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From Cytotoxic to Senolytic: Decitabine and Venetoclox as the New 7+3 for AML Induction, Crossing the Barrier of Frailty

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ABSTRACT:

Background: nowadays Hypomethylating arm (HMA) with venetoclax (VEN) arm, became standard for care patients with acute myeloid leukemia (AML). The venetoclax was recommends as continuous 28-day cycles, but shortened VEN durations may induce similar response rates and improve tolerability.

Methods: We performed a descriptive prospective, single center study. Twenty one AML patients (both unfit and fit patient), were enrolled in non-randomized trial, for chemotherapy of venetoclax with decitabine (DEC3-VEN) regimen, by (DEC; 20 mg/m2; IV days 1-3) Patients admitted for 7 days oral venetoclax 200mg daily for induction).

Results: Between January and December, 2024, we enrolled 21 Adults newly confirmed AML patients. The median age was 53 years (26–80) and 62% patients had ECOG performance state of 2 or higher. Endpoints of the trial included response rates evaluated as remission rate as (complete remission [CR]in 52% of patients, CR with incomplete blood count recovery [CRi] in 10%, partial remission (PR) 14% while not response (NR) in 24%. The best age for CR was forties and the worst non responded age was (60 yrs). The noted toxicity effects appeared as neutropenia (90.5%), anemia (38.1%), thrombocytopenia (33.3%), and typhlitis (19%) pericarditis, splenic infraction, skin rash and sepsis represent (4.8%) for each. Also the responders had the lowest HB, white blood cell, platelets, and myeloid blasts counts, than non-responders.

Conclusions: the venetoclax combined with short three sessions of DEC (DEC3-VEN) is so effective and relatively safe induction therapy regimen for AML patients from different age. Nevertheless, the relatively limited survival benefits and response rates necessitate the need for further digging in this field.

INTRODUCTION

Acute myeloid leukemia (AML) is a non-homogenous disorder of clonal myeloid precursors, have varying fates based on genetic and molecular abnormalities. AML primarily diagnosed in patients aged 65 and more [1], whom are at increased risk of treatment-related mortality (TRM) with aggressive chemotherapy (IC) [2]. In the geriatric population, survival rates and cure rates have unchanged over the past two decades in spite of many research and recognized efforts to improve therapy. [3]. Intensive medicines such as 7 + 3 cytarabine (Ara–C) with anthracycline backbone were highly myelotoxic to the most of elderly patients whose adverse pictures were intensified by their general weakness and the process of aging diseases [4, 5] therefore, the complete response was noticed in 65- 75% of (≤60 years) patients while it was 40- 60% in (>60 years) AML patients [6].

Venetoclax (VEN) is BCL-2 inhibitor, surprisingly improved the fate of newly diagnosed older or physically unfit AML patients. [7]. While decitabine which a hypomethylating agent (HMA) that reactivates tumor suppressor genes and promotes differentiation or death of leukemia cells [8]. Previously known that HMA monotherapy provided an important option for patients unfit for intensive induction chemotherapy, but overall survival has typically been <7–8 months. [9, 10] There has been ongoing debate about the true utility of venetoclax and HMA regimens such as (decitabine) in AML. [11,12] in contrast with (IC), lower-intensity regimens of venetoclax (VEN) in combination with low- dose hypomethylating agents (HMA) has shown safety and efficacy in older patients with newly diagnosed AML ineligible for IC, however (VEN –HMA) became attractive options for such patients.[13,14]. As a result of the such success, the Hematologist open the use of (VEN –HMA) treatment plan to include patients with clear clinical challenge or not , such as the younger, those with less chronic diseases, and those who are non-frail, who have become targets for 7&3 study [15]. The ugly consequences of aggressive chemotherapy that older adults often see, such as low rates of complete normalization, also preclude the ability to transfer patients to stem cell transplantation (allo-HSCT) [16, 17]. Therefore, an urgent need exists to assess the efficacy and safety of VEN-based model in younger adults with newly diagnosed, bad-risk AML the (VEN –HMA) treatment model can give same efficacy with less myelotoxicity and less need for intensive care. Up to date there are sparse data available from prospective trials assess less myelosuppressive model such as DEC3-VEN as induction arm for less than 70 years AML patients in Iraq. This study of a three-day course of decitabine with low dose venetoclax (DEC3-VEN) showed new window in reducing therapy related mortality TRM in AML patients under 60 years of age.

PATIENTS AND METHODS

Ethics approval and consent to participate this study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was obtained under IRB log Number: --IQ.UTQ.MED. 2026.035 From the Institutional Review Board of Thi Qar Medical College.

