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Research paper

Efficacy and toxicity of Decitabine in patients with acute myeloid leukemia (AML): A multicenter real-world experience

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ABSTRACT

Background: The hypomethylating agent Decitabine (DAC) is a valuable treatment option in acute myeloid leukemia (AML), particularly in elderly patients (pts) not suitable for intensive chemotherapy (CHT). However, limited data are available about efficacy and safety of DAC in clinical practice.

Patients and methods: We retrospectively reviewed data of 104 AML pts treated with DAC in eight Italian Hematological Centers from 2015 to 2017. The objective of this study was to evaluate the efficacy and safety of DAC in older AML pts outside of clinical trial. Seventy-five (75%) pts received DAC as first line treatment (Cohort 1) and 29 pts as salvage therapy (Cohort 2). All pts received a DAC schedule of 20 mg/sqm IV for 5-days, every 28 days. The median age was 72.5 years (74 in cohort 1 and 66 in cohort 2) and 16% of pts had an ECOG performance status > 2 at the start of DAC treatment (with non-significant difference in the two cohorts). The cumulative illness rating scale (CIRS) was > 6 in 27% of pts. Forty-five pts (43%) had secondary AML. Bone marrow blast count was > 30% in 64% of patients (67/104). In the relapsed cohort 17/29 (59%) patients were treated with DAC after conventional CHT, 5/29 (17%) after allo-SCT and 7/29 (24%) after azacitidine therapy.

Results: A total of 469 DAC cycles were given to the 104 pts with a median of 3 cycles (range 1–21) and 45/104 (43%) pts received > 4 cycles. The Overall Response Rate (ORR = Complete Remission-CR plus Partial Remission-PR) was 33%, significantly higher in Cohort 1 (42%) compared to Cohort 2 (14%) ($p = 0.009$). The median duration of response was 6 months (range 1–20). In Cohort 1 the best response (CR or PR) was obtained between 3th and 6th cycle. In multivariate Cox regression analysis, achievement of CR or PR (HR = 0.78; $p = 0.0004$), CIRS < 6 (HR = 0.9; $p = 0.04$) and complex karyotype (HR = 0.8; $p = 0.03$) were significant predictors of better overall survival (OS). Median OS from the start of DAC therapy was 11 months for the whole population with a significant OS advantage in Cohort 1 (median OS 12.7 mths vs 6.3 mths; $p = 0.003$); median OS was significantly longer in responders compared to non-responders (22.6 mths vs 5.7 mths; $p < 0.0001$). At the last follow-up, 56 patients (54%) are still alive and 48 (46%) are dead (71% due to disease progression). The most common toxicities were myelosuppression and documented infectious complications that occurred mainly during the first 4 cycles.

Conclusion: These data confirm the efficacy (ORR 33%) and the acceptable safety profile of DAC in the real life management of AML in elderly pts unsuitable for intensive CHT, with a significant better performance in first line therapy (ORR 42%, median OS 12.7 mths). The efficacy of DAC, both in first line and as salvage therapy,

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may probably be improved with combined treatment strategies and/or with different DAC schedules that could increase its anti-leukemic effect.

1. Introduction

Acute myeloid leukemia (AML) treatment options for older patients with AML either for first line or in relapsed/refractory cases are limited, with very poor outcomes [1–3]. Elderly patients are often ineligible for intensive anti-leukemic chemotherapy (CHT) or participation to clinical trial due to poor performance status and/or organ dysfunction. This population has an increased incidence of pre-existing myelodysplastic syndrome (MDS), unfavorable cytogenetics and multi-drug-resistant phenotype, any of which can impair the efficacy of intensive antileukemic CHT [1–3]. In fact, for patients with adverse prognostic features and unable to receive intensive CHT, complete response (CR) rate is less than 20%, early mortality can be as high as 50% and 1-year survival is < 10% [2,3]. Furthermore, even younger patients fit for intensive CHT but relapsing early after first CR have poor outcome with overall survival (OS) inferior to 30% at 2 years [1,4].

