Received: 25 November 2022 | Revised: 4 January 2023 | Accepted: 12 January 2023

DOI: 10.1002/ajh.26846

CORRESPONDENCE

Prospective multicenter study on infectious complications and clinical outcome of 230 unfit acute myeloid leukemia patients receiving first-line therapy with hypomethylating agents alone or in combination with Venetoclax

To the Editor:

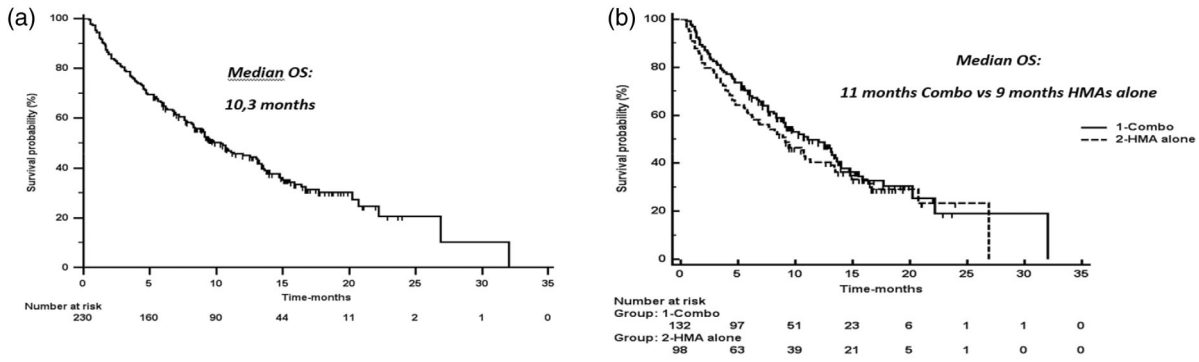
Hypomethylating agents (HMAs) are an important therapeutic option for older patients with acute myeloid leukemia (AML) and have become the backbone for combination regimens s1–s5. However, there are very limited real-life prospective studies investigating the infectious complications in AML treated with HMAs ± Venetoclax (VEN) outside of clinical trials.[1–5]

In this prospective study, designed and conducted by the SEIFEM group (Sorveglianza Epidemiologica Infezioni nelle Emopatie), we evaluated the infectious complications in a cohort of patients unfit for intensive chemotherapy, treated in first-line with HMAs alone or in combination with VEN, immediately after the introduction of this combination in clinical practice in Italy (between 2019 and 2020). Methods are reported in the Appendix S1.

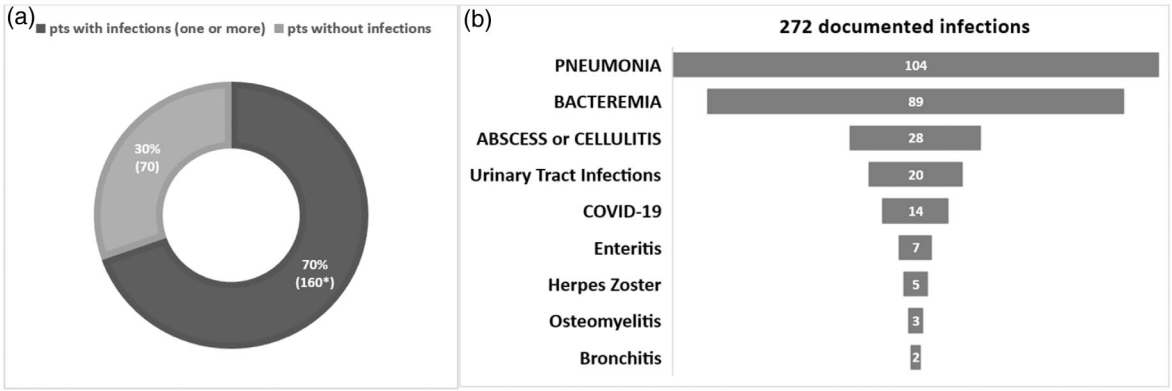
We enrolled 230 consecutive patients with a median age of 75 years (range 25–94); 157 patients (68%) had ≥2 relevant comorbidities. Patients' and AML characteristics are reported in Table S1. Of the 230 cases, 132 (57%) received first-line therapy with a combination of HMAs+VEN, while 98 (43%) were treated with HMA monotherapy. A total of 1552 HMAs cycles were administered (888/1552 with HMAs+VEN) with a mean number of cycles/patients of 6.7 ± 5.5. Notably, 82.5% (1281/1552) of cycles were administered in an outpatient setting. Table S2A shows the characteristics and duration of therapy. The best responses achieved with HMAs treatment were CR in 44% of cases with an ORR of 61% (72% for HMAs+VEN and 46% for HMAs alone, $p = .0007$)-Table S2B. After a median follow-up of 10 months (range 1–24) from the start of HMAs therapy, 144 (63%) patients had died and 86 (37%) were alive. The 1-year OS probability of the entire patient population was 46% with a median OS of 10.3 months (11 months in the HMAs+VEN cohort and 9 months in the HMAs alone cohort; p = ns)-Figure 1A. The primary causes of death were AML progression (42%), infection (26%-37/144), infection+AML (24%-35/144), and other causes (8%-12/144). The Infectious Related Mortality (IRM) was 26%, and 19/144 (13%) patients died of infectious complication while in AML response (16 in HMAs+VEN group and only 3 in the HMAs group; $p = .005$)-Table S2C.

