

Original Article

Hypomethylating agents+venetoclax induction therapy in acute myeloid leukemia unfit for intensive chemotherapy - novel avenues for lesser venetoclax duration and patients with baseline infections from a developing country

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Received March 7, 2021; Accepted May 5, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Both elderly acute myeloid leukemia (AML) patients and those with baseline infections, when treated with intensive chemotherapy, are associated with high induction mortality. We report 24 patients (16-newly-diagnosed, 8-relapsed/refractory) with AML deemed unfit for intensive chemotherapy (by virtue of age >60 years, ECOG-PS 3-4, or those with non-resolving infections at baseline), treated with azacytidine-venetoclax combination as induction chemotherapy. Median follow-up of the study group was 8 months. The overall complete remission (CR)+CR with incomplete count recovery (CRi) rate was 58.3%. 1-year progression-free survival and overall survival of the whole cohort was 44.4% and 55.8%, respectively. On subgroup analysis, newly-diagnosed AML ($p=0.05$), intermediate-risk cytogenetics ($p=0.007$), and HMA-naïve ($p=0.05$) patients had a significantly better outcome. AML patients with baseline infections (versus without infections) treated with azacytidine-venetoclax induction, have lesser induction mortality (compared with historic intensive chemotherapy) with equivalent response rates. A detailed analysis amongst cohorts with different venetoclax durations revealed that, shorter duration (<21 days) venetoclax (versus 21-28 days duration) in induction therapy leads to similar response rates and similar severity of myelosuppression, however, with early count recovery and lesser duration of intravenous antibiotics.

Keywords: Acute myeloid leukemia, azacytidine, venetoclax duration, elderly, infections, intensive chemotherapy, India

Introduction

Acute Myeloid leukemia (AML) is a disease of the elderly (median age at diagnosis-68 years). Two large studies in elderly AML treated with intensive chemotherapy (ICT), have reported complete remission (CR)+CR with incomplete count recovery (+CRi) rates of 45%, albeit with a significantly high induction mortality (IM) of 29-36% [1, 2]. On the other hand, DNA hypomethylating agents (HMAs) in patients unfit for ICT have: low response rates (CR/CRi rates 10-28%), a latency period of 4 months for best response i.e. non-curative, and a median overall survival (OS) of <1 year [3-6]. A meta-analy-

sis of 1822 medically-unfit elderly AML patients treated with HMAs or low-dose cytarabine (LD-AC), showed 15% CR rates, with a dismal survival of 6.3 months [7]. However, it has been shown that those who achieve CR have better survival [6]. Apart from age, some patients present with baseline infections, and their management with ICT is a huge challenge. Nearly one-third patients in developing world have infections at time of diagnosis, and these have high rates of IM with ICT [8]. An Indian study in acute leukemia subjects with baseline infections [n=124], showed that >50% patients died prior to treatment initiation. An additional one-third succumbed after ICT [9]. Hence, there is

an unmet need of an efficacious treatment protocol (like ICT) (to achieve CR) with less IM (like HMAs) in both above cohorts.

Felipe et al., demonstrated that relapse/refractoriness in AML can be attributed to small numbers of quiescent leukemic stem cells (LSC) that are resistant to conventional chemotherapy [10]. In their landmark study, Lagadinou et al., showed that targeting oxidative phosphorylation by inhibition of B cell lymphoma-2 (BCL2) would selectively eradicate these quiescent LSCs [11]. A phase-2 study of Venetoclax (BCL2-inhibitor) monotherapy in relapsed-refractory (R/R) AML revealed promising response rates of 19% [12]. Interestingly, venetoclax in combination with HMA depletes Adenosine-triphosphate in LSCs, thereby “draining their fuel” [13]. Moreover, Azacytidine reduces levels of MCL-1, thereby overcoming venetoclax resistance. A priori above concept, Venetoclax was used in combination with Azacytidine. Subsequently, Dinardo et al., published their phase 1b study of Venetoclax+HMAs in 145 treatment-naïve, elderly patients (≥ 65 years) with unprecedented CR/CRi rates of 67% [14]. Hence, we believe that HMA+Venetoclax, could be the combination that could achieve the efficacy of ICT, with IM of HMAs, for those patients at high-risk for IM, either due to elderly age, poor performance status, or baseline infections.

An important point of debate, yet to be answered in large studies, is the duration of venetoclax. With standard 28-day venetoclax duration, nearly half of patients treated with LDAC+venetoclax achieved CRi [28], whereas more than three-fourth patients treated with azacytidine-venetoclax in VIALE-A study required post-remission cycle delays for count recovery. Consequently, nearly 70% patients in azacytidine-venetoclax arm required curtailment of venetoclax duration to ≤ 21 days after remission [30]. Similarly, in combination with FLAG-IDA, after observation of gram-negative bacteremia/sepsis and severe myelosuppression, venetoclax duration was reduced to 14 days [31]. However, there is no data of reduced duration venetoclax in combination with HMA, prior to achieving remission. We, hereby present, our data of both reduced and standard duration venetoclax, and propose that lesser duration venetoclax is equivalent in efficacy with less myelosuppression.

Methods

We retrospectively analysed our efficacy and safety data of Azacytidine+Venetoclax combination as induction therapy, from November 2018-January 2020. Our study was approved by Institutional review board.