This was a descriptive prospective, single center study, conducted at Nasseriah hematology center. The objective was to determine activity of this regimen as measured by overall response. Between January 2024 and December 2024, 21 patients with newly diagnosed AML (both unfit and fit patient) were recorded to receive an adopted DEC3-VEN as a prospective trial of induction treatment. All patients applied the AML criteria of the WHO (2022) classification. Patients receiving DEC3-VEN as following regimen: Venetoclax was given at a fixed dose of 200 mg daily for 7 consecutive days (Day 1 to Day 7), in combination with voriconazole 200 mg twice daily as antifungal prophylaxis to account for CYP3A4 interaction. Decitabine was administered at 20 mg/m² intravenously daily for 3 days. The efficacy of studied regimen is combines with age, Eastern Co-operative Oncology Group performance status (ECOG PS) score, AML subtypes, and laboratory values. The response was assessed from initiation of therapy until death, or censored at last follow-up. The Inclusion Criteria were: confirmed diagnosis of AML, adult's ≥18 years, informed consent and negative pregnancy test of females. While Exclusion Criteria were: Acute promyelocytic leukemia (APL), Active CNS leukemia Prior intensive chemotherapy or previous use of decitabine/azacitidine or venetoclax in some protocols, other malignancies and Pregnant or breastfeeding women

Statistical analysis

A Descriptive statistics were measured for baseline characteristics of AML patients group. The variables in blood including hemoglobin (Hb, WBCs platelets and marrow blast counts). The groups were further analyzed separately for gender distribution. For continuous variables, means and standard deviations for symmetric distributions, medians and frequencies for categorical or ordinal variables such as Platelet count were recorded as mean ± standard deviation for each group. Patients were further classified by age groups to assess the effect modification given prior work. All statistical analyses were done by using excel application within Microsoft office 2011 version.

RESULTS

The baseline characteristics of 21 patients are summarized in Table 1.

Table 1. Baseline characteristics of the 21 patients

Characteristic		
Total number of patients		21
Median age, years (range)		53 (26–80)

Gender		
Male		14 (66.6%)
Female		7(33.3%)
ECOG (0–5)	0	4(19%)
	1	4(19%)
	2	0(0%)
	3	2(9.5%)
	4	10(48%)
	5	1(4.8%)
AML subtype	0	3(14.3%)
	1	3(14.3%)
	2	5(23.8%)
	3	0(0%)
	4	6(28.6%)
	5	2(9.5%)
	6	2(9.5%)
age range	26-30	3(14.3%)
	31-40	3(14.3%)
	41-50	2(9.5%)
	51-60	5(23.8%)
	61-70	4(19.0%)
	71-80	4(19.0%)
HB(mg/µL)	8.16±1.75	
WBC*10^3/µl	67.96±59.8	
Platelet*10^3/µl	75.1±105	
marrow blast*10^3/µl	88.1±9.6	
Abbreviations: AML acute myeloid leukemia,		
ECOG Eastern Cooperative Oncology Group score		
WBC white blood count		

The median of age was 53 (26–80) years, and 14 (66.6.%) patients were male. ECOG (0–5) score which assess a patient's overall level of activity revealed the majority of patients 10 (48%) were 4 score (very inactive). The classification into AML subtypes based on the type and maturity of the leukemia cells, as well as chromosomal and genetic changes explained the majority 6 (28%) were at 4 sub class (having Acute myelomonocytic leukemia), followed by having subclass 2 (AML with maturation) till 3(14.3%) at subclass (0) (Undifferentiated AML). When divided the patients according to age ranges with ten years intervals, all age ranges were close to each other with beak 5(24%) in 51-60 years range (see table 1 and figure 3A). About hematological parameters: the mean of HB was (8.16 ±1.75mg/dl). The median WBC was 67.12×10^3 ±59.8//µL. mean of platelets count was (75.1×10^4 ±105 /ul). The primary outcome was ECOG Eastern Cooperative Oncology Group score, defined as time from diagnosis to the end of study period on December 30, 2024. After one cycle of induction treatment, the response assessment was performed on Day 28, based on ELN 2022 criteria: Complete remission (CR), complete remission with incomplete hematologic recovery (CRi), Partial response (PR) and No response (NR) were evaluated. As a result, one patient died, and 20 patients were included for efficacy. The overall response rate (CR + CRi+ PR) was 52% (11/21) with CR, three patients gained PR (14%), two patients (10%) achieved complete remission with incomplete hematologic recovery (CRi) and unfortunately five (24%) were non-responds to this regimen, as well as one patient died because of sepsis (80 years old) .(see figure1). Among patients treated with DEC3-VEN, 4(19%) were older than 70 years, 62% patients had ECOG PS ≥2 (see table 1).