In recent years the hypomethylating agent Decitabine (DAC) has emerged as a valid option as first line therapy in elderly AML as reported in DACO-016 trial [5]. Based on results of this multicenter, randomized, open-label, phase III trial, DAC was approved by European Medicine Agency (EMA) for the treatment of elderly patients with newly diagnosed AML not eligible for standard CHT [5,6]. Recently, some studies have also suggested that DAC (with a variable schedules) may have a role as salvage treatment [7–12]. The use of hypomethylating agents for the treatment of AML is currently increasing, however scarce data are still available regarding efficacy and safety of DAC outside of clinical trials in daily clinical practice.

We retrospectively reviewed data of 104 AML patients treated with DAC (with a total of 469 DAC cycles) in 8 Italian Hematological Centers (in the last 2 years, from February 2015 to August 2017) in order to evaluate the efficacy and safety of DAC in daily clinical practice.

2. Patients and methods

The study population included 104 AML patients treated with DAC in 8 Italian Hematological Centers (Divisions of Hematology of north east of Italy: Udine, Padua, Trieste, Verona, Vicenza, Pordenone, Treviso, Aviano) from February 2015 to August 2017. AML was defined by World Health Organization criteria [13]. All patients provided written informed consent for treatment with DAC and this study was approved by the institutional review board. All participating centers received a specific Case Report Form to register all AML patients treated or under treatment with DAC. Patient data were queried for hematological disease characteristics, medical history, performance status and comorbidities, number of DAC cycles, response, survival, relapse, hematologic and extra hematologic toxicity.

This is an observational study and the primary objective was to evaluate efficacy of DAC (approved schedule of 20 mg/sqm IV for 5-days, every 28 days) in a real life setting in terms of Complete Remission (CR), Partial Remission (PR), Overall Response Rate (ORR), Overall Survival (OS) and Disease Free Survival (DFS). The aim of this study was also to evaluate the toxicity (especially infectious complications) during DAC treatment.

Cohort 1 consisted of 75 patients who received DAC as first line treatment; **cohort 2** of 29 patients who were salvaged with DAC after relapse or lack of response to the previous therapies. All patients received the same DAC schedule, 20 mg/sqm intravenously over 1 h for 5 days cycles every 28 days. Treatment was continued if there was evidence of clinical, hematologic and/or marrow response or at least stable disease (SD).

Response was evaluated according to National Cancer Institute (NCI) criteria revised by the International Working Group (IWG) [14]. Time to response was calculated from start of DAC until detection of best response (CR or PR); duration of response was defined as time from best response until loss of response, last follow-up or death. Adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 3.0. [15]. FLT3 mutational analyses were performed according to the method described by Gale and colleagues [16].

To categorize the comorbidities and to assess the performance status (PS) of patients before the start of DAC treatment we used the Cumulative Illness Rating Scale for geriatrics (CIRS) and the Eastern Cooperative Oncology Group (ECOG) scale [17,18]. The CIRS > 6 indicates a high comorbidity burden, CIRS 0 a low comorbidity burden and CIRS < 6 an intermediate comorbidity burden [17].

During DAC treatment, to check the response, bone marrow biopsies and aspiration were performed, every 1–2 months, at the discretion of the attending physicians. Patients received, according to the Center policy, supportive care including transfusions, antibacterial, anti-fungal and anti-viral prophylaxis.

2.1. Statistical analysis

Descriptive statistics (including mean, standard deviation, median, range, frequency, percentages) were calculated to analyze and compare the two study cohorts. Overall survival (OS) (defined as the interval between the date of initial treatment and death) was estimated by Kaplan–Meier survival analysis. OS curves were compared using the log-rank test. The independent effect of demographic/clinical predictors on OS was assessed by multivariate Cox proportional hazards regression analysis. All of the above analyses were performed separately for first diagnosed AML patients (cohort 1) and patients with relapsed/refractory AML (cohort 2). Adjusted hazard ratios were computed and 95% confidence intervals (CIs) for the hazard ratios and median OS time estimates are presented to assess the precision of the obtained estimates. All p-values are two-sided, with statistical significance evaluated at the 0.05 alpha level. Fisher's exact test was used to compare group differences in categorical variables. Data were analyzed with MedCalc software (version 12.5.0.0; MedCalc Software bvba, Ostend, Belgium).

