for response—age (continuous variable), LDH (continuous variable), percentage of blasts in bone marrow (continuous variable), percentage of circulatory blasts (continuous variable), cytogenetics risk group, number of treatment lines prior to venetoclax, number of courses of HMA prior to venetocalx, prior HCT, and the dose of venetoclax. Only the percentage of bone marrow blasts and circulatory blasts was found to predict remission inversely (OR 0.45, 95% CI 0.23–0.51, $p = .041$ and OR 0.51, 95% CI 0.39–0.65, $p = .009$, respectively). The dose of venetocalx did not correlate with the achievement of remission state.

Survival analyses

At data analysis, there were 17 deaths and 6 patients are still alive. The incidences of survival at 6 and 12 months were 74% and 25%, respectively. Median OS was 5.6 (95% 4.9–6.2) months, Fig. 1a. OS in patients who undergone allogeneic HCT was 6.5 months (95% 0–17.3), with no statistical difference when compared with patients who did not undergo HCT ($p = .96$, log-rank test). In the group of patients who achieved CR ($n = 10$), the median OS was better when compared with the group of patients who did not achieve CR ($n = 13$) (10.8 months, 95% CI 6.2–15.4 vs. 2.8 months, 95% CI 0.9–4.8, $p < .001$) and the 6-month projected OS was 80% vs. 12% (Fig. 1b**)**. Median OS for patients achieving CR was longer when compared with patients achieving CRi (12.5 months, 95% CI 9.7–15.3 vs. 5.6 months, 95% CI 5.4–5.8, $p = .07$).

The following factors were evaluated as predictors for mortality: age (continuous variable), cytogenetics risk group, ELN risk stratification, WHO classification, LDH (continuous variable), percentage of blasts in bone marrow (continuous variable), percentage of circulatory blasts (continuous variable), number of treatment lines prior to venetoclax, number of courses of HMA prior to venetocalx, prior HCT, and the maximal given dose of venetoclax.

WBC count prior to the initiation of venetoclax, high LDH levels, and a higher percentage of blasts in both bone marrow and peripheral blood were all associated with increased mortality rate (Table 2).

Discussion

HMA failure in patients with AML defines a particular high-risk group of patients with dismal outcome and limited salvage options [9–11]. We showed in this difficult-to-treat patient cohort that the addition of venetoclax to low-intensity therapy resulted in significant response rates with a CR/CRi rate of 42% with a median time to response of less than 2 months. We were also able to identify factors that are associated with response and survival, most of which are correlated with leukemia burden. The toxicity was manageable, expected, and mainly related to infectious complications. The dose intensity of venetoclax was maintained in most patients throughout the treatment period.

In the upfront setting, venetoclax in combination with low-intensity therapies such as low-dose cytarabine and HMA demonstrated significant activity in older patients and in those not eligible for intensive chemotherapy [7]. In this group of patients, the overall CR/CRi rate was 74% and the median time to response was within 2 cycles of therapy [7, 12]. Venetoclax in combination with low-dose cytarabine was also shown to be safe and active with a CR/CRi rate of 54% [13]. The results of large randomized, controlled phase 3 trials comparing venetoclax or placebo with either azacitidine (NCT02993523) or low-dose cytarabine (NCT03069352) are eagerly awaited for, but several regulatory agencies including the Food and Drug Administration (FDA) have already approved these combinations for the first-line setting in patient ineligible for intensive induction based on comorbidity or age (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm626499.htm, accessed 01/07/2019).

The safety and efficacy of low-intensity therapy in combination with venetoclax in the context of relapsed or refractory

