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Comparison between azacitidine and decitabine as front-line therapy in elderly acute myeloid leukemia patients not eligible for intensive chemotherapy

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ABSTRACT

We compared the efficacy of azacitidine (AZA) and decitabine (DEC) in elderly patients with untreated AML, diagnosed according to WHO criteria. In the two groups, we evaluated complete remission (CR), overall survival (OS) and disease free survival (DFS). The AZA and DEC groups included 139 and 186 patients, respectively. To minimize the effects of treatment selection bias, adjustments were made using the propensity-score matching method, which yielded 136 patient pairs. In the AZA and DEC cohort, median age was 75 years in both, (IQR, 71–78 and 71–77), median WBCc at treatment onset 2.5×10^9/L (IQR, 1.6–5.8) and 2.9×10^9/L (IQR, 1.5–8.1), median bone marrow (BM) blast count 30% (IQR, 24–41%) and 49% (IQR, 30–67%), 59 (43%) and 63 (46%) patients had a secondary AML, respectively. Karyotype was evaluable in 115 and 120 patients: 80 (59%) and 87 (64%) had intermediate-risk, 35 (26%) and 33 (24%) an adverse risk karyotype, respectively. Median number of cycles delivered was 6 (IQR, 3.0–11.0) and 4 (IQR, 2.0–9.0), CR rate was 24% vs 29%, median OS and 2-year OS rates 11.3 (95% CI 9.5–13.8) vs 12.0 (95% CI 7.1–16.5) months and 20% vs 24%, respectively. No differences in CR and OS were found within the following subgroup: intermediate- and adverse-risk cytogenetic, frequency of WBCc at treatment $\geq 5 \times 10\hat{}9$ L and $< 5 \times 10\hat{}9$/L, de novo and secondary AML, BM blast count $<$ and $\geq 30\%$. Median DFS for AZA and DEC treated patients was 9.2 vs 12 months, respectively. Our analysis indicates similar outcomes with AZA compared to DEC.

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1. Introduction

Acute myeloid leukemia (AML) is a disease that mostly affects elderly people, with a median age of 67 years at diagnosis [1]. In the last decades, unlike for young adults, overall survival (OS) of older/elderly patients has not changed meaningfully, with less than 10% of them being alive 5 years after the diagnosis and nearly 80% dying within 1 year [2,3]. Advanced age is frequently associated with greater prevalence of comorbidity, inferior performance status (PS) and organ impairment, conditions which discourage the use of intensive chemotherapy (IC) [4]. Moreover, age is associated with adverse molecular, cytogenetic, and biologic features that confer chemo-resistance and predict inferior outcomes [4,5]. All these elements explain the poor outcome of AML of older/elderly patients pointing out the importance of delivering as personalized as possible alternative treatment strategies, supplanting the conventional "one-size-fits-all" approach. In this regard, hypomethylating agents (HMAs), have proved to be a valid alternative for older/elderly patients with AML. In fact, several clinical trials and real life studies [6–13], have shown that azacytidine (AZA) and decitabine (DEC) are well tolerated, improve overall survival (OS) compared to best supportive care or low-dose cytarabine (LDAC), and can be administrated in an outpatient setting, making them the ideal agents for patients who are unfit to receive intensive treatment or haematopoietic stem cell transplant (HSCT). Furthermore, in current clinical practice, there is an ever increasing tendency to use HMAs as a backbone for combination therapy with other drugs, such as venetoclax (VEN) [14–16]. Despite the widespread use of these agents, there are still questions pending, that pertain which of the two is more efficacious and results in a superior clinical benefit. Actually, a head-to-head comparison between AZA and DEC has not been performed in randomized trials, and the available studies are characterized by a remarkable variability, in terms of results. Indeed, the choice of which HMA to use is still a dilemma, depending mostly on the experience and the attitude of the attending physician and patients' decision.

The aim of this observational retrospective multicentric study was to compare the efficacy and safety of AZA and DEC, in two matched cohorts of older/elderly patients, with untreated AML and unfit to receive intensive chemotherapy or HSCT.