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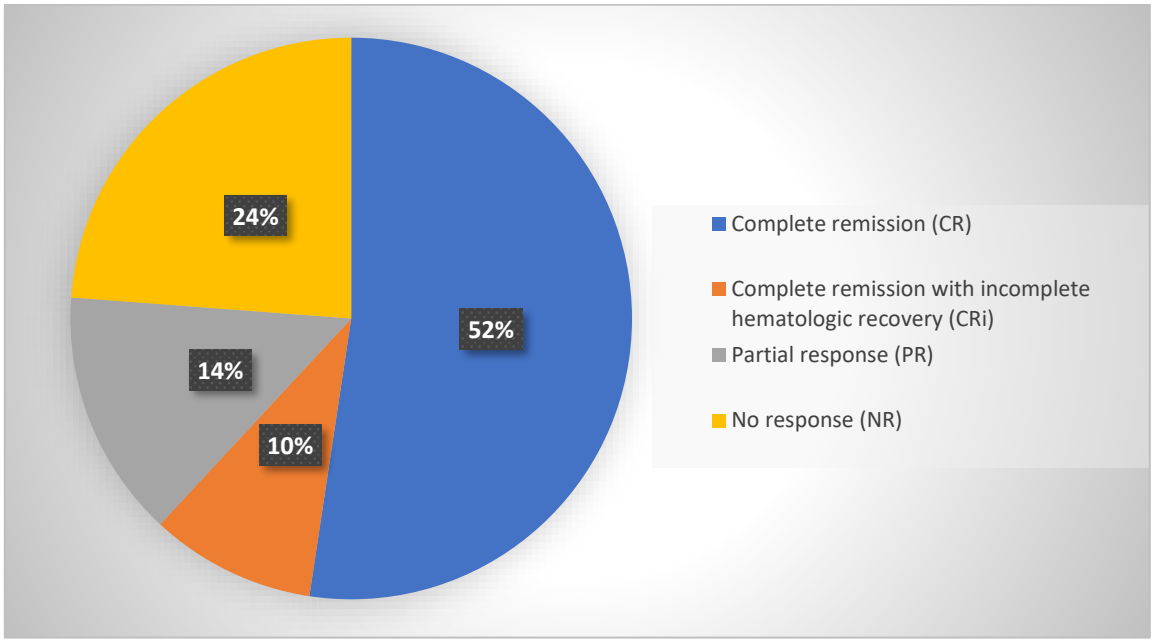

Figure 1: Percentage of DEC3-VEN regimen responsiveness of AML cases that recorded in hematology Nasseriah center during one years (2024). Note a majority of patients gain complete remission (CR).one quarter of patients didn't response

The toxicity of the studied treatment regimen was demonstrated by the appearance of signs such as decreased neutrophil count, anemia, decreased platelet count, and pneumonia etc. (figure 2). The AML patients suffering from neutropenia 19/21(90.5%), Anemia 8/21(38.1%), thrombocytopenia 7/21(33.3%), Typhlitis 4/21(19%), pneumonia 3/21(9.5%), while pericarditis, splenic infraction, skin rash and sepsis represent 1/21(4.8%). (Figure 2).