3. Results

3.1. Patient's characteristics

The demographic characteristics of the whole population (104 patients) and per single cohort are shown in Table 1. The median age of patients was 72.5 years (74 in cohort 1 and 66 in cohort 2). Only 16% of patients had an ECOG scale > 2 before starting DAC treatment (with non-significant difference in the two cohorts). The cumulative illness rating scale (CIRS) was > 6 in the 27% of patients (32% in cohort 1 and 14% in cohort 2). There were no patients with CIRS 0. Forty-five patients (43%) had secondary AML (44% in cohort 1 and 41% in cohort 2). Bone marrow blast count was more than 30% in 64% of patients (67/104) without differences between the two cohorts (p = 0.11). According to CALGB criteria, 22% of patients had a complex cytogenetics. Molecular diagnostics were available for 67 patients with mutations of FLT3-ITD in 10 (15%). In the cohort 2, 17/29 (59%) patients were treated with DAC after conventional CHT, 5/29 (17%) after Allo-SCT and 7/29 (24%) after azacitidine therapy.

A total of 469 DAC cycles were administered to the 104 patients with a median of 3 cycles (range 1–21) in cohort 1 and 2 cycles (range

Table 1
Baseline characteristics of patients.

	ALL PATIENTS N = 104	COHORT 1 (first line therapy) N = 75	COHORT 2 (salvage therapy) N = 29
M/F	**57/47**	40/35	17/12
Median age (range)	**72.5 (25-84)**	74 (65-84)	66 (25-82)
Secondary AML	**45/104 (43%)**	33/75 (44%)	12/29 (41%)
ECOG P.S.	**87/104 (84%)**	66/75 (88%)	21/29 (72%)
< = 2	**17/104 (16%)**	9/75 (12%)	8/29 (28%)
> 2			
CIRS > 6	**28/104 (27%)**	24/75 (32%)	4/29 (14%)
Bone marrow blast cells > 30%[b]	**67/104 (64%)**	52/75 (69%)	15/29 (52%)
WBC median (range)	**2.9 (0.2-255)**	3.4 (0.8-255)	2.9 (0.2-21.8)
Complex karyotype	**18/83**[a] **(22%)**	11/55[a] (20%)	7/28[a] (25%)
FLT3-ITD pos	**10/67**[a] **(15%)**	5/44[a](11%)	5/23[a] (22%)
Number cycles-Total	**469**	383	86
median (range)	**3 (1-21)**	3 (1-21)	2 (1-7)
> = 4 cycles (%)	**45 (43%)**	36 (48%)	9(31%)

AML: acute myeloid leukemia; CIRS: Cumulative Illness Rating Scale; BC: Blast Cells; WBC: white blood cells x10^3/μl.
[a] evaluable patients.
[b] All other cases have bone marrow blast cells between 20% and 30%.

1–7) in cohort 2. Forty-five of 104 patients (43%) received ≥ 4 cycles (36/75;48% in cohort 1 and 9/29;31% in cohort 2).

3.2. Response to DAC and survival

Overall, 94/104 patients were evaluable for response (10 patients were too early with less than 2 DAC courses). The Overall Response Rate (ORR = CR + PR) was 33%, significantly higher in Cohort 1 compared to Cohort 2 (42% vs 14%; p = 0.009) (Table 2). CR was achieved in 31% patients of newly diagnosed AML (without significant differences in response rate between de novo and secondary AML; p = 0.07) whereas in the salvage AML group no CR was obtained. None of the relapsed cases previously treated with another hypomethylating agent (AZA) achieved a DAC response. The median duration of response was 6 months (range 1–20). In the cohort 1, 74% of the overall responses (CR or PR) were obtained between the 3th and 6th cycle. Median response duration in cohort 1 was 6 months (range 1–20).

In multivariate Cox regression analysis, achievement of CR or PR (HR = 0.78; p = 0.0004), CIRS < 6 (HR = 0.9; p = 0.04) and a complex karyotype (HR = 0.8; p = 0.03) are significant predictors of better overall survival (Table 3).

Table 3
Factors affecting OS in cohort 1 of AML patients trated with DAC. Multivariate Cox regression analysis.