2. Materials and methods

2.1. Patients and treatment regimens

In the present multicentric study, criteria to receive AZA or DEC were a diagnosis of AML according to the WHO classification, age $\geq$ 60 years, ECOG PS 0–3, adequate cardiac, renal and hepatic function, and the absence of uncontrolled infections. All patients or their guardians provided written informed consent to allow collection of personal data in accordance with the Declaration of Helsinki and Italian privacy laws. The AZA and DEC groups included 139 and 186 AML patients, respectively. Patients were seen and treated between February 2005 and July 2018 in 15 haematological centers, across Italy. All participating institutes received a specific Case Report Form (CRF) to register all the patients treated with AZA or DEC and to collect their data. The CRF captured patients' data inherent disease characteristics, medical history, PS and comorbidities, number of delivered AZA or DEC cycles, response, survival, relapse, hematologic and extra hematologic toxicity. Median age was 75 years [Interquartile range (IQR): 71–78], 58.5% of patients were males, median white blood cells count (WBCc) at treatment onset 2.8 $\times$ 10^9/L (IQR: 1.62–65.5). Karyotype was evaluable in 281 patients (86%); according to refined Medical Research Council (MRC), 188 (66%) had intermediate, 88 (32%) unfavourable and 5 (2%) favourable risk; 58% of the patients had blasts $\geq$ 30%, and 45% of patients had a secondary AML (sAML). AZA was administered subcutaneously 75 mg/m^2 /day for 7 days or 100 mg/day flat dose every 28- day cycle in 132 (95%) and 7 (5%) patients, respectively. Fourteen patients with a WBCc $>$ 30 $\times$ 10^9 /L required the addition of hydroxyurea until their WBC count declined to $<$ 10 $\times$ 10^9 /L. DEC was administered at the registered schedule of 20 mg/m^2/iv daily for 5 days every 4 weeks. AZA or DEC were administered until disease progression, unacceptable toxicity, or patient decision to withdraw consent. Growth factors were not administered routinely during treatment. After a maximum of 30 months of follow up (median follow up 27 months), the median OS for the entire population was 11.4 months (IQR 9.3–13.6).

2.2. Assessment of efficacy

BM aspiration for response assessment was performed every 4 cycles, in both the regimens. Response evaluation was scored according to criteria of the revised recommendations of the International Working Group (IWG) in AML [17]. Accordingly, a morphologic CR was defined as $\leq$ 5% BM blasts with an absolute neutrophil count $\geq$ 1 $\times$ 10^9/L and platelets $\geq$ 100 $\times$ 10^9/L. A CR with incomplete blood count recovery (CRi) required the same CR criteria but prolonged neutropenia (absolute neutrophil count $<$ 1 $\times$ 10^9/L) or thrombocytopenia (platelets $<$100 $\times$ 10^9/L). A partial remission (PR) required that all criteria for CR were met, but a BM blast percentage between 5% and 25%. Patients with $>$ 25% blasts or reduction $<$ 50% were assessed as resistance. Patients were classified as non-responders after four-six cycles, unless they showed progressive disease (PD) or died before. The evaluation of response was centrally reviewed as detailed elsewhere [18].

2.3. Statistical analysis and outcome definitions

Patients and disease characteristics were expressed as median and IQR for continuous variables and count and percentages for categorical ones.

Overall Survival (OS) was defined as the time interval from starting treatment until death from any cause. Patients who did not have an OS events were censored at the date they were last known to be alive. Disease-free survival (DFS) was measured from the date of achieving morphological CR until the date of relapse or death from any cause. Patients who did not have DFS events were censored at their last disease assessment date.

The DFS and OS probabilities were estimated in each treatment group using the non-parametric Kaplan-Meier method and displayed graphically. The treatment difference in DFS and OS were assessed by the log-rank test. A Cox proportional hazard model was used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment groups. The hazard ratio and its 95% confidence interval from the Cox model were reported. The proportional hazards assumption was verified using graphical methods; scaled Schoenfeld residuals and graphical checks proposed by Klein and Moeschberger were performed.

To adjust for baseline differences between treatment groups a propensity score matching method was applied by using a nearest neighbour matching algorithm that pairs patients with the closest propensity scores within a defined limit (calipers of width equal to 0.2). Analyses were performed by Free Software R version 4.0.0.

3. Results

Propensity score matching based on age, WBCc at diagnosis, sAML, ECOG PS and karyotype, yelded two matched cohorts of 136 patients. Clinical characteristics of the two cohorts are reported in Table 1.

3.1. Outcomes comparison between AZA and DEC cohorts

Overall, 272 patients were selected for comparative analysis. The median time from AML diagnosis to initiation of AZA and DEC and the median number of cycles delivered was 29 (IQR, 14.0–56.0) vs 20 days (IQR, 12.0–34.5) and 6 (IQR, 3.0–11.0) vs 4 (IQR, 2.0–9.0), respectively.

Table 1
Clinical characteristics of azacitidine and decitabine treated patients.