Inclusion and exclusion criteria

Inclusion criteria included patients unfit for ICT i.e. elderly AML (>60 years), poor ECOG-PS (3-4), and/or baseline infections in clinical sepsis, despite ≥ 7 days of antibiotics and/or antifungals. All patients in latter cohort who fulfilled criteria of sepsis [15] i.e., documented infection + any two of: temperature $>38^{\circ}\text{C}$, heart rate $>90/\text{min}$, respiratory rate $>20/\text{min}$, hypoxia needing oxygen support. AML was diagnosed as per updated 2016 criteria of World Health Organisation (WHO) [16]. Those patients who received at least 14 days venetoclax were included in retrospective analysis. Patients with central nervous system involvement, renal dysfunction (creatinine clearance <50 ml/min), hepatic dysfunction (bilirubin >2 mg/dl) and any prior receipt of venetoclax were excluded. Informed consent was taken for off-label use of Azacytidine-venetoclax induction in patients <75 years of age. 16 newly diagnosed (ND) and 8 R/R patients were included (including secondary AML, and prior treatment with HMAs).

Treatment protocol and response assessment

Azacytidine was given at standard protocol (75 mg/m²/day \times 7 days subcutaneously) along with ramp-up venetoclax in cycle 1 (50 mg \times 2 days, 100 mg \times 2 days, 200 mg \times 2 days), followed by 400 mg for 14-21 days. This accounted for a total venetoclax duration of 21-28 days. Responses were assessed by bone marrow (BM) examination at day 21 or day 28 (last day of venetoclax). All patients received antifungal prophylaxis (Liposomal Amphotericin-B or caspofungin), with standard tumor-lysis (TLS) precautions, as per institution policy. Azoles, being CYP3A inhibitors, interact with venetoclax necessitating its dose reduction, and hence, were not used. After attainment of CR, further treatment was as per age/fitness and baseline risk stratification. Young, fit patients were consolidated with high-dose cytarabine (HiDAC) (European leukemia net (ELN) favourable-risk)

or Allo-transplant (aSCT) (ELN-intermediate/adverse risk) [18], whereas ≥ 60 years, or unfit patients were continued on Azacytidine \pm Venetoclax (till disease progression). After achieving a CR/CRi, those on Azacytidine+Venetoclax combination, received venetoclax at 400 mg OD for a lesser duration (7-14 days) in a 28 day cycle till disease progression. Responses were assessed as per International Working Group (IWG) criteria. After achieving CR, any blasts in peripheral blood or $>5\%$ BM blasts, was defined as relapse [17]. Patients not in CR after at least 4 cycles were deemed non-responsive.

Objectives of study

Primary endpoint was efficacy (attainment of CR/CRi, as per IWG criteria) [17] with azacytidine-venetoclax induction regimen. Secondary endpoint was safety analysis with azacytidine-venetoclax, reported as frequency of grade 3-4 adverse events (IM, anemia, neutropenia, thrombocytopenia, gastrointestinal, infections, hypokalemia), graded as per CTCAE v5.0 [19]. Both endpoints were also analysed with respect to different venetoclax durations.

Statistical methods

All continuous variables were expressed as mean \pm standard deviation or median depending on the distribution of the data. Categorical variables were expressed as numbers with their respective percentages. Differences in binary and ordinal variables between two independent groups were analysed by the exact chi-square test. Difference between two independent groups were assessed with the independent t-test. Survival curves and rates were estimated using the Kaplan-meier method. Log-rank method was used to compare the survival between two groups. All these statistics were accompanied by 95% confidence intervals (CI). All the reported p -values were two sided and p -values <0.05 was considered to indicate statistical significance. All data entries and statistical analyses were performed by using MedCalc® Statistical software version 19.7.2 (MedCalc software LTD, Ostend, Belgium <https://www.medcalc.org>; 2021).

Results

Baseline characteristics

Baseline characteristics are enlisted below in **Table 1**. 24 patients (ND=16; R/R=8) were

included with a minimum 2-month follow-up. Median age of the cohort was 60 years (range: 30-79 years), wherein half of our cohort had comorbidities and poor performance status (ECOG-PS ≥ 2). Majority of our patients were de novo AML (84%). Three-fifth (60%) presented with infections at diagnosis. Most common site of baseline infection was lungs (33%) (pneumonia). Nearly 90% of our cohort had intermediate-high risk cytogenetics as per ELN-2017 [19]. Baseline next-generation sequencing (NGS) was available in 14 patients (58.3%), of which most common were fms-like tyrosine kinase 3 (*FLT3*) (63%) and nucleophosmin-1 (*NPM1*) (42%) mutations. Median prior lines of therapy in R/R AML were 2 (range: 1-4). Eight (32%) received prior HMAs, majority of which were HMA refractory (75%). Median number of cycles in HMA treated patients were 2 (range: 2-20). At relapse, all patients had a medullary relapse, including one with extramedullary disease (leukemia cutis). Median time from diagnosis to treatment initiation was 9.5 days (range: 1-35 days). During treatment, due to persistent myelosuppression in our first 8 patients, venetoclax protocol was modified - rapid ramp-up (50 mg \times 1 day, 100 mg \times 1 day, 200 mg \times 1 day) followed by 400 mg OD for 14 days (total duration <21 days). BM examination was done on last day of venetoclax.