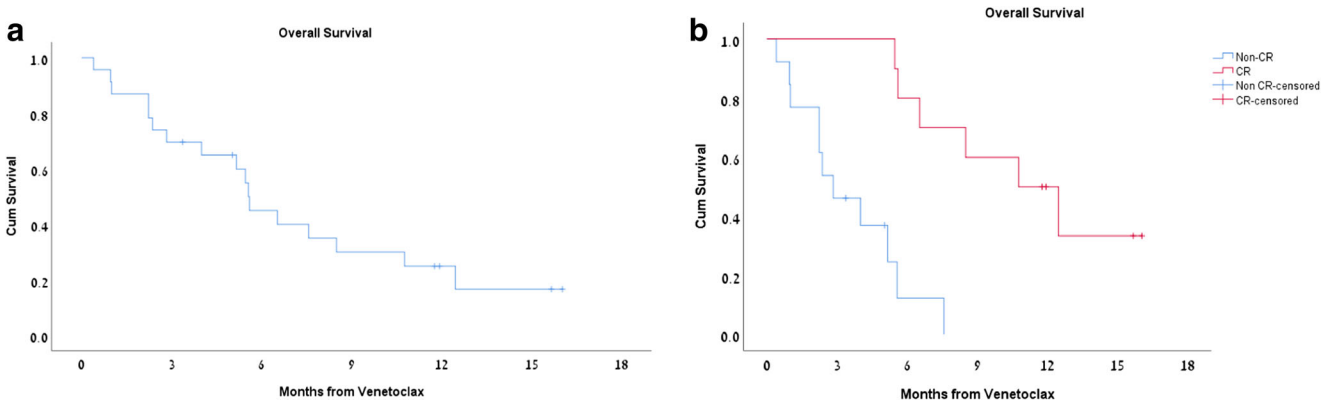

Fig. 1 Overall survival of **a** all cohort; **b** stratification according to CR/CRi vs. non-CR/CRi

(R/R) AML are less clear. As with most therapies in advanced AML, the reported response rates for venetoclax-based combination therapies are lower than those reported in the upfront setting. Pollyea et al. demonstrated that the combination of azacytidine and venetoclax in untreated patients with AML targets leukemia stem cells by disrupting crucial energy metabolism pathways and decreasing oxidative phosphorylation, an effect that was lost in the R/R setting [12, 14].

DiNardo et al. reported on 43 patients with R/R AML and related myeloid malignancies that received venetoclax in combination with low-intensity therapies. This cohort included older (median age 68 years) and heavily pretreated patients (median number of prior treatment lines = 3), and most patients (77%) had previous exposure to HMA. The overall response in this cohort was rather low (21%) with 12% of the patients attaining a CR/CRi [15]. Better overall responses were reported by Aldoss et al. who reported on 33 adult patients with R/R AML (median age 62 years), 60% of whom had previous exposure to HMA. The overall response rate was 64% and best response was achieved after a median of 2 cycles [16].

Table 2 Cox regression analyses of factors associated with mortality

Datum	HR	95% CI	*p*
Age	0.98	0.95–1.02	0.45
ELN risk stratification*	1.21	0.15–99	0.86
High-risk cytogenetics	1.43	0.8–2.1	0.16
WHO classification**	1.3	0.4–21.3	0.725
Previous *n* lines	2.3	0.27–20.4	0.45
Previous HCT	1.03	0.37–20.4	0.96
WBC at relapse	*1.58*	*1.1–1.82*	*0.046*
% blasts in marrow	*1.26*	*1–1.53*	*0.050*
LDH	*1.31*	*1.13–1.52*	*0.027*
% blasts in peripheral blood	*1.29*	*1.1–1.75*	*0.09*
Maximal dose of venetoclax	1.1	0.9–1.3	0.64

*High risk vs. low/intermediate risk

**AML with myelodysplasia-related features vs. other

ELN, European Leukemia Net; *WHO*, World Health Organization; *HCT*, hematopoietic cell transplantation

Our results are similar, showing a CR/CRi of 43%, even though the patients in our cohort were older (median age 76 years), with one-quarter of patients treated for post-transplant relapse.

The use of venetoclax in the post-transplantation relapse setting is increasingly described [17, 18]. Among the 6 patients in our study, CR/CRi was achieved in 67% of the patients. The combination of DLI with venetoclax seems to be safe and potentially effective and may represent an attractive therapeutic approach in this setting. Whether venetoclax affects graft-versus-leukemia properties needs to be proven and further insights into the pathobiology of this potential effect are needed.

Median OS was 10.8 months for the responding patients in our cohort, yet 1-year OS was 25% which is inferior to the 53% reported by Aldoss et al. This was probably because of the older age in our cohort and the fact all of our patients were failures of previous HMA treatment (as compared with only 61% in the cohort report by Aldoss et al.) [16]. Febrile neutropenia was common in our cohort, similar to the other studies including patients with refractory AML, yet none of our patients developed TLS and median hospitalization period during the study period was 13 days, suggesting that this treatment does not significantly compromise patients' quality of life. The relative safe profile and the fact that patients can remain in the outpatient setting should be considered when discussing with these patients treatment goals and options.

Our study has several limitations. The cohort of patients analyzed is relatively small and rather heterogeneous. Nonetheless, this is one of the first reports on the use of venetoclax as a sensitizing agent to salvage patients with AML that failed HMA, a common clinical scenario. Furthermore, the combination of DLI with venetoclax is a novel salvage approach and might have potential utility in the treatment of the high-risk post-transplant relapse setting.

To conclude, this study shows the feasibility of adding venetoclax to patients relapsing post-HMA treatment.

Validation of these results in a prospective trial and addition of other potential target therapies are needed.

Compliance with ethical standards

Conflict of interest RR and OW served on an advisory board for AbbVie. OA, TZ, RG, PR, YB, and IR declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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