Covariate	SE	95% CI	p value
AGE (< 70 vs > 70)	1.0402	0.8006 to 46.2711	0.0825
CIRS (< 6 vs > 6)	0.9066	1.0287 to 35.3072	0.0476
PS-ECOG (< 2 vs > 2)	0.9323	0.0418 to 1.5844	0.1453
Secondary to MDS	0.6489	0.1455 to 1.8273	0.3073
BC in BM > 30%	0.7146	0.3685 to 5.9795	0.5805
WBC > 10,000	0.8824	0.4008 to 12.5174	0.3608
Complex or monosomic Karyotype	0.8359	0.0345 to 0.8981	0.0377
Response to DAC (CR or PR)	0.7828	3.5065 to 74.2676	0.0004

CIRS: Cumulative Illness Rating Scale; BC: Blast Cells; WBC: white blood cells x10^3/μl; MDS: Myelodysplastic Syndrome.

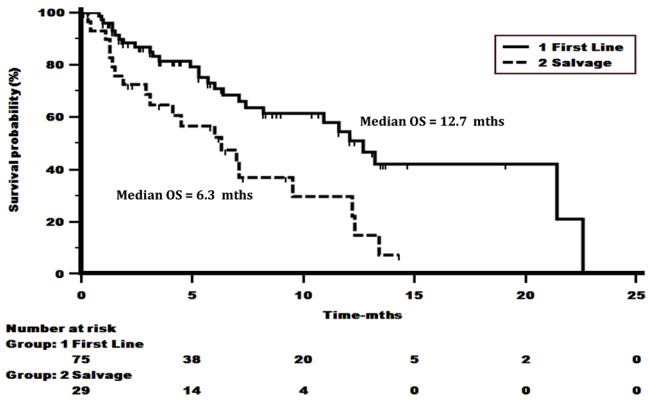

Fig. 1. Overall survival of first line (chort 1) and salvage pts (chort 2): median OS 12.7 mths vs 6.3 mths, p = 0.003 (Log-rank).

The probability of OS at 12 and 18 months from the start of DAC of the whole population were 44.5% and 30%, respectively. The median OS from the start of DAC therapy was 11 months for the whole population with a significant OS advantage in Cohort 1 compared to Cohort 2 (median OS 12.7 mths vs 6.3 mths; p = 0.003) (Fig. 1). Median OS was significantly longer among responders compared to non-responders patients (22.6 mths vs 5.7 mths; p < 0.0001) (Fig. 2A). Median disease-free-survival (DFS) in the 20 patients who reached a CR was 10.7 mths (Fig. 2B).

At the last follow-up, 56 patients (54%) are still alive and 48 (46%) are dead. The main cause of death was disease progression (71%); 19% of patients died for infectious complications (all these patients were in CR or had stable disease) and 10% died for their comorbidities (mainly cardiovascular events).

Table 2
Response and outcome.

	ALL CASES N=104	COHORT 1 (first line therapy) N=75	COHORT 2 (salvage therapy) N= 29	p value
RESPONSE				
Evaluable patients	94/104	65/75	29/29	
• CR	20/94 (21%)	20/65(31%)	0/29	0.0002
• PR	11/94 (12%)	7/65 (11%)	4/29 (14%)	
• SD	35/94 (37%)	25/65 (38%)	10/29 (34%)	
• PRO	28/94 (30%)	13/65 (20%)	15/29 (52%)	
• ORR	31/94 (33%)	27/65 (42%)	4/29 (14%)	0.009
Response duration (mths) median (range)	6 (1-20)	6 (1-20)	/	/
FOLLOW-UP (mths) median (range)	4.5 (0.3-22)	5 (0.3-22)	4 (0.3-12)	/
STATUS				
• ALIVE	56/104 (54%)	47/75 (63%)	9/29 (31%)	
• DEATH	48/104 (46%)	28/75 (37%)	20/29 (69%)	0.004
Median OS (mths)	11	12.7	6.3	0.003

CR: complete remission; PR: partial remission; SD: stable disease; PRO: progressive disease; ORR: Overall Response Rate.