Efficacy

24 patients received total 110 cycles. Regarding efficacy, nearly three-fifth patients (58.3%) achieved CR/CRi. (**Table 2** below) Median number of cycles to achieve CR/CRi were 2. Two patients (IM: 8%) succumbed to disease progression during first two cycles (60-day mortality). At a median follow-up of 8 months, median progression free survival (PFS) and overall survival (OS) of the whole cohort was 6 and 8 months, respectively (**Figure 1A, 1B**). Of all ND-AML patients ($n=16$), CR/CRi rate was 81.2% ($n=13$), with median duration of response of 8.1 months. However, amongst R/R cohort ($n=8$), six were HMA refractory (including two post-aSCT), of which one responded to azacytidine-venetoclax. On subgroup analysis, low+intermediate-risk cytogenetics ($p=0.0079$), ND-AML ($p=0.05$) (**Figure 2**) and HMA-naïve ($p=0.05$) (**Figure 3**) patients had a significantly better outcome. *FLT3*-mutation negative patients had a trend towards favourable outcome ($p=0.096$). Amongst ND-AML patients, after

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Table 1. Baseline features of all patients

| Variables | Value (%) |
|--|--|
| Median age | 60 years [30-79] |
| >65 years | 11 (45.8%) |
| 60-65 years | 6 (25%) |
| Sex | |
| Male | 11 (45.8%) |
| Female | 13 (54.1%) |
| ECOG PS [¶] | |
| 0-1 | 12 (50%) |
| 2 | 9 (37.5%) |
| 3-4 | 3 (12.5%) |
| Newly diagnosed AML | 16 (66.6%) |
| Relapsed/Refractory AML | 8 (33.3%) |
| Comorbidities (16 comorbidities in 14 patients) | |
| • Diabetes Mellitus | 3 (12.5%) |
| • Hypertension | 5 (20.8%) |
| • Coronary Artery Disease | 2 (8.3%) |
| • Benign prostatic hypertrophy | 3 (12.5%) |
| • Others (Hypothyroidism, Bronchial asthma) | 2 (8.3%) |
| Grade ≥3 documented baseline infection (Clinical Sepsis) (5 sites of infections in 16 patients) | 15 (60%) [¶] |
| • Blood | 3 (12.5%) |
| • Urinary tract infection | 2 (8.3%) |
| • Pneumonia | 8 (33.3%) |
| • Others (Cellulitis, Enterocolitis) | 2 (8.3%) |
| AML Subcategory | |
| > Denovo AML | 20 (83.3%) |
| > Secondary AML | 2 (8.3%) |
| > Therapy-related AML | 1 (4.1%) |
| Relapsed status (n=8) | |
| > Salvage 1 | 3 (30%) |
| > Salvage ≥2 | 2 (20%) |
| > Prior allogeneic SCT [†] | 2 (20%) |
| > Treated AHD [§] | 2 (20%) |
| > Extramedullary disease | 1 (10%) |
| Prior HMA [†] refractory | 6 (24%) |
| Baseline CBC parameters | |
| > Median Hb (g/dl) | 8.25 (4.9-11.2) |
| > Median TLC (cells/mm ³) | 15180 (880-189710) |
| > Median Platelet (cells/mm ³) | 55 (13-195) |
| > TLC [‡] >25,000 | 9 (37.5%) |
| ELN risk (n=24) | |
| > Favourable | 3 (12.5%) |
| > Intermediate | 15 (62.5%) |
| > Poor | 6 (25%) (1 patient with complex karyotype) |
| Mutations (30 mutations in 14 patients) | |
| > NPM1 [¶] | 6 (42.8%) |
| > FLT3-ITD [‡] | 3 (21.42%) |
| > FLT3-TKD [‡] | 6 (42.8%) |
| > FLT3 [‡] (unknown) | 3 (21.42%) |
| RUNX1 [‡] | 2 (14.2%) |
| IDH1 [¶] | 2 (14.2%) |
| BCOR [¶] | 2 (14.2%) |
| Others (CEBPA [‡] , TP53 [§] , EZH2 [¶] , PHF6 [‡] , DNMT3A [‡] , ATRX [‡]) | 6 (42.8%) [1 each] |
| Concomitant antifungals | |
| > Caspofungin | 8 (33.3%) |

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> Amphotericin-B

16 (66.6%)

Values in the table are presented as the number of patients with the percentage in parenthesis unless indicated otherwise. Abbreviations: ¶: Eastern Cooperative Oncology Group Performance Status, \$: Total leukocyte count, !: Stem cell transplant, I: Hypomethylating agent, \$: AHD - Antecedent hematologic disorder, *NPM1: Nucleophosmin, [†]FLT3-TKD/ITD: Fms-like tyrosine kinase 3 - tyrosine kinase domain/internal tandem duplication, [‡]CEBPA: CCAAT Enhancer Binding Protein Alpha, [§]RUNX1: Runt-related transcription factor 1, [¶]IDH1: Isocitrate dehydrogenase 1, ^{*}BCOR-BCL6 co-repressor, [†]TP53: Tumor protein 53, [‡]EZH2 - Enhancer of zeste homolog-2, [§]PHF6: Plant homeodomain finger 6, [¶]DNMT3A-DNA methyl transferase-3A, ^{*}ATRX: Alpha thalassemia/mental retardation syndrome, a: 15 patients had documented infections, one patient had pneumonia+UTI both.