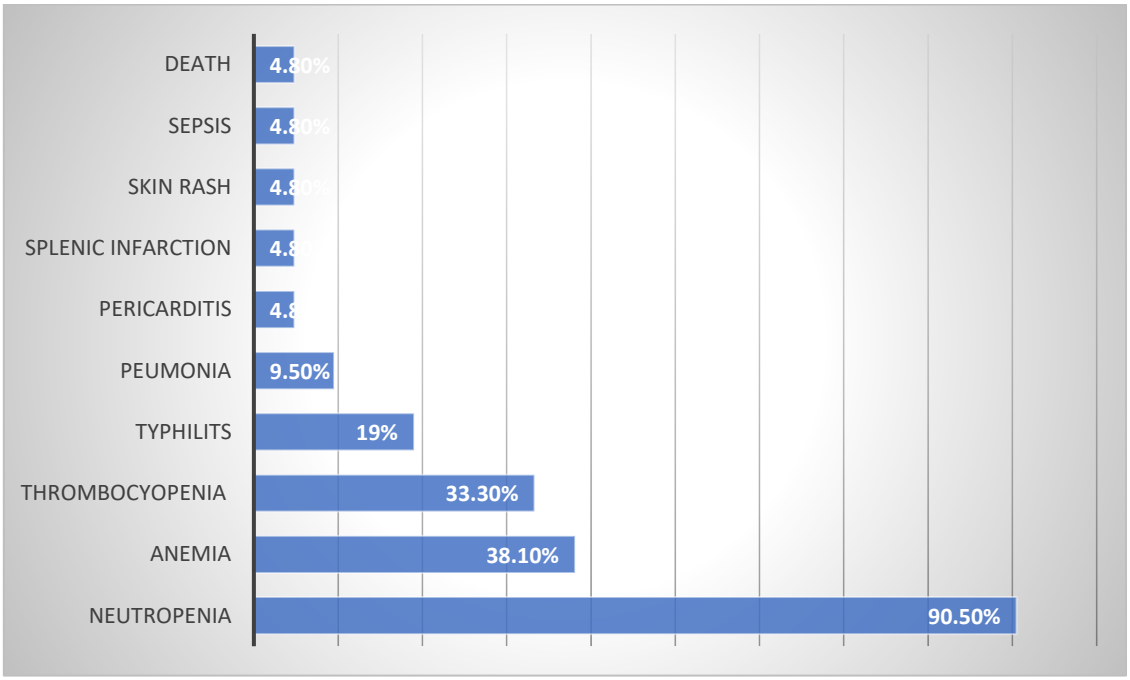

Figure 2: side effects of DEC3-VEN regimen Neutropenia, anemia, and thrombocytopenia were the most prevalent hematological adverse events during the induction treatment

When the AML patients responses after therapy regimen was correlate with various anthropophagic and hematologic parameters. We noticed that the average age of those who gain complete remission (CR) was the lowest age (49 years), and

conversely, the average age of those who had not responding (NR) was the mean of (60 years), but the age was not significant between (CR vs. NR) p value < 0.5 , as shown in Figure 3B. As expected, those who completely responded (CR) were those with the least disease subtype (FAB classification) (2), and had lower subtype (<0.00001) in comparison with those who did not respond (NR) with the most disease burden (highest subtype=4.4) see figure3A. By the same way, the ECOG score of non-respondents patients (NR) was significantly high (P=0.0006) than completely respondents (CR) (figure4A). It also became clear that the responders had significantly the lowest white blood cell (p=0.0005), platelets (p=0.002), and peripheral myeloid blasts counts (p=0.37), while the non-responders had the highest percentage of these cells, respectively. (Figure 4B). In general (all patients suffered from anemia, including those who responded to treatment, but the non-responders had a lower percentage compared to others (p=0.10). (Figure 3D).