Clinical characteristics	AZA	DEC
N (%)	136 (50)	136 (50)
Median age [yrs] (IQR)	75 (71.7–79)	75 (71–77.2)
Age		
60–70	32 (23.5)	22 (16.2)
71–80	78 (57.4)	98 (72.1)
> 80	26 (19.1)	16 (11.8)
Median WBCc x10^9/L at treatment onset (IQR)	2.5 (1.6–5.8)	2.9 (1.5–8.1)
Median BM blast count [%]	36	35
20–29	74 (56.1)	38 (28.4)
30–50	35 (26.5)	46 (34.3)
> 50	23 (17.4)	50 (37.3)
Secondary AML	59 (43)	63 (46)
Karyotype		
Intermediate risk	80 (58.8)	87 (64)
Adverse risk	35 (25.7)	33 (24.3)
Failure	21 (15.5)	16 (11.7)
ECOG PS		
0–1	123 (90.4)	95 (70)
≥ 2	13 (9.6)	41 (30)
Median number of cycles (IQR)	6 (3.0–11.0)	4 (2.0–9.0)
ORR	53 (39)	48 (36)
CR+CRi	32 (24)	39 (29)
PR	21(15)	9 (7)
2-yr OS	20	24
Median OS [m] (95% CI)	11.3 (9.5–13.8)	12.0 (7.1–16.5)
Mortality rate [%]		
30 days	8 (6)	8 (6)
1 year	59 (50.2)	51 (50.7)
Median DFS [m] (95% CI)	9.2 (7.93–16.3)	11.9 (9.08–21.2)

Abbreviations: N: number of patients; AZA: Azacytidine; DEC: decitabine; Y: Years; WBCc: white blood cells count; BM: bone marrow; PS = performance status; AML: acute myeloid leukemia; ORR: overall response rate; CR: complete response; PR: partial response; OS: overall survival; DFS: disease free survival; m: months; CI = confidence interval

In the AZA and DEC cohorts, 72% and 57% of the patients received ≥ 4 cycles of therapy, respectively. As reported in Table 1, CR, and overall response rate (ORR), i.e. CR + CRi + PR, were not significantly different between patients who received AZA and DEC. Eighty-three and 88 patients were classified as not responding: 45 (33%) showed a stable disease (SD) in both groups, 21 (15%) and 13 (10%) experienced a major hematological improvement (HI) in at least one lineage, respectively.

The mortality rate at 30 days and 1-year was not statistically different between AZA and DEC cohorts (Table 1). Early death in patients treated with AZA occurred from disease progression (4 patients) and infection (4 patients), while in those treated with DEC from disease progression (2 patients), infection (3 patients), cerebral haemorrhage (1 patient) and other causes (2 patients). Of 32 patients who obtained CR with AZA treatment, 21 (65%) experienced a relapse, 2 died in CR, 9 were alive at the last follow up. Patients who achieved a response (CR, CRi, PR) showed a significantly longer OS than patients who did not (14 vs 7.3 months, respectively, $p < 0.001$). Of 39 patients who obtained CR with DEC treatment, 22 (56%) experienced a relapse, 2 died in CR, 15 were alive at the last follow up. Patients who achieved a response showed a significantly longer OS than patients who did not (13.5 vs 4 months, respectively, $p < 0.001$). The greatest efficacy of AZA and DEC was observed in patients with intermediate cytogenetic risk and WBCc < 5.0 x $\times$ 10^9 /L (median OS 17.3 and 13.8 months vs 15.8, and 13.5 months, respectively). Only 8 (6%) and 6 (4%) patients after AZA and DEC treatment, received salvage therapy, respectively.

3.2. Overall survival comparison between AZA and DEC cohorts

Survival estimates were not significantly different between AZA and DEC treated patients, being median OS and 2-year OS rates 11.3 (IQR 9.5–13.8) and 12 (IQR 7.1–16.5) months (p = ns) and 20% and 24%, respectively (Fig. 1). Median DFS of patients who achieved a response with AZA or DEC was 9.2 (95% CI: 7.9-16.3) vs 11.9 (95% CI: 9.08-21.2) months (p=ns), respectively (Fig. 2).

3.3. Subgroup analysis for response and survival between AZA and DEC cohorts

In a further step of analysis, we evaluated the effect of AZA vs DEC according to the following patient and disease related prognostic factors: sex, intermediate and unfavourable risk cytogenetic, age (60–70, 71–80, >80 years), ECOG performance status < 2 and ≥ 2, de novo and sAML, WBCc at treatment $\geq 5 \times 10^9$ L and $< 5 \times 10^9$/L, BM blast count (20–29% 20–50%, >50%), number of cycles delivered (0–4, 5–10, >10). Again, we did not find any statistically significant difference in OS, CR and ORR rate between AZA and DEC treated patients (Figs. 3, 4 and 5, respectively).