Table 2. Treatment efficacy/safety data

Responses to HMA/Venetoclax and toxicities in 24 patients

| | |
|--|--|
| > Venetoclax+HMA (cycles received) | |
| 1 | 10 (41.6%) |
| 2 | 3 (12.5%) |
| 3 | 4 (16.6%) |
| ≥4 | 7 (29.1%) |
| > ND [§] +R/R [¶] (n=24) | |
| ORR | 58.3% |
| CR/CRi [@] | 54.3% |
| PR | 4% |
| > ND [§] only (n=16) | |
| ORR [§] | 81.2% |
| CR/CRi [@] | 75% |
| > R/R [¶] only (n=8) | |
| ORR [¶] | 12.5% |
| CR/CRi [@] | 12.5% |
| Death (Within 60 days) | 2 (8%) |
| Median Overall survival (months) | 8 months (2-26 months) |
| Median Progression-free survival (months) | 6 months (1-26 months) |
| Grade 3-4 adverse events | 24 patients received 110 cycles |
| > Myelosuppression | |
| Anemia | 54 (49.2%) |
| Neutropenia | 77 (70%) (100% during first two cycles) |
| Thrombocytopenia | 42 (38%) |
| > Gastrointestinal | |
| Nausea | 40 (36%) |
| Vomiting | 31 (28%) |
| Diarrhoea | 23 (21%) |
| > Infections (Grade 3-4) | |
| • Infection sites | |
| Blood | 10 (9%) |
| Pneumonia | 30 (27%) |
| Urinary tract infection | 8 (7.2%) |
| Skin | 2 (1.8%) |
| • Febrile neutropenia | 36 (33%) [All cycles] 32 (64%) [First 2 cycles] |
| • Duration of febrile episodes | 6 days (1-17) |
| > Tumor lysis syndrome (Lab) | 2 (1.8%) |
| > Hypocellular bone marrow at end of induction | 6 (25%) |
| > Hypokalemia | 20 (18%) |

Values in the table are presented as the number of patients with the percentage in parenthesis unless indicated otherwise. Abbreviations: [§]ND: Newly diagnosed, [§]ORR: Objective response rate, [¶]RR: Relapse/Refractory, [@] - CR/CRi - Complete Remission/Complete Remission with incomplete count recovery.

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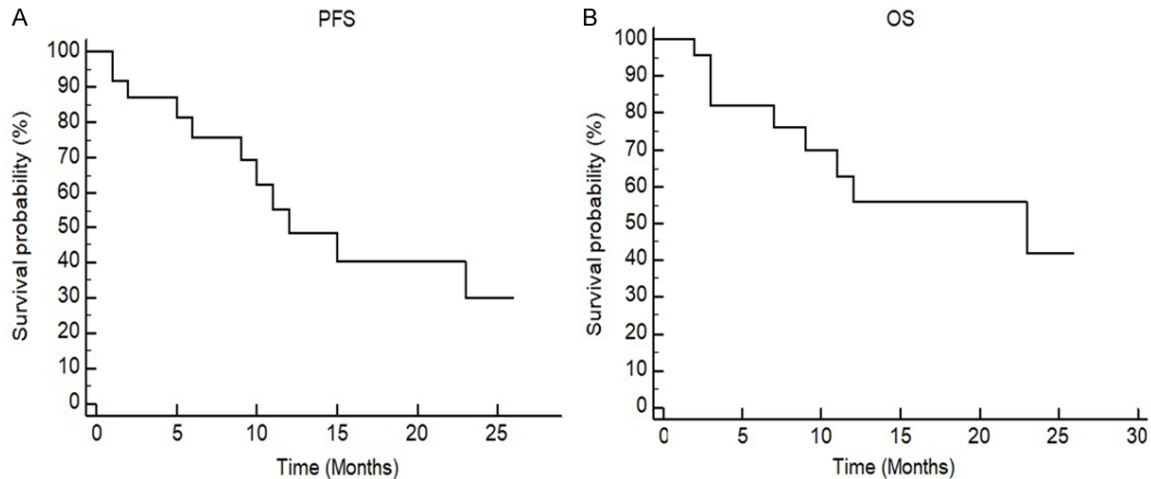


Figure 1. Kaplan meier curves of Progression free survival (PFS) and Overall survival (OS) of entire cohort. A: Kaplan meier curve of Progression free survival. B: Kaplan meier curve of Overall survival.

responding to azacytidine-venetoclax induction, 3 (18.8%) patients proceeded to HiDAC consolidation, 8 (57.1%) continued azacytidine+venetoclax, 1 (7.1%) on HMA hypomethylating agent alone and 1 (7.1%) patient proceeded to aSCT. One R/R AML patient who responded was continued on azacytidine+venetoclax combination.

Venetoclax duration was reduced to <21 days, after prolonged myelosuppression for those on 21-28 days (explained in Adverse events section below). The response rates (CR/CRi) in both venetoclax cohorts (**Table 3A**), and in patients with baseline infections versus (vs) without (**Table 3B**), were similar.

Safety (Adverse events)

Adverse events are enlisted in **Table 2** below.

Myelosuppression: Regarding safety, myelosuppression was the most common adverse event. Grade 3-4 neutropenia was seen in nearly three-fourth (70%; n=77) and grade 3-4 infections in nearly half (45%; n=50) of all treatment cycles. Median duration of grade 3-4 neutropenia was 26 days (range: 2-60) and grade 3-4 thrombocytopenia was 17 days (range: 3-38). Median nadir ANC and platelet count during therapy in first two cycles was $0.04 \times 10^9/L$ (range: 0.0036-1.41) and $9 \times 10^9/L$ (range: 7-14) respectively. Median day for nadir ANC and platelet was on day 12 and day 10, respectively. Median number of RBC and platelet

transfusions during first two cycles was 7 and 4, respectively. Median day of ANC and platelet recovery, before achieving CR (first two cycles) was 29 and 18, respectively. Overall, approximately one-third patients (36%; n=9) patients required venetoclax interruptions due to myelosuppression.

