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Letter to the Editor

Venetoclax in combination with low dose Cytarabine and Actinomycin D for primary refractory acute myeloid leukemia patients failing intensive chemotherapy

1. Introduction

Despite evolving molecular risk-stratified treatment strategies, intensive cytotoxic induction remains the cornerstone in the treatment of fit acute myeloid leukemia (AML) patients. Unfortunately, 10–40 % of patients fail to achieve complete remission (CR) after standard chemotherapy regimens and are diagnosed with primary refractory (PR) AML facing a very poor prognosis [1]. To date, the only potentially effective treatment for PR AML patients is allogeneic hematopoietic stem cell transplantation (alloSCT), yet optimal bridging strategies remain an unmet need [2–5].

2. Materials and methods

We performed a retrospective single-center study of patients diagnosed with PR AML who were treated with Venetoclax, low-dose Cytarabine and Actinomycin D (ACTIVE) salvage therapy during 2018–2021 at Vilnius University Hospital Santaros Klinikos in Vilnius, Lithuania. Informed consent was obtained from all patients. The study protocol was approved by the local institutional review committee and corresponded to the Declaration of Helsinki.

The primary endpoint was overall response rate (ORR) which included complete remission (CR), complete remission with incomplete platelet recovery (CRp) and morphological leukemia free state (MLFS). The secondary endpoints were all-cause mortality on days 30 and 60 as well as relapse free survival (RFS) and overall survival (OS), as defined by 2017 European Leukemia Network criteria (ELN 2017). We assessed hematological recovery by median times to absolute neutrophil count (ANC) $>1 \times 10^9$/l and platelets $>100 \times 10^9$/l. In addition, we evaluated grade 4−5 non-hematological adverse events (non-HAEs) during treatment. Patients who proceeded to alloSCT during aplasia with bone marrow clearance of <5 % were considered to have achieved MLFS since their hematological recovery could not be evaluated. Early bone marrow (BM) assessments (on day 3) were performed in the setting of a different clinical trial. Data cut-off date was June-04, 2021.

3. Results

The investigational ACTIVE regimen consisted of Venetoclax600 mg p/o on days 1–28, Cytarabine 20 mg/m^2 s/c on days 1–10, Actinomycin D 12.5 μg/kg via short i/v infusion on days 1, 2 and 3 for patients < 65 years or on days 1 and 2 for patients ≥65 years. Indications for stopping Venetoclax before day 28 were life-threatening infections or faster hematological recovery in responders. In addition to the ACTIVE treatment regimen, Dasatinib, Trametinib and Gilteritinib were administered in three patients with targetable *BCR-ABL1*, *NRAS* and *FLT3* mutations. Responding patients proceeded to alloSCT either in the period of aplasia (sequential approach) or after hematological recovery upon finishing ACTIVE therapy.

A total of 15 patients (median age 66; range 35−74) were included in the analysis. Nine patients (60 %) presented with secondary AML. The majority of patients (80 %; 12/15) were classified as adverse risk group according to ELN 2017. Primary refractory disease was diagnosed after failing either only 7 + 3 induction (27 %; 4/15) or high dose cytarabine based regimens (73 %; 11/15). Twelve patients (80 %) had received 1 cycle of investigational ACTIVE induction, whereas the remaining 3 (20 %) were treated with two cycles. Detailed characteristics are summarized in Table 1.

The responses were evaluated in 14 patients, as one patient died during treatment. The ORR and CR/CRp rates following ACTIVE were 64 % (9/14) and 36 % (5/14), respectively. Forty-four percent (4/9) of responders successfully achieved minimal residual disease (MRD) negativity (multiparameter flow cytometry [MFC] <0.1 %). Overall, 57 % (8/14) of patients proceeded to alloSCT after ACTIVE treatment (3 patients in aplasia after achieving MLFS). The median time to ANC and platelets recovery was 22 (18–27) and 23 (20–24) days, respectively, among CR/CRp patients. The median RFS and OS were 4.5 and 5.7 months, respectively (Fig. 1). The median OS of 18.1 months was observed in patients achieving CR/CRp.

Five patients (33 %) experienced grade 4−5 non-HAEs due to ACTIVE therapy. Day 30 and day 60 mortalities were 20 % (3/15) and 27 % (4/15), respectively. One early death was caused by E. Coli sepsis during aplasia period (response to treatment could not be evaluated), another was due to intracranial haemorrhage (response was evaluated on day 19, and MLFS with MRD negativity was confirmed) and the third early death was caused by pneumonia and flu (response was evaluated on day 20, and 8 % of residual blasts in the BM confirmed the residual disease).