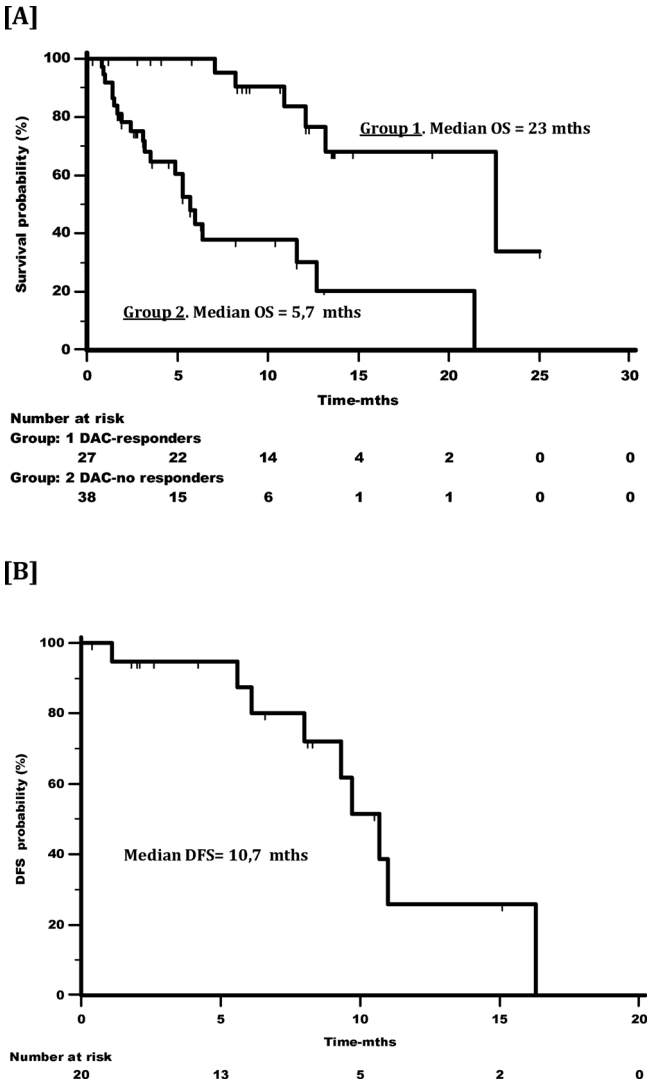

Fig. 2. [A] OS in first line DAC-cohort 1 according to DAC-response (DAC-responders median OS = 22.6 mths, DAC-no responders median OS = 5.7 mths; p < 0.0001). [B] DFS in CR patients of cohort 1 (Median DFS 10.7 mths; DFS at 12 mths = 26%).

3.3. Hematologic and extra hematologic toxicity

Of note, 76% of patients had AML related-severe cytopenia at baseline, as reported in Table 4A. Clinically the DAC (20 mg/sqm-5-days schedule) was well tolerated and no nausea, vomiting or other clinical symptoms were reported during DAC administration. Hematological toxicities were the most frequent adverse events (AE). Ninety-one percent of evaluable patients (74/81) experienced grade ≥ 3 cytopenia, without any difference between the two groups (Table 4A). Hematological toxicity occurred mainly in the first 4 cycles (69% in cohort 1 and 94% in cohort 2) whereas it was detected after the fourth cycle of DAC only in 30% of cases of cohort 1.

The most frequent extra-hematologic AE were infectious complications (63% in the whole evaluable population) with a prevalence in the salvage cohort (81% vs 56%-Table 4B). The most frequent infectious events were fever with unknown origin (FUO) and pneumonia (31% and 30%, respectively). Viral infections and colitis were rare events and occurred in 7% and 1% of evaluable cases, respectively. The incidence of infections were greater in patients with active disease (no-responders) and in the first cycles of therapy (79% of infectious events).