4. Discussion

Although AZA and DEC similarly lead to DNA hypomethylation by inhibiting DNA methyltransferase, however, different mechanisms of action of the two drugs on cell viability, protein synthesis, cell cycle and gene expression have been reported [19]. In addition, from a clinical point of view, comparative analyses regarding the efficacy and safety of AZA and DEC are very limited. In the present study, we first confirmed the efficacy of AZA and DEC in a large "real world" setting. In fact in our series, CR rate and median OS of patients treated with AZA and DEC were 24% vs 29% and 11.3 vs 12 months, respectively. These results compared consistently with those reported in two large multicentre, open-label, randomized, phase 3 trials in which, CR rate and median OS of the AZA and DEC cohort were 27.8% and 12.1 months [6], and 17.8% and 7.7 months [10], respectively. Secondly, we found no significant difference in survival between AZA and DEC treatment, when used in routine practice. The results of a recent real-world study confirmed the similar effectiveness of the two drugs, being the median OS from diagnosis of AZA and DEC treated patients 7.1 and 8.2 months, respectively [20]. Notably, our results confirm the strict association between duration of exposure, the delivery of a HMA effective dose and patient survival. Indeed, the disparity of outcome between our DEC cohort and DACO-016 trial, can be explained by the relatively more cycles of DEC received by our patients compared with those of the DACO-016 trial (median number of cycles delivered 6 vs 4, respectively). For the same reason, the OS of our cohort treated with AZA is comparable to that of

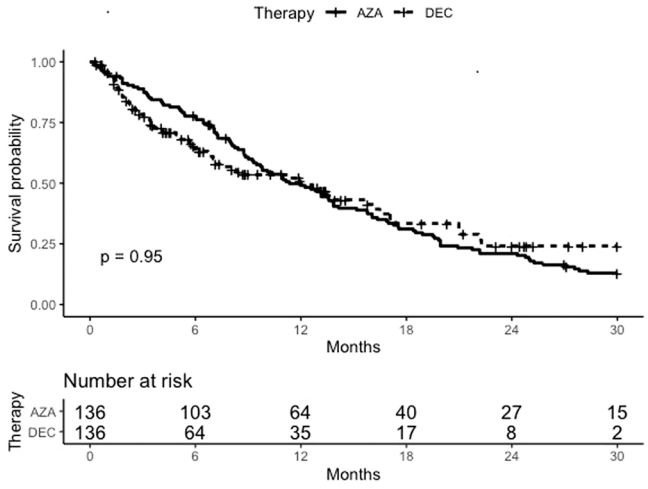

Fig. 1. Overall Survival among patients treated with azacitidine and decitabine.