Microbiologically or radiologically documented infectious complications (at least one) occurred in 160/230 (70%) of patients (Figure 1B). A total of 272 episodes of infection were reported in 160 patients (1.7 episodes per patient). The most common infections were pneumonia (104 episodes-42%), followed by bacteremia (89 episodes-33%), abscess or cellulitis (28 episodes-10%), and urinary tract infections (20 episodes-7%). In addition, 14 cases of COVID-19 were reported (5% of documented infections). Febrile neutropenia (one or more episodes) occurred in 38% of patients. Patients treated with HMAs+VEN had more documented infectious complications than those treated with HMAs alone (99/132–75% vs. 61/98–62%, $p = .04$) but, according to the type of hypomethylating agent used (AZA or DEC), no differences were found in the two groups (HMAs +VEN or HMAs alone). Indeed, in the HMAs+VEN group, at least 1 infection was documented in 79% of DEC + VEN-treated patients and in 72% of AZA + VEN-treated patients ($p = .41$). In the HMA single agent group, at least 1 infection was documented in 68% of DEC-treated patients and in 59% of AZA-treated patients ($p = .51$). Table S3A summarizes the characteristics of pneumonia and bacteremia, which were the most common infections. As reported, 42% of patients had at least one episode of pneumonia (a total of 104 episodes of pneumonia in 97 patients), mainly occurring within the first 3 treatment cycles (65%). The etiology of the pneumonia was bacterial in 46% of cases (47/104) or fungal in 25% of cases (26/104). At diagnosis of pneumonia, the median neutrophil count was 250/μl (range 0–19 500/μl). Notably, 86% of patients with pneumonia required hospitalization, and the related death rate (as a primary cause) was 16% (15/97 patients). The characteristics of bacteremias are reported in Table S3B. Overall, 29% of the entire patient population had at least one episode of bacteremia (with a total of 89 bacteremias in 67 patients), occurring mainly within the first three cycles of therapy. The most frequently isolated bacteria were *Escherichia coli* and *Staphylococcus spp*. At the onset of bacteremic fever, the median neutrophil count was 190/μl (range 0–20 000/μl); 94% of patients with bacteremia were hospitalized, and the related death rate was 33% (29/89 patients). Regarding antimicrobial prophylaxis in the entire patient cohort, 115/230 (50%) patients received at least anti-bacterial prophylaxis (mainly with levofloxacin-102/115) and 126/230 (55%) received at least anti-fungal mold-active prophylaxis (mainly with posaconazole-105/126). Only 90/230 patients (39%) received both prophylaxis (anti-bacterial+anti-mold). Interestingly, only 28% (13/47)

(A) Overall Survival. [a] All 230 cases. [b] OS in patients treated with HMAs alone versus HMAs+VEN.