4. Discussion

The treatment of elderly AML patients remains a significant clinical challenge [2,19–21]. The hypomethylating agents have documented activity in these patients both in MDS and in AML and some clinical trials demonstrated the efficacy of DAC in newly diagnosed and relapsed older AML patients with an acceptable toxicity profile [5,22–28]. The current approved standard dose and schedule of DAC (20 mg/sqm daily for 5 days every 4 weeks) has been evaluated in two principal studies [5,25]. The first one was a phase II study including 55 AML patients older than 60 years. In this study, the ORR was 25%, the median OS was 7,7 months and the patients received a median of 3 cycles of DAC (range 1–25) (25). The subsequent phase III, randomized clinical trial (DACO-106) included 485 elderly AML patients with intermediate or poor cytogenetic risk; this study compared DAC with physician's treatment choice (TC) including best supportive care or low dose cytarabine [5]. The CR rate was higher in DAC arm (17.8% versus 7.8%; p = 0.001) but without significant benefit in terms of OS compared to TC arm (7.7 mths versus TC 5.0 mths). These studies allowed the approvation by EMA of DAC (schedule of 20 mg/sqm/daily for 5 days) for treatment of elderly pts with AML. However, scarce data are still available on efficacy and safety of DAC outside of clinical trials, particularly in Caucasian populations [11,29]. Our observational study reports a multicentre experience with DAC (standard schedule of

Table 4
[A] hematological toxicity and **[B]** infectious complications.

[A] Hematological toxicity	TOTAL evaluable patients N = 81	COHORT 1 evaluable patients N = 60	COHORT 2 evaluable patients N = 21
Cytopenia grade ≥ 3 at baseline	76%	74%	80%
Cytopenia grade ≥ 3	74/81 (91%)	54/60 (90%)	20/21 (95%)
• anemia	37/81 (46%)	18/60 (30%)	19/21 (90%)
• thrombocytopenia	57/81 (70%)	38/60 (64%)	19/21 (90%)
• neutropenia	61/81 (75%)	(41/60 (68%)	20/21 (95%)
Timing of Cytopenia grade ≥ 3			
Evaluable cycles	343/423	279/353	64/70
• cycles with cytopenia ≥ 3	183/343 (53%)	125/279 (45%)	58/64 (91%)
• Onset before 4th cycle (N°)	116/152 (76%)	72/105 (69%)	44/47 (94%)
• Onset after 4th cycle (N°)	67/191 (35%) (p = 0.0001)	53/174 (30%) (p = 0.0004)	14/17 (82%) (p = ns)

[B] Infectious Events	Total evaluable patients N = 90	COHORT 1 evaluable patients N = 64	COHORT 2 evaluable patients N = 26
Incidence of infections	57/90 (63%)	36/64 (56%)	21/26 (81%)
Incidence in responders	**14/57 (25%)**	13/36 (36%)	1/21 (5%)
Incidence in no-responders	**43/57 (75%)**	23/36 (64%)	20/21 (95%)
Total infectious events	83	47	36
FUO	26/83 (31%)	15/47 (32%)	11/36 (31%)
Pneumonia	24/83(30%)	14/47 (30%)	10/36 (28%)
Bacteriemia	13/83 (15%)	9/47 (19%)	4/36 (11%)
Skin and soft tissue infec.	9/83 (11%)	6/47 (13%)	3/36 (8%)
Others	4/83 (5%)	2/47 (4%)	2/36 (5%)
Colitis	1/83 (1%)	1/47 (2%)	0
Viral reactivation	6/83 (7%)	0	6/36 (17%)
Timing of infectious events			
Evaluable events	73/83	38/47	35/36
• Onset before 4th cycle (N°)	58/73 (79%)	30/38 (79%)	28/35 (80%)
• Onset after 4th cycle (N°)	15/73 (21%)	8/38 (21%)	7/35 (20%)

FUO: fever of unknown origin.

20 mg/sqm daily for 5 days) in AML patients (first line and relapsed/refractory cases) describing its clinical activity in the real-world setting. The 75 patients treated in first line (cohort 1) were judged unfit by the clinician (for age and/or comorbidity) and therefore not suitable for receiving treatment with conventional CHT.

Of interest, we found that the evaluation of the patients' performance status according to the ECOG scale was not reliable due to the extreme subjectivity in scoring, that prevented a right classification of patients in fit or unfit. In fact, in the report forms of our study, more than 80% of patients were classified with ECOG scales ≤ 2 by the attending physician even if the patient was considered "unfit" for intensive CHT. We found that a more objective functional status was measured using the cumulative illness rating scale (CIRS) which allows, in a more standardized way, to establish the comorbidity burden and the fitness in the geriatric population [18,30,31]. In our study 32% of patients treated with DAC in front line had a CIRS > 6 (evaluated after collection of data according to the comorbidities), while no cases with low CIRS were reported. In addition, the CIRS score (but no ECOG scale) significantly impact OS in multivariate analysis (Table 3).