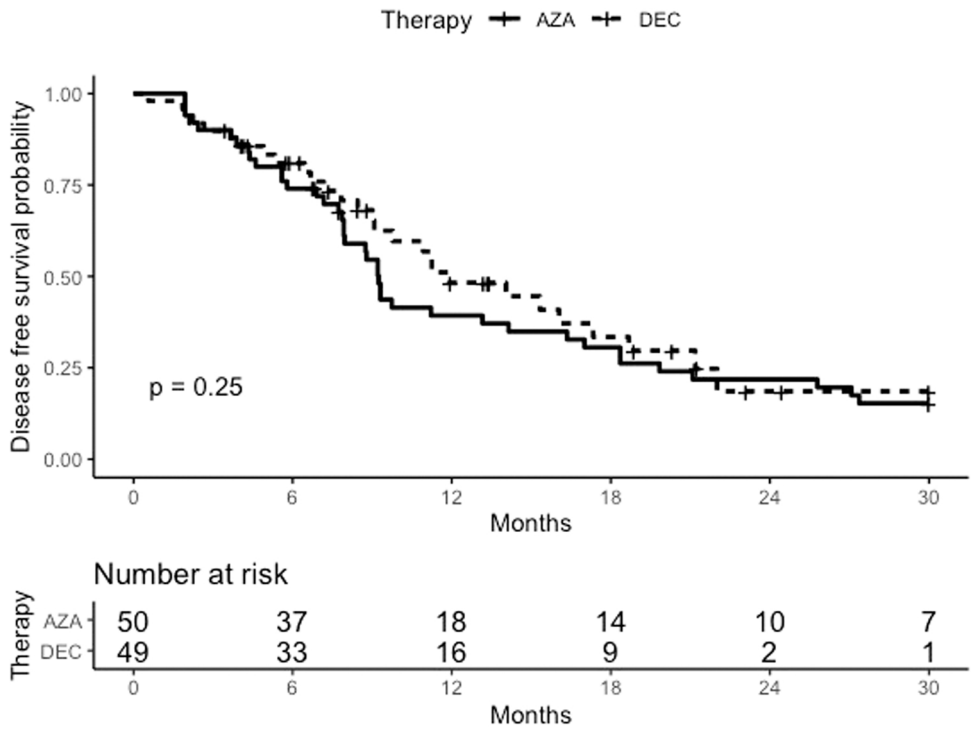

Fig. 2. Disease Free Survival among patients treated with azacitidine and decitabine.

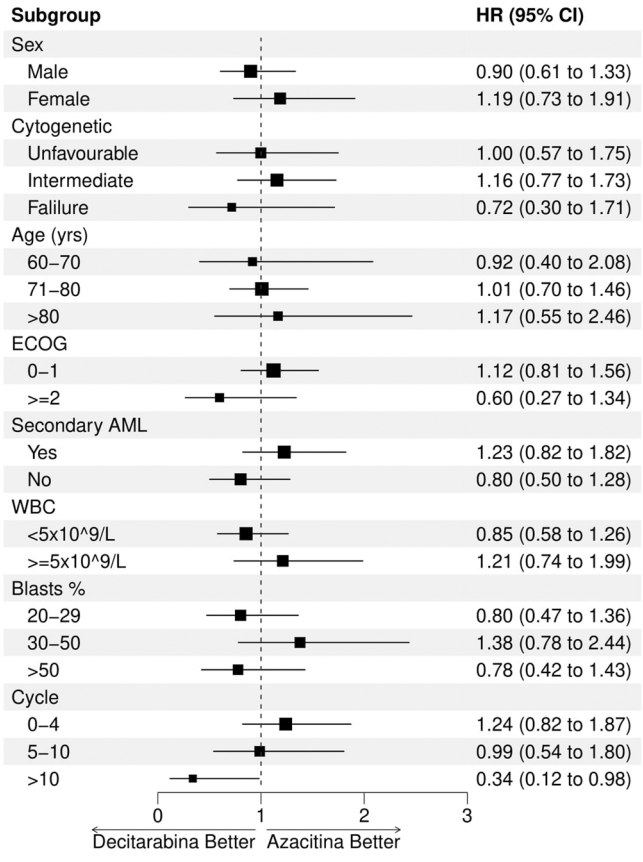

Fig. 3. Forest plot of hazard ratios for overall survival.

patients treated in the AZA-001 protocol (median number of cycles delivered 6 in both groups). Likewise, the better OS of our patients compared to those in Zeidan's real-world study, depends not only on the shortened duration of exposure (in the Zeidan's study the median number of cycles delivered was 3 for both HMAs, with only 41.8% of patients receiving $\geq$ 4 cycles), but also on the use of a non-optimal dosage, as only 34.3% of patients treated with AZA followed a 7-day regimen, whereas in our study > 90% of patients followed the classic 7-day schedule. A recent meta-analysis confirms our observation and supports the superior effectiveness of the standard dose scheme of AZA over reduced dosages (median OS 10.83 months, 95% CI: 9.07–12.59 vs 6.28 months, 95% CI: 4.23–8.32, respectively p = 0.002) [21]. It is also noteworthy that our study has the advantage of comparing two homogeneous cohorts of patients, matched for clinical-biological characteristics. From this point of view, our results compare favorably with those of the randomized Phase 3 ASTRAL-1 trial [22]. In the ASTRAL-1 trial, treatment naïve AML patients, not eligible for IC (because of age $\geq$ 75 years or comorbidities including ECOG PS 3) were randomized to either guadecitabine, or a preselected investigators' Treatment Choice (TC), that was AZA (171 patients), DEC (167 patients), or low dose Ara-C (LDAC). Similarly to our study, age, PS, adverse cytogenetic risk group and secondary AML frequency were well balanced between AZA and DEC groups and the analysis showed a CR rate of 17.5% vs 19.2% (p = 0.70), an overall CR (CR+CRp+CRi) of 22.2% vs 25.1% (p = 0.53) and a median OS of 8.7 vs 8.2 months, respectively (p = 0.8).