(B) [a] N° of patients with one or more infectious episodes (clinically or radiologically documented). [b] 272 documented infections.



*61/98 (62%) in HMA alone group and 99/132 (75%) in HMA+VEN group.

(C) Factors affecting OS in univariate and multivariate analysis.

UNIVARIATE analysis-HMAs single agent (98 cases)				MULTIVARIATE analysis HMAs			
Covariate	HR	95% CI	P	SE	Exp(b)	95% CI	P
Age ≥ 75 years	0,62	0,40-1,05	0,074	0,2766	0,893	0,52 to 1,53	0,6823
Comorbidities ≥ 3	0,59	0,63-0,98	0,03	0,3018	0,6182	0,34 to 1,11	0,1111
High Risk cytogenetic molecular	0,6	0,35-1,02	0,038	0,3017	1,0777	0,59 to 1,94	0,8042
WBC ≥ 30000/µL	0,88	0,48-1,6	0,677				
Secondary AML	0,8	0,49-1,30	0,36				
Response to therapy (CR/PR)	6,69	4,01-11,1	<0,0001	0,3255	8,7528	4,63 to 16,51	<0,0001
Pneumonia	1,05	0,64-1,72	0,83				
Bacteremia	0,69	0,38-1,24	0,17				

UNIVARIATE analysis-HMAs+VEN (132 cases)				MULTIVARIATE analysis HMAs+VEN			
Covariate	HR	95% CI	P	SE	Exp(b)	95% CI	P
Age ≥ 75 years	0,8	0,51-1,27	0,34				
Comorbidities ≥ 3	0,81	0,49-1,32	0,37				
High Risk cytogenetic molecular	0,66	0,42-1,05	0,06	0,2431	1,1003	0,68 to 1,76	0,6943
WBC ≥ 30000/µL	1,37	0,77-2,33	0,33				
Secondary AML	0,79	0,50-1,24	0,29				
Response to therapy (CR/PR)	5,6	2,91-10,8	<0,0001	0,264	5,9212	3,53 to 9,90	<0,0001
Pneumonia	0,51	0,32-0,81	0,0026	0,2377	0,6488	0,40 to 1,03	0,0488
Bacteremia	0,54	0,33-0,88	0,0053	0,237	0,7421	0,46 to 1,17	0,2081

FIGURE 1 (A) Overall survival: (a) All 230 cases. (b) OS in patients treated with HMAs alone versus HMAs+VEN. (B) (a) *Number* of patients with one more infectious episodes (clinically or radiologically documented). (b) 272 documented infections. (C) Factors affecting OS in univariate and multivariate analysis.

of patients with bacterial pneumonia had received anti-bacterial prophylaxis, compared to 63% (84/133) of patients who did not develop any pneumonia (133/230) during treatment ($p = .0002$). In addition, only 31% (8/26) of patients with fungal pneumonia had received mold-active prophylaxis compared to 61% (81/133) of those who did not develop any fungal pneumonia ($p = .008$). A total of 28/67 patients (31.5%) with bacteremia had received anti-bacterial prophylaxis, compared to 90/163 patients (55%) without bacteremia ($p = .08$). Table S4 shows the factors affecting OS for all 230 cases. In multivariate analysis, the only factor affecting OS in the entire patient population and in the HMAs alone subgroup, was the achievement of AML response during therapy ($p < .0001$, 95% CI 4.26–8.95 and $p < .0001$, 95% CI 4.63–16.51, respectively). However, in the HMAs +VEN group, the OS was influenced not only by the achievement of AML response but also by the development of pneumonia ($p < .0001$, 95% CI 3.53–9.9, and $p = .046$, 95% CI 0.4-1.03, respectively) (Figure 1C). The following baseline factors were tested, in univariate and multivariate models, as possible factors affecting infection onset (predictive or protective factors) during HMAs±VEN therapy: antimicrobial prophylaxis (anti-bacterial+anti-mold), age ≥ 75 years, leukopenia at onset (WBC < 2000/μl), leukocytosis at onset (WBC > 30 000/μl), marrow blasts percentage (>or <50%), molecular cytogenetic risk (high risk vs. other) and secondary AML. Univariate and multivariate analysis showed secondary AML as a predictive factor for infection ($p = .05$ in univariate analysis and $p = .02$ in multivariate analysis), while combined antimicrobial prophylaxis (anti-bacterial+anti-mold agent) was a protective factor against pneumonia development ($p = .0003$ in univariate analysis and $p = .0001$ in multivariate analysis).