Importantly, our first two patients on 28 days venetoclax, had grade 3-4 neutropenia till day 35, and grade 3-4 thrombocytopenia till day 39, with a hypoplastic marrow, although in remission (CRi). Therefore, we reduced the total duration of venetoclax to 21 days (n=6) and <21 days (n=16). Importantly, amongst patients with venetoclax duration of <21 days vs 21-28 days, median duration of grade 3-4 neutropenia (19.5 vs 27.5; p=0.07) and grade 3-4 thrombocytopenia (17 vs 13; p=0.6) was lesser in former cohort (**Table 3A**).

Infections: One-third of all cycles (n=36; 33%) were complicated with febrile neutropenia. Median duration of febrile neutropenia was 6 days (range: 1-17). Nearly two-third (64%) of these occurred in the first two cycles before achieving a CR/CRi, of which 3 patients' clinical course was complicated with septic shock. Venetoclax was discontinued subsequently in these 3 patients.

Median duration of antibiotic use was significantly less in <21 day (8 days) vs 21-28 day venetoclax (14 days) cohort (p=0.0001). Nearly three-fifth patients (62.5%) in both veneto-

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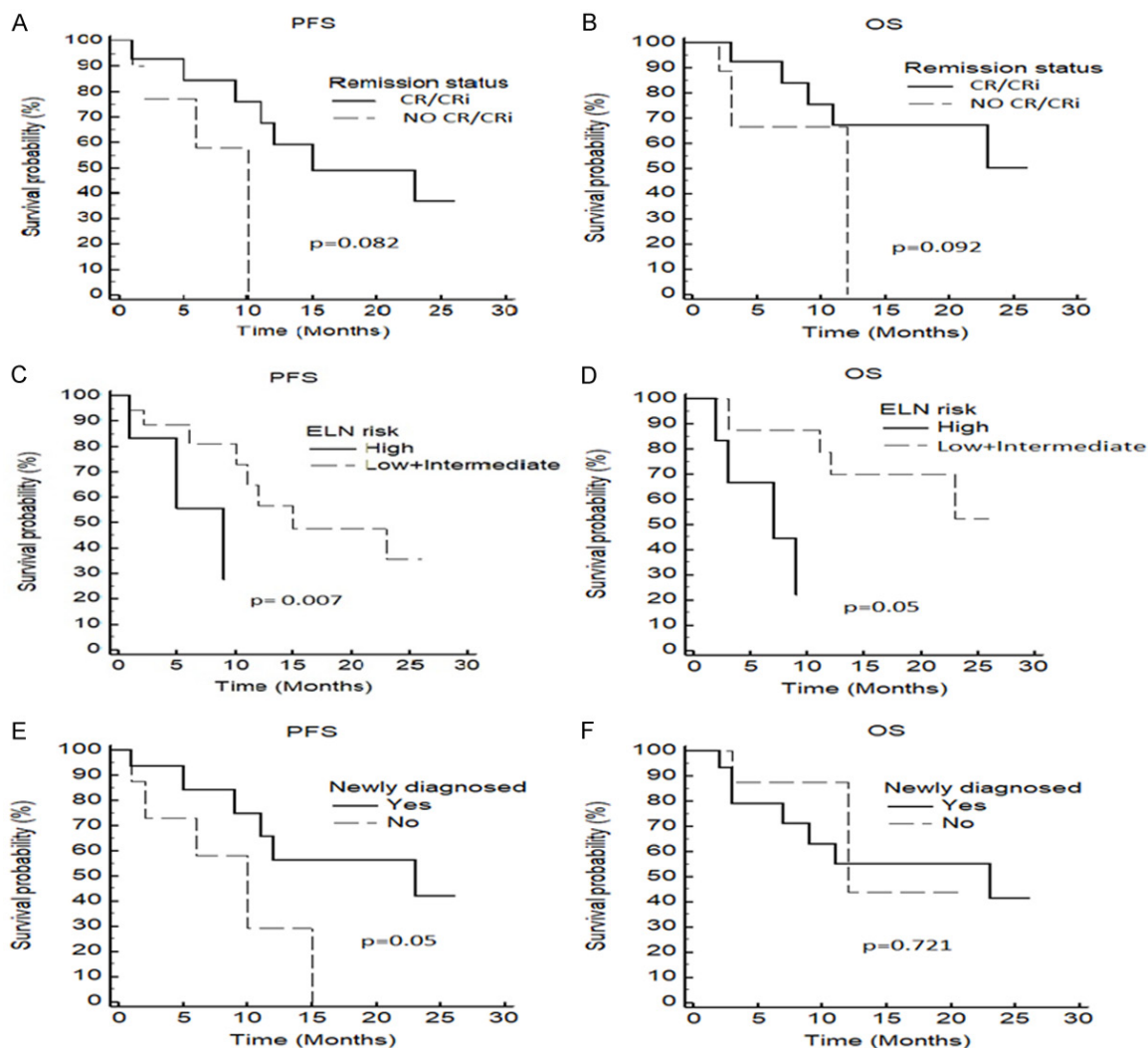