Another important aspect of our study is that we found no differences in the efficacy of the two drugs within specific clinical-biological subgroups. Over the last years, several published experiences have alternatively suggested a higher efficacy of AZA or DEC in patients with poor risk cytogenetics [23,24] with BM blast counts < 30% [7] or $\geq$ 30% and WBC $< 15 \times 10^9$ /L [25], or in patients with myelodysplastic-related changes AML [26]. Both AZA and DEC were most effective in patients with intermediate cytogenetic risk and WBCc $< 5.0 \times 10^9$ /L. Previous studies have shown that it is possible to identify certain subgroups of patients who can benefit most from HMAs therapy [8,27–30], thus emphasizing the importance of an appropriate selection of candidates to be treated with these drugs. In our study, the 30-day and 1-year mortality rate was 6% for both drugs and 50.2% vs 50.7%, respectively. These findings are very consistent with those of a recent Spanish "real-world" study [30], and with a recent meta-analysis on more than

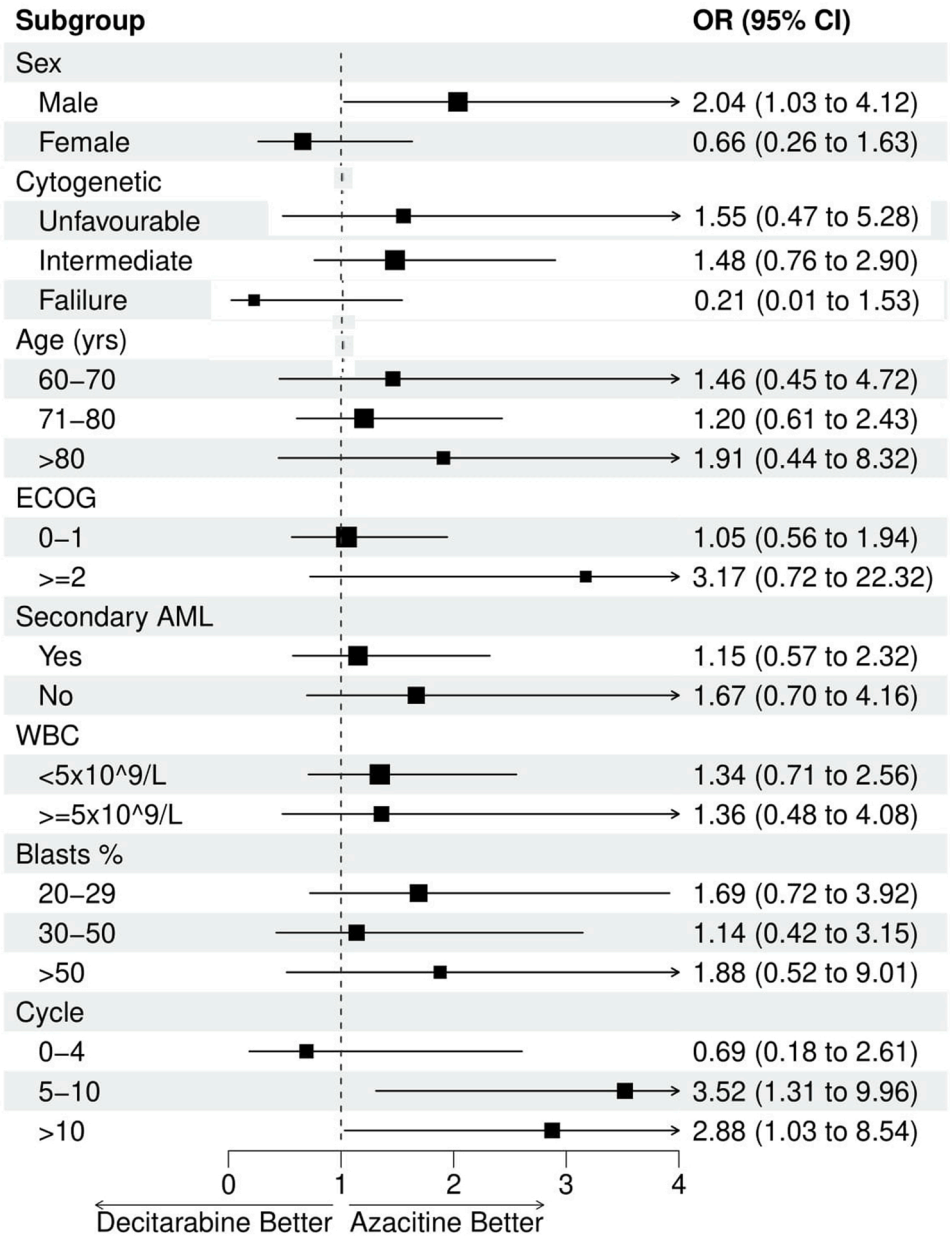

Fig. 4. Forest plot of hazard ratios for complete remission achievement.