Although relevant to patients' outcomes, the issue of infectious complications in AML treated with HMAs±VEN, has not been prospectively investigated, and only retrospective studies are available. s6–s10 Some information on infectious complications is obtained from pivotal studies, which, however, did not include infections in either primary or secondary trial endpoints and, therefore, reported incomplete data. 2,s5 Recently, a few large retrospective observational studies on infectious complications in patients treated with HMAs+VEN, primarily focusing on invasive fungal infections (IFIs), have been published. However, these studies are not easily comparable due to differences in patients' characteristics and endpoints (some reporting only the incidence of fungal or bacterial infections). Furthermore, available information on prophylaxis (anti-bacterial, antifungal, or antiviral) and infection features (type of complication, timing of event, type of isolates, related mortality) is often incomplete. In addition, all these retrospective studies include patients who were treated with HMAs + VEN not only at diagnosis but also in a relapsed/refractory AML setting, thus making the treated population very heterogeneous.[3–5] The results of these studies are reported in the Supplementary Material.

The analysis of our study population (100% receiving a first-line therapy) reveals that infectious complications are very common (at least one infectious complication in 70% of patients), as reported in the VIALE-A trial (documented infections in 84% of patients), accounting for the primary cause of death in 26% of cases and being a contributing cause (associated with AML) in another 24%. Furthermore, in our study, infectious complications were found to affect the patients' outcome and survival, especially in the HMAs + VEN treated group. Indeed, in multivariate analysis, one of the factors that significantly and adversely affected OS in patients treated with the combo therapy, was the presence of pneumonia. Regrettably, a high rate of deaths in the CR phase was reported in the HMAs+VEN cohort (16/78–21%), 94% of whom were due to pneumonia or other infectious complications. Consequently, even if this prospective study confirms, in a real-life setting, a higher overall response rate (ORR) of HMAs + VEN therapy compared to monotherapy (ORR 72% vs. 46%), this finding did not translate into a significant OS benefit (median OS of 11 months in the HMA + VEN group versus 9 months in the HMAs monotherapy group; p = ns). However, it must be underlined that the patients included in this prospective observational study were the first cohort of patients treated with the HMAs + VEN combination in Italy. Therefore, the observed unsatisfactory results in terms of OS also probably reflect an early learning phase in the management of this treatment, in which the high risk of serious infectious complications was probably not properly assessed, being prophylaxis of complications is very heterogeneous and, perhaps, not always appropriate. In fact, we found that only 28% (13/47) of patients with a bacterial pneumonia had received anti-bacterial prophylaxis, only 31% (8/26) of patients with fungal pneumonia had received mold-active prophylaxis and only 31.5% (28/67) of patients with bacteremia had received anti-bacterial prophylaxis. Notably, the multivariate analysis demonstrated a significant preventive role against pneumonia for antimicrobial prophylaxis, while secondary AML represents a predictive factor for infection (this is in line with the results of Lee et al.).[5]

In conclusion, the results of this multicentric, prospective study confirm a higher ORR rate in patients treated with HMAs+VEN compared to HMAs alone ($p = .0001$). However, we found a high rate of infectious complications with a higher infection-related deaths in responder patients who were treated with the HMAs+VEN combination ($p = .005$). Multivariate analysis showed a significant preventive role against pneumonia of antimicrobial prophylaxis (anti-bacterial +mold-active prophylaxis). From a practical point of view, this study shows that infectious mortality adversely impacts the OS of this frail AML population and highlights the relevance of anti-infective prophylaxis during HMAs+VEN therapy in AML.[2,6]

DATA AVAILABILITY STATEMENT

All relevant data are within the paper. The full database are available from the Division of Hematology, University of Modena (IT) (contact: acandoni@unimore.it) for researchers who meet the criteria for access to confidential data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.