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Table 1
Baseline characteristics of PR AML patients treated with ACTIVE.

	n/N (%)
Baseline characteristics	
Male	8/15 (53 %)
Age (median, range)	66 (35–74)
ECOG (median)	1 (0–3)
ECOG 0	1/15 (7 %)
ECOG 1	8/15 (53 %)
ECOG 2	4/15 (27 %)
ECOG 3	2/15 (13 %)
Newly diagnosed AML	6/15 (40 %)
Secondary AML	9/15 (60 %)
Therapy related AML	2/9 (22 %)
AML post MDS	4/9 (44 %)
AML post MPN	3/9 (33 %)
Adverse karyotype	6/15 (40 %)
ELN2017 adverse risk group	12/15 (80 %)
FLT3 mutation	4/15 (27 %)
IDH1/2 mutation	5/15 (33 %)
Number of previous treatment lines (median, range)	2 (1–5)
Previous 7 + 3 only	4/15 (27 %)
Previous HDAraC regimens (FLAG-Ida, HAM)	11/15 (73 %)
Response evaluation	
ORR	9/14 (64 %)
MRD negativity (MFC, <0.1 %)	4/9 (44 %)
CR + CRp rate	5/14 (36 %)
CR	4/14 (29 %)
CRp	1/14 (7 %)
MLFS	1/14 (7 %)
MLFS, sequential alloSCT in aplasia	3/14 (21 %)
Proceeded to alloSCT	8/14 (57 %)
Toxicity	
D30 mortality	3/15 (20 %)
D60 mortality	4/15 (27 %)
Grade 4–5 non haematological AEs	5/15 (33 %)

AML response criteria were defined according to ELN2017: CR was diagnosed in the setting of bone marrow blasts <5%, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease, ANC ≥ 1.0 × 109/L (1000/μL), platelet count ≥100 × 109/L (100 000/μL), whereas MRD could be positive or unknown. To diagnose CRp, all CR criteria had to be met except for residual thrombocytopenia (<100 × 109/L [100 000/μL]). MLFS was confirmed in the setting of bone marrow blasts <5%, absence of blasts with Auer rods, absence of extramedullary disease, hematologic recovery was not required.
Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; ELN, European Leukemia Network; HDAraC, high dose Cytarabine; FLAG-Ida, Fludarabine, Cytarabine, granulocyte colony-stimulating factor, and Idarubicin; HAM, high dose Cytarabine and Mitoxantrone; ORR, overall response rate; CR, complete remission; CRp, complete remission with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; MFC, multiparameter flow cytometry; AlloSCT, allogeneic hematopoietic stem cell transplantation; D30 and D60 mortality, mortality within the first 30 or 60 days from the initiation of ACTIVE treatment; AEs, adverse events.

4. Discussion

The optimal curative PR AML treatment strategies are mostly directed to bridge patients to alloSCT [4–6]. The fludarabine, cytarabine, amsacrine (FLAMSA) or clofarabine + cytarabine aplasia-inducing salvage regimens followed by sequential reduced intensity conditioning (RIC) have been introduced as effective strategies among PR AML patients [7,8]. Recently, a different chemo-free approach with Flotetuzumab, an investigational bispecific antibody-based molecule targeting CD3ε and CD123 antigens, demonstrated an ORR of 30 % and a median OS of 10.2 months in the settings of early relapsed or PR AML [9].

The BCL-2 inhibitor Venetoclax-based combinations show potential in different AML settings but the data on its efficacy in PR AML remains scarce. Low intensity Venetoclax + hypomethylating agents/low dose Cytarabine regimens showed highly variable responses in R/R AML with the CR/CRi rate reaching 32.8 % [10]. A recent study by DiNardo et al. reported an ORR 56 % among refractory AML patients who were treated with Venetoclax in combination with FLAG-Ida [11]. Of all relapsed or refractory AML patients, 46 % proceeded to alloSCT, however, the exact number of PR patients was not specified.

Herein, we present the results of PR AML patients who were treated with Venetoclax, low-dose Cytarabine and Actinomycin D triplet in our center in 2018–2021. The addition of Actinomycin D to the backbone of Venetoclax and low-dose Cytarabine is based on its potential inhibition of the MCL-1 protein which plays an important role in resistance to BCL-2 inhibitors [12]. Recent findings by Wu et al. demonstrate synergism between Actinomycin D and Venetoclax and therefore support efficacy of our triplet [13]. Moreover, we recently reported the superiority of ACTIVE triplet over the standard FLAG-IDA regimen for R/R AML patients after alloSCT in terms of cumulative CR/CRp rate (70 % vs 34 %, respectively) and OS (13.1 vs. 5.1 months, respectively) [14].

Our presented cohort consisted of prognostically unfavorable patients, as most were elderly, 60 % had high-risk secondary AML and 40 % had an Eastern Cooperative Oncology Group (ECOG) performance status 2 or 3. Most of the patients (11/15, 73 %) were diagnosed with PR AML after failing