2000 patients ([21]. In our series, the most frequent cause of 1-year mortality (equally distributed across AZA and DEC cohort) was disease progression (52%) compared to infectious or haemorrhagic complications (24%). These findings highlight the acceptable haematological toxicity of HMAs, allowing outpatient treatment in the majority of these frail patients while maintaining moderate disease control, which reflects the low quality of response typically achieved with HMAs alone. Indeed, even in patients who obtained a remission, the duration of DFS was short, thus suggesting that responses are associated with an inadequate clearance of residual disease. These rather disappointing results have paved the way to therapies combining HMAs with new drugs, capable of increasing the CR rate and prolonging the duration of response. Combination of HMAs with VEN, is now becoming the new standard of care for AML patients unfit for intensive chemotherapy. Our results stand for a remarkable lower response rates and OS, of AZA and DEC as single agents, as compared to the combination with VEN (39% vs 35% vs 67% and 12.6 vs 13.1 vs 17.5 months, respectively), which was tested in the VIALE-A trial. Importantly, 41% of patients treated with combination therapy achieved measurable residual disease (MRD) negativity by flow cytometry and had a 70% likelihood of sustained remission at 18 months [31]. Recent studies, have reported similar response rates and OS in patients treated with VEN-AZA and VEN-DEC [14,16]. Despite the higher efficacy of the HMAs-VEN combination, however the toxicity of this schedule is not negligible, particularly when elderly patients are treated on outpatient basis. The latest update of the VIALE A study [32] confirmed similar early mortality in both arms, but higher rates of febrile neutropenia and adverse events which led to more discontinuation and interruption in the AZA-VEN than in the AZA-Pbo arm. This toxicity may have a greater impact on treatment outcome in real-world populations of elderly patients who, treated outside of research protocols, are less clinically selected and thus more frail for multiple comorbidities and polypharmacy.

In conclusion, the results of this study suggest that AZA and DEC have comparable efficacy but poor and limited disease control in elderly patients with newly diagnosed AML deemed unfit for IC. Therefore, currently, HMAs-VEN should generally be the first line of treatment,