Figure 2. Graph showing effect of different prognostic factors on PFS and OS. A: PFS according to CR/CRi vs No CR/CRi. B: OS according to CR/CRi vs No CR/CRi. C: PFS according to baseline ELN risk group. D: OS according to baseline ELN risk group. E: PFS according to ND AML vs RR AML. F: OS according to ND AML vs RR AML. CR/CRi ($p=0.05$), low+intermediate-risk cytogenetics ($p=0.0079$) and ND-AML ($p=0.05$) patients showed better outcome. P -value <0.05 considered statistically significant. Abbreviations: ELN: European leukemia net, CR/CRi: Complete Remission/Complete Remission with incomplete count recovery.

clax cohorts developed grade 3-4 infections. Pneumonia was the most common site ($n=30$; 27%) of grade 3-4 infection (**Table 3A**). Majority of pneumonias were due to breakthrough invasive fungal infections (IFI) ($n=27$; probable IFI=22, possible IFI=5). Importantly, IM in patients with baseline infections were like those without (one patient in each group) (**Table 3B**).

Other adverse events: (Gastrointestinal, TLS, hypokalemia) are listed in **Table 2**.

Discussion

Unlike other studies [14, 20-23], which included either ND [14, 20, 23] or R/R [21, 22] AML

subjects, we analysed both these groups. Similar to literature [14, 20-23] majority of our patients were aged >60 (68%), denovo-AML (84%), with intermediate-high risk cytogenetics (87%). However, in contrast [14, 20], 80% of our cohort had ECOG-PS ≥ 2 , including 56% ($n=14$) with comorbidities. Two phase Ib/II studies have shown that venetoclax in combination with HMAs or low-dose cytarabine (LDAC) gives durable remissions in elderly AML cohort [14, 20]. The same benefit of venetoclax addition to HMAs/LDAC was confirmed recently in a randomised fashion [27, 28]. However, in comparison to previous studies [14, 20]; the above two randomised studies [27, 28] also includ-

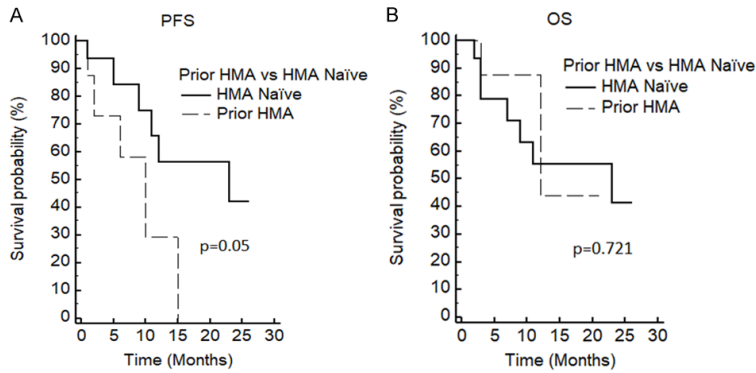


Figure 3. Survival according to HMA naïve and Prior HMA. A. Kaplan meier curves of Progression free survival according to HMA naïve and Prior HMA. B. Kaplan meier curves of Overall survival according to HMA naïve and Prior HMA.

ed young AML patients (between 18-65 years) deemed unfit by virtue of presence of comorbidities. Intriguingly, in contrast to comorbidities in western countries, the main problem in our country is presence of baseline infections [9, 24, 25], which precludes the ability to give ICT. Hence, there is a dire need for less toxic regimens for this cohort. An Indian study has shown that infections are the primary cause of IM [24]. A recently published multivariate model from India, showed that any baseline infection needing intravenous antibiotics within 7 days prior to induction, was one of the primary factors for IM [25]. Ferrara et al., have mentioned active infection resistant to anti-infective therapy, as a criteria for unfit for ICT [29]. More than half (60%; n=15) of our patients had baseline grade 3-4 infections, majority with pneumonia (including n=3, on oxygen support). Hence, although they were young ND AML patients, they were treated with HMA+venetoclax, in-order to reduce the IM. To our knowledge, no study till date has included patients with non-resolving grade 3-4 infections on this protocol.

Similar to literature, 60% of our subjects achieved a response (CR/CRi: 52%), with a median time to CR of 2 cycles [14, 20, 21]. However, CR/CRi rates were a dismal 12.5% in R/R-AML, similar to data reported by DiNardo et al. [22]. Their poor outcomes might have been due to a highly refractory cohort (\geq CR2, prior HMA exposure, one-fourth with TP53 mutations) [22]. Importantly, more than three-fourth of our ND-AML patients achieved a CR/CRi, comparable to others [14, 23]. This shows that young unfit or elderly patients, not previously exposed to