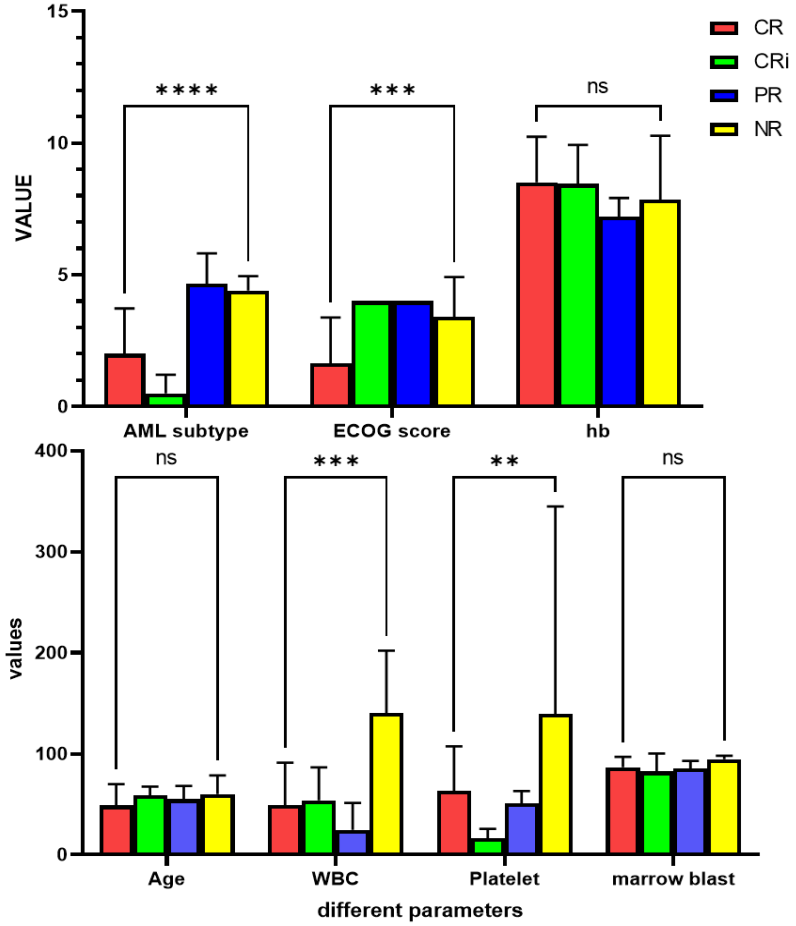

Figure 3: the association between response pattern (complete remission CR vs. non-respondent NR) and different anthropophagic and hematological parameter (AML subtype, ECOG score, HB concentration mg/ul, age, WBC, platelet count, and marrow blast cell count) the asterisks above the line indicate the level of significant difference with a confidence interval (CI) of 95%,.ns: not significant

DISCUSSION

AML patients from a highly heterogeneous group with different comorbidities, performance status, level of impaired physical function, nutritional problems, impaired cognition and Depression [18], therefore the standard therapy regimen normally associated with undesirable outcomes. Some of AML therapeutic programs included promising new regimens which have not been tested in younger age groups of patients. Therefore, we retested this treatment regimen, (which has proven remarkably effective with patients over 65), with younger patients, anticipating even better results than those observed in older patients. Although VEN with HMA has been demonstrated to be more effective than HMA alone [19], it is unclear how these regimens affect patients according to their "fitness" for intense therapy, and how to combine VEN and HMA reasonably, to reinforced

efficacy, and reduce myelo-suppression [20]. In elderly or intensive chemotherapy-intolerant patients, the induction model DEC3-VEN elicited a clear efficacy and reasonable tolerability [21]. Our study here was designed to try to answer the possibility of using a dual treatment regimen as an alternative to intensive chemotherapy for AML patients who are not elderly. The efficiency of the treatment regimen followed in this study was estimated by evaluating indicators such as: responses after 28 days, in correlation with toxicity signs and ECOG score. From previous research it is known that the response of patients may vary greatly between genetic subgroups of patients. [22-25]. Consistent with previous reports [26-29], our AML patients have been shown different responses to studied regimen, may be related to specific genetic abnormalities. Regarding to DEC3-VEN regimen, we demonstrated that newly diagnosed AML regardless of age, and even individuals who are at a high risk of TRM with rigorous IC (According to verified models TRM may increase to 30–40% or more, depending on health status and comorbidities [30]) did not have a higher early death rate with DEC3-VEN and looks like narrowing the duration of exposure according to the VEN regimen resulted in a reduction in bone marrow suppression, and patients showed reasonable tolerance to it (as elevated CR rate). TRM was 1/21(5%) after short follow-up period (28 days) although, we get 52% of CR lower than 2025 published data demonstrate CR rates of up to 74% [31]. May be this different because unlike others, we run only one cycle of the induction and in several age group of AML patient at the same time. We need a useful analysis in excluding any possible confounding effect that might have arisen as a result of the advancements in salvage therapy and supportive care throughout trial period. The further supportive means practically give additional advantage appear as an observed unexpected findings. Despite promising results manifested as 62% (CR+CRi) still a subset (24%) of AML patients do not respond to (VEN-HMA) therapy, and majority of them having recurrent /refractory AML, may be due to specific genetic characteristics [32,33]. The prospective design of this study has inherent limitations. Firstly small sample size, in addition to the sample was collected from single center experience over a full year. Also small sample size what prevent reliable statistical analysis. Secondly, the possible drawback of DEC3-VEN was its shorter course interval when compared to previous studies, due to the multiplicity of options available to patients in consulting and reviewing many specialized oncology centers inside and outside the country [34]. Also such models in practice need for periodic recalibration with incorporation of advancements in therapeutics and supportive care. [35]. our research also lacks the ability to analyze genetic abnormalities in patients, as this is not yet possible in our newly established diagnostic center. The current study here provided further evidence that alternative approach (such as less intensive regimens like Decitabine + Venetoclax), can improve response and potentially reverse the deleterious effects of methylation mutations, without increasing toxicity even in population of younger than 60 years AML patients. So, this regimen preferred not only for elderly or frail AML patients, due to having lower treatment related mortality , but also for younger AML patients due to better tolerability especially in outpatient settings and offering meaningful remission rates.

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