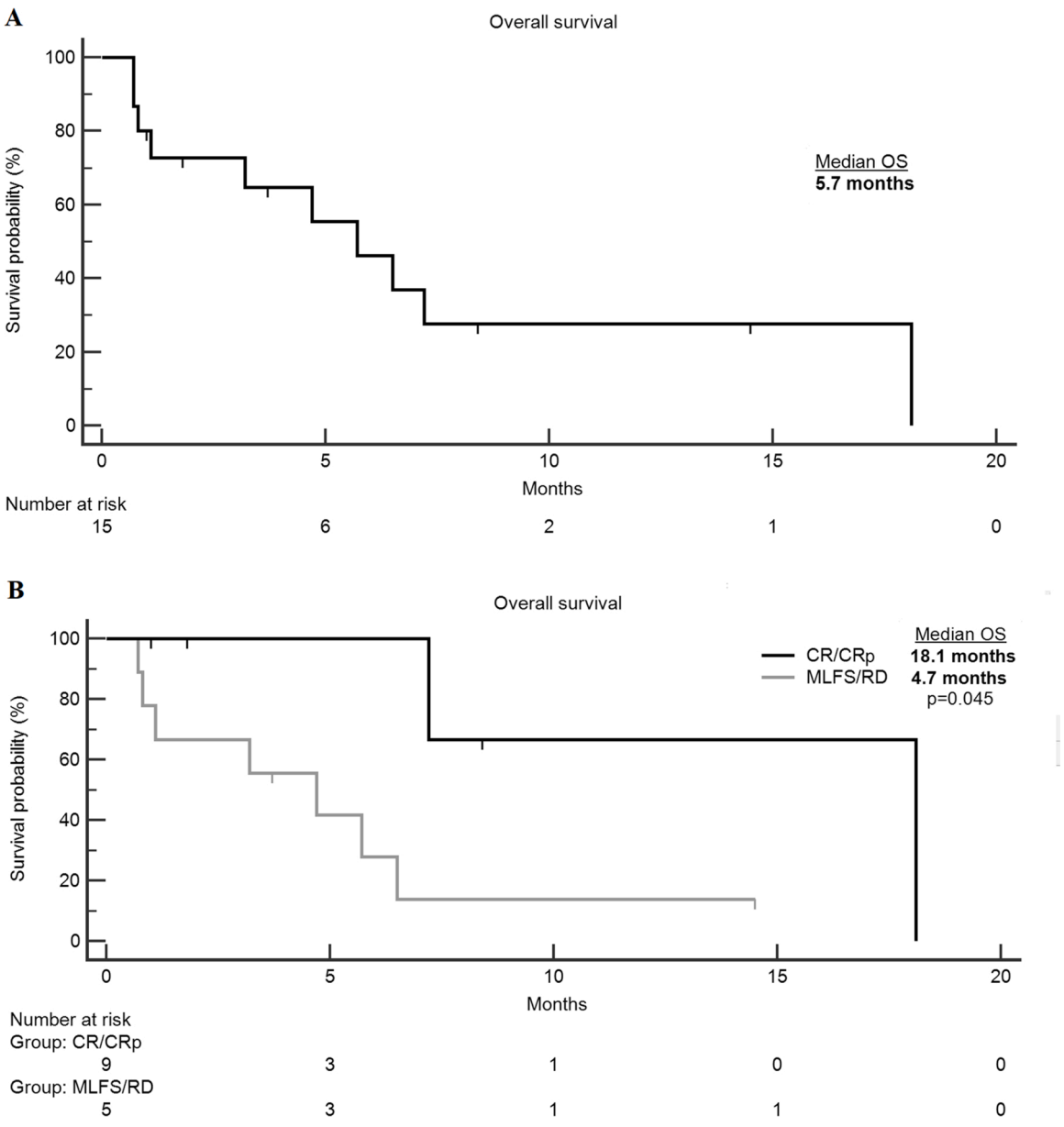

Fig. 1. A: Overall survival of all 15 PR AML patients.
B: Overall survival of PR AML patients achieving CR/CRp vs non responders/MLFS.

high dose Cytarabine based regimens, while the minority were ineligible for further intensive treatment after failing 7 + 3 induction and received Venetoclax-based treatment as salvage therapy. The investigational ACTIVE treatment regimen helped to obtain a high ORR (64 %), 44 % of responders became MRD negative and as many as 57 % proceeded to alloSCT. The less encouraging CR/CRp rate of 36 % may be somewhat underestimated as several patients proceeded to alloSCT in aplasia and were considered as responders with MLFS since their hematological recovery after ACTIVE therapy was unevaluable. Nevertheless, remission duration and OS were poor, emphasizing the importance of post-transplant maintenance strategy for relapse prevention in these very high-risk patients. Early mortality following ACTIVE treatment was due to infections and bleeding events in the setting of myelosuppression and a poor ECOG performance status, as both patients with ECOG performance status 3 died during the first 30 days of ACTIVE therapy.

Of note, ACTIVE regimen induced very early responses (day 3 bone marrow blast count <5 %) in three *IDH2* mutated patients. This finding allowed us to suspend Venetoclax earlier and start administration of the granulocyte colony-stimulating factor to successfully prevent further treatment-related toxicities as these patients had started ACTIVE with unresolved infectious complications (pneumonia and CNS aspergillosis) or acute kidney injury after 7 + 3 induction.

In conclusion, alloSCT remains the only curative therapy for PR AML and new approaches towards successful bridging strategies are needed. Our study suggests the possible efficacy of Venetoclax-based ACTIVE regimen in the pre-transplantation treatment of patients who fail standard chemotherapy induction. Larger prospective studies are warranted to confirm the role of ACTIVE in PR AML.

Declaration of Competing Interest

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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