HMA, might respond favourably to Venetoclax-HMA (**Figure 3**). Importantly, in contrast to others [14, 23], although NGS was done only in nine patients, neither *FLT3* or *NPM1* was predictive of response in our cohort. After *NPM1* and *FLT3*, presence of *IDH* [14, 20, 23] mutations predict likelihood of CR/CRi, while *ASXL1* remains a poor prognostic marker [23]. On subgroup analysis by cytogenetics in our cohort, 54% (n=9) intermediate-risk and one-third high-risk (n=3) patients achieved a CR, lesser

as compared to DiNardo et al. [14], but similar to others [20, 21]. This difference might be because the latter study, included all ND fit (ECOG-PS \leq 1) patients without baseline infections [14]. The overall PFS and OS of our cohort was 41.7% and 54.7%, respectively (**Figure 1**). On comparing outcomes between patients who attained a CR/CRi vs no response, 1-year OS [61.5% vs 35% (p=0.092)] and PFS [64.8% vs 0% (p=0.082)] was significantly better for the former group (**Figure 2**). Importantly, IM in our cohort was similar to western data [14, 20-23, 27, 28] (**Table 4**), and much lesser than reported from India for patients with baseline infections [8, 9]. Although minimal residual disease (MRD) was not done in our study, 30-50% patients have been shown to become MRD negative with this combination [14, 21], with survival benefit for MRD $<10^{-3}$ [14]. One of our patients proceeded to aSCT, and is alive in remission at 160 days post aSCT. Similarly, as per literature, 9-14% [14, 21] patients have proceeded to aSCT. A recent study on aSCT outcomes after prior venetoclax-based therapy, showed that nearly 40% had durable remissions for \geq 2 years [26]. It would be worthwhile to further explore the role of HMA+Venetoclax as a bridge to aSCT.

In comparison to others (**Table 4**), our frequency of severe myelosuppression (grade 3-4 leukopenia) was 70%, much higher than other studies [14, 20, 23, 27]. Whether this difference is due to ethnicity (altered venetoclax pharmacokinetics in Indians) or presence of R/R-AML patients (compromised marrow reserve due to prior chemotherapy) in our cohort, cannot be answered at present. Frequency of

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Table 3. Subgroup analysis with respect to venetoclax duration, and presence/absence of baseline infection

| A. CR/CRi [®] and Cytopenias with respect to venetoclax duration | | | |
|--|--------------------|------------------|---------|
| | <21 days (n=16) | 21-28 days (n=8) | p-value |
| Response (CR/CRi) [®] [n (%)] | 9 (56.2%) | 5 (62.5%) | 0.887 |
| Neutropenia (Grade 3-4) [n (%)] | 12 (75%) | 7 (87.5%) | 0.631 |
| Anemia (Grade 3-4) [n (%)] | 13 (76.4%) | 5 (62.5%) | 0.361 |
| Thrombocytopenia (Grade 3-4) [n (%)] | 12 (75%) | 4 (50%) | 0.362 |
| Infection (Grade 3-4) [n (%)] | 10 (62.5%) | 5 (62.5%) | 0.913 |
| Median duration of grade 3-4 neutropenia (days) | 19.5 | 27.5 | 0.07 |
| Median duration of grade 3-4 thrombocytopenia (days) | 17 | 13 | 0.66 |
| Median duration of antibiotics for infections (days) | 8 | 14 | 0.0001 |
| Newly diagnosed AML (n=16) | | | |
| n=16 | 12 (75%) | 4 (25%) | p-value |
| CR/CRi [®] [n (%)] | 9 (75%) | 4 (100%) | 0.528 |
| B. Baseline features, response rates, induction mortality with respect to presence or absence of baseline infections | | | |
| | Baseline infection | | p-value |
| | Yes (n=12) | No (n=12) | |
| Median age (years) | 59 | 64 | n/a |
| Male:Female ratio | 1:1 | 1.8:1 | n/a |
| Median Hb [§] (g/dl) | 8.5 | 8 | 0.88 |
| Median TLC ^{&} (/mm ³) | 23555 | 4160 | 0.15 |
| Median platelets (/mm ³) | 81000 | 40500 | 0.009 |
| Hb [§] ≤8 g/dL [n (%)] | 5 (41.6%) | 7 (58.3%) | 0.083 |
| TLC ^{&} >10 × 10 ⁹ /L [n (%)] | 10 (83.3%) | 5 (41.6%) | 0.362 |
| Platelets <20 × 10 ⁹ /L [n (%)] | 1 (8.3%) | 2 (16.6%) | 0.889 |
| CR/CRi [®] [n (%)] | 8 (66.6%) | 6 (50%) | 0.067 |
| Newly diagnosed AML (n=16) | | | |
| n (16) [n (%)] | 9 (56.2%) | 7 (43.7%) | n/a |
| Response | | | |
| CR/CRi [®] [n (%)] | 7 (53.8%) | 6 (46.1%) | 0.089 |
| Induction mortality [n (%)] | 1 (11.1%) | 1 (14.2%) | n/a |

Values in the table are presented as the number of patients with the percentage in parenthesis unless indicated otherwise, p-value <0.05 was considered statistically significant. §: Hemoglobin, &: Total Leucocyte count, @ - CR/CRi - Complete Remission/Complete Remission with incomplete count recovery.

FN was higher in our study (64% in first 2 cycles) than others [14, 20, 21, 27, 28], probably reflecting an effect of baseline infections and prolonged neutropenia. This was halved, once response was achieved (Table 2). Meanwhile, unlike DiNardo et al. [14], we did-not use hydroxyurea (cytoreduction) for TLC>25,000; and none of our patients developed clinical TLS.