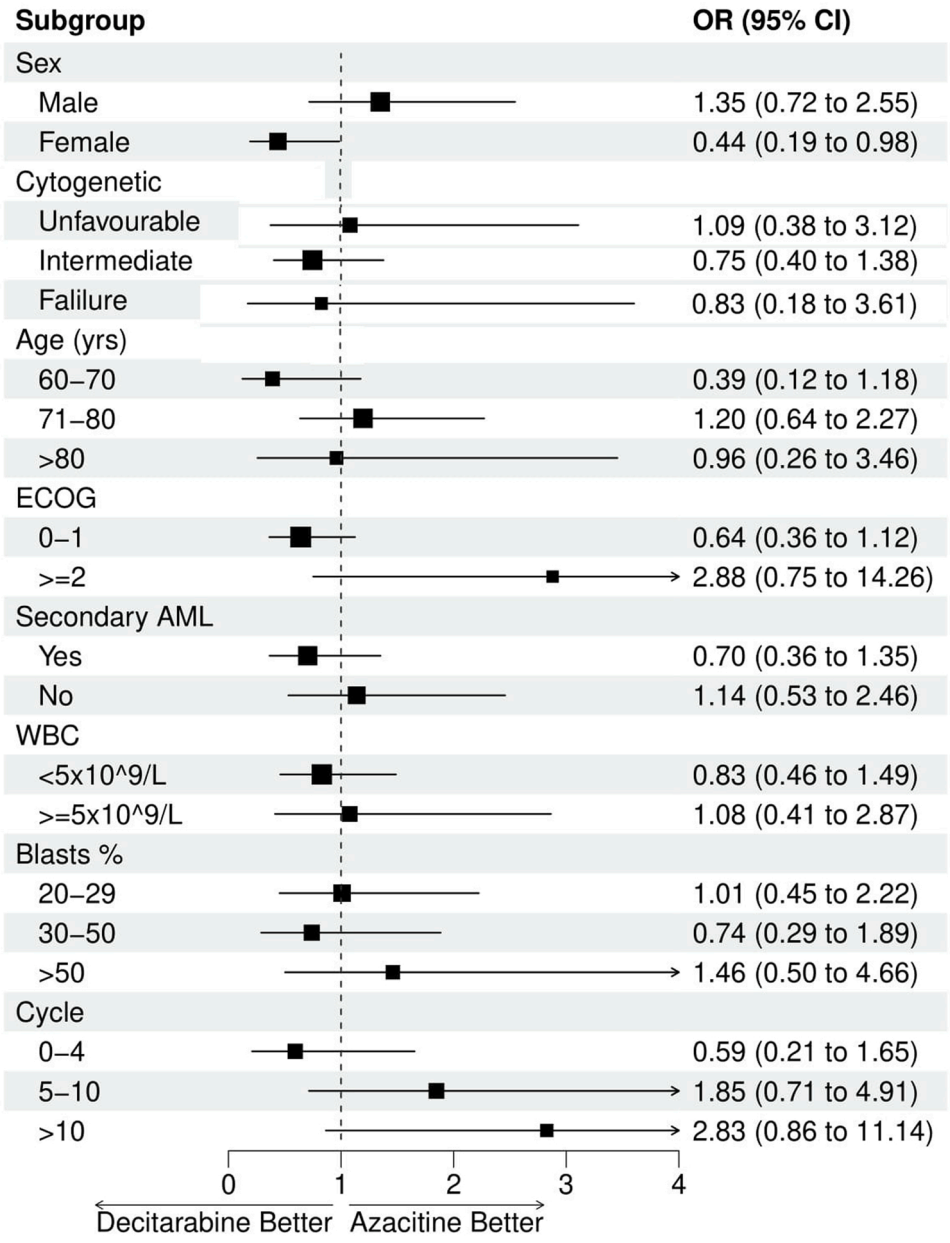

Fig. 5. Forest plot of hazard ratios for overall response rate achievement.

particularly for patients with specific genetic signature, with highly proliferative disease or those in urgent need of achievement response. However, since uncertainties about the toxicities associated with VEN are still a subject of debate, monotherapy with HMAs may still have a role in specific subgroups of frail or very frail patients in whom BSC would be the only option. The patient's priorities, socioeconomic conditions (e.g. presence of a care giver), the treatment-related side effects, the quality of life and the pharmaeconomic impact, should all be considered when selecting the treatment. Accordingly, it appears necessary, in the near future, to establish new fitness criteria to identify the most appropriate therapy in different subsets of elderly patients.

Ethical approval

All procedures performed in the study 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.

CRediT authorship contribution statement

All the authors contributed to the study conception and design, Material preparation and data collection were performed by Luca Maurillo, Anna Candoni, Cristina Papayannidis, Erika Borlenghi, Davide Lazzarotto, Luana Fianchi, Mariarita Sciumè , Maria Elena Zannier, Francesco Buccisano, Maria Ilaria Del Principe, Valentina Mancini, Massimo Breccia, Renato Fanin, Elisabetta Todisco, Monia Lunghi, Raffaele Palmieri, Nicola Fracchiola, Pellegrino Musto, Giuseppe Rossi, Statistical Analysis was performed by Alessandra Spagnoli. Luca Maurillo, Anna Candoni, Giuseppe Rossi, Pellegrino Musto, Adriano Venditti collected and interpreted data, The first draft of the manuscript was written by Luca Maurillo and Adriano Venditti, All authors commented on previous versions of the manuscript, All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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Declaration of interest

LM received a speaker honorarium from BMS/Celgene and Janssen. AS declares she has no conflict of interest. AC received a speaker honorarium from BMS/Celgene and Janssen. CP received a speaker honorarium from BMS/Celgene and Janssen. EB declares she has no conflict of interest. DL received a speaker honorarium from Janssen. LF received a speaker honorarium from BMS/Celgene. MS declares she has no conflict of interest. MEZ received a speaker honorarium from Janssen. FB received a speaker honorarium from BMS/Celgene and Janssen. MIDP received a speaker honorarium from Janssen. VM declares she has no conflict of interest. MB received a speaker honorarium from BMS/Celgene. RF declares he has no conflict of interest. ET declares she has no conflict of interest. ML declares she has no conflict of interest. RP received a speaker honorarium from Janssen. NF received a speaker honorarium from BMS/Celgene and Janssen. PM received a speaker honorarium from BMS/Celgene and Janssen. GR received a speaker honorarium from Janssen. AV received a speaker honorarium from BMS/Celgene and Janssen.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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