In this real life observational study DAC confirms a good antileukemic activity, mainly in first line cohort (cohort 1) where the ORR and CR reached 42% and 31%, respectively, even better than the registrative clinical trials [5,22]. Consistently with previous reports, in the majority of cases, the best response (CR or PR) was obtained between the 3th and 6th cycle suggesting that treatment efficacy should be judged not earlier than 2 or 3 of DAC cycles. Conversely, the rate of response in cohort 2 (relapsed/refractory AML) was disappointing with an ORR of 14% and without any CR.

In the cohort 1, according to the multivariate analysis, the factors having a significant favorable impact on the OS were: CIRS < 6, achievement of a CR or PR and a high molecular-cytogenetic risk; this data are in line with the recent reports suggesting the ability of DAC to induce a favorable clinical response in patients with adverse cytogenetic-molecular profile [32,33]. In addition, patients achieving CR have an excellent median OS (22.6 months with a 12-month OS of 76%) even higher than data reported by registrative studies [5,6]. However, in the majority of cases the responses are not "long-lasting"(median duration of response 6 months, range 1–20). For this reason and considering its favorable safety profile, DAC is an attractive agent for combination therapy: in fact phase I and II studies examining DAC in combination with low-dose cytarabine, bortezomib, FLT3 inhibitors (such as midostaurin, sorafenib, gilteritinib), venetoclax and other drugs, are currently under way [10,24,34,35].

Our study confirms that DAC is well tolerated during administration but, after therapy, myelosuppression represents the major adverse event (AE). It should be underlined that DAC-related hematological toxicity can be hardly distinguishable from cytopenias due to underlying hematologic disease. With this limit, 91% of patients experienced hematological toxicity of degree ≥ 3, mainly in the first 3 cycles of DAC.

The infectious complications were not negligible with a global prevalence of 63% (higher in the salvage cohort treatment: 81% in the cohort 2 vs 56% in the cohort 1). The most frequent manifestations were FUO and pneumonia (with 3 pulmonary aspergillosis); 17% of the patients treated in the salvage cohort showed a viral reactivation (CMV or HSV), and this is likely to be related to a previous allogeneic stem cells transplantation as a predisposing condition. The incidence of infections was greater in patients with active/non-responsive hematologic disease (64% of infections in cohort 1 with non-responsive disease) and in the early cycles (79% of infectious complications occurred within the first 3 cycles). Infectious related mortality was 19% (Table 4).

In conclusion, this is an observational, multicenter study in which the main limitation and the point of critique is the retrospective design and the heterogeneity of the patient population. Unfortunately, in this observational study, no specific biological studies are available and for this reason we could not correlate the mutational status of TP53 with the decitabine response.

Despite these limitations, we believe that this study provides a good picture of the clinical use of DAC in the real life of Italian Hematologic Centers, confirming its efficacy in elderly AML patients in terms of ORR and OS advantage, especially as first line treatment whereas in the salvage setting there is no clear benefit and the ORR rates are unsatisfactory.

Of interest, in this study we retrospectively evaluated the comorbidity burden with the Cumulative illness Rating Scale (CIRS) accounting the exact number of specific comorbidities [30,31]. A pretreatment higher Comorbidity burden (CIRS > 6) results more informative of fitness than ECOG performance status and exerts a significant impact on OS in multivariate analysis (Table 3).

Even if the overall toxicity profile of DAC is favorable, infectious complications are common during the first cycles of therapy. For this reason, a broad-spectrum antimicrobial prophylaxis could be advisable during the initial 2–3 cycles of treatment with the aim to reduce the incidence of AE.

Our favorable real-life results support the ongoing research efforts to explore alternative DAC schedules (for example 10-day DAC) or combinations with other agents in the context of clinical trials. Further genomic profiling studies may also identify those older AML patients most likely to benefit from DAC or other hypomethylating agents [10,23,34,35].

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