The million-dollar question with this combination, is the duration of venetoclax, both in induction and subsequent cycles. Consequent to

hypocellular marrow in our first two patients (28 days venetoclax), we amended our protocol to 21 days venetoclax, with a BM at day 21. Nonetheless, 66% (4/6) patients (on 21 day venetoclax) needed interruption for grade 3-4 neutropenia, with septic shock in 3 (50%) patients. Hence, we further modified our protocol to a rapid 3 day ramp-up followed by 400 mg OD × 14 days (<21 day venetoclax). It was continued (till day 28), if >5% BM blasts on day 21, and stopped for those in remission on day 21 marrow. If in remission, GCSF support and/or granulocyte transfusions were given for clini-

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Table 4. Comparison of our study with available literature

| Study | DiNardo CD et al. (2019) [14] | Wei et al. (2018) [20] | Aldoss et al. (2018) [21] | DiNardo et al. (2018) [22] | Winters AC et al. (2019) [23] | DiNardo et al. (2020) [27] | Wei et al. [28] | Our study |
|--------------------------------------|---|------------------------|--|---|-------------------------------|--|---|--|
| Patient population | ND* (n=145) | ND* (n=82) | R/R^ (n=33) | R/R^ (n=39) | ND* (n=33)/ (n=36) | ND* (n=433) | ND* (n=211) | ND*+R/R^ (n=24) |
| Venetoclax (Ven) along with - | HMA ^s (Aza [®] /Dac [#]), LDAC [*] | LDAC [*] | HMA ^s (Aza [®] /Dac [#]) | HMA ^s (Aza [®] /Dac [#]), LDAC [*] | HMA ^s | HMA ^s +Ven (n=286) vs HMA ^s +placebo (n=145) | LDAC [*] +Ven (n=143) vs LDAC [*] +placebo (n=68) | HMA ^s (Aza) [®] |
| Venetoclax dose (mg)/duration (days) | 400 OD (28) | 600 OD (28) | 400 OD (28) | 400/600 OD (14-28) | 400 OD (28) | 400 OD (28) | 600 OD (28) | 400 OD (14-28) |
| CR/CRi [†] (%) | 67 | 54 | 51.5 | 12 | 63/84 | 66.4 vs 28.3 | 48 vs 13 | 58.3 |
| Median Time to CR (months) | 2.1 | 2.5 | 2 | 1 | 1 | 1.3 | n/a [‡] | 2 |
| CR duration (months) | 11.3 | 8.1 | 8.9 | n/a | 11/not reached | 17.5 vs 13.3 | n/a [‡] | 8.1 |
| Grade 3-4 leukopenia (%) | 31 | 34 | n/a | 100 | 40 (n=28) | 21 vs 12 | 46 vs 16 (neutropenia) | 70 |
| % mortality | 8 (60-day) | 6 (30-day) | n/a [‡] | 12 (30-day) | 13 (30-day) | 7 vs 6 (30-day) | 13 vs 16 (30-day) | 8 (60-day) |
| FN [§] | 43% | 42% | 42% | 72% | n=14 | 42 vs 19 | 32 vs 29 | 36 (33%) [All cycles] 32 (64%) [First 2 cycles] |
| TLS [¶] | n=0 | n=2 | n/a [‡] | n=0 | n/a [‡] | n/a [‡] | 6 vs 0 | n=2 (1.8%) |
| OS [‡] | 17.5 months | 10 months | 53% (1 year) | 3 months | 12 months/29 months | 14.6 months vs 9.1 months | 7.2 months vs 4.1 months | 8 months (55.8%, 1 year) (whole cohort), 15 months (responders) |

[§]FN: Febrile neutropenia, [†]CR/CRi: Complete Remission/Complete Remission with Incomplete Hematologic Recovery, ^{*}LDAC: Low dose Cytarabine, [¶]TLS: Tumor Lysis syndrome, [‡]OS: Overall survival, [§]HMA: Hypomethylating agents, [®]Aza: azacytidine, [#] - Dac: Decitabine, % - ND: newly diagnosed, ^ - R/R: Relapsed/refractory, (- n/a: not available).

cal sepsis until ANC>500/ μ L. As venetoclax combinations (HMA/LDAC) - lead to 'CRi' as half of the responses [14, 20], need drug interruptions or discontinuation during induction [14, 20] and majority (77%) of patients face delays in subsequent cycles [30], experts propose reducing the duration of venetoclax after achievement of remission [30]. We propose that lesser venetoclax duration would result in more 'CR's as compared to 'CRi's, without compromising efficacy, and safer with respect to lesser grade 3-4 neutropenia, as seen in our cohort. This is important because patients in CR have better outcomes than CRi [11, 15]. This would also imply less myelosuppression, and less financial burden for supportive treatment. Further randomised studies should compare various durations of venetoclax, to address this question.

Limitations of our study include retrospective nature of study, short sample size, off-label use of study combination in young patients, a short follow-up, and a lack of comparison with ICT in young patients. Nonetheless, it is the first data of this combination from India, and paves the way for future studies, especially for different dosing durations of venetoclax, both for those with and without baseline infections.

Conclusion

To our knowledge, this is the first study of HMA+Venetoclax induction from India. Our experience suggests that this combination is well-tolerated with a reasonable efficacy and lower induction mortality in patients unfit for intensive chemotherapy.

Acknowledgements

The authors would like to thank Anurag Sharma, Biostatistician, Rajiv Gandhi Cancer Institute and Research Centre Rohini, Delhi, India for providing support in statistical analysis. Authors also acknowledge all the staff and team members of department of Hemato-oncology and Bone Marrow Transplant unit, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India in performing this study. IRB has decided to approve the study to be conducted in its present form and given a waiver from consenting process. (Approval No. -RGCIRC/IRB/149/2020).

Disclosure of conflict of interest

None.

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