Research Article

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The use of hypomethylating agents in hematologic malignancies: treatment preferences and results

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Aim: The objective of this article was to compare the efficiency of azacitidine (AZA) and decitabine (DAC) in patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) who are not suitable for high-dose chemotherapy. **Materials and methods:** MDS and AML patients who were treated with hypomethylating agents (HMAs) between January 2005 and 2020 were evaluated retrospectively. **Results:** No statistically significant difference was found between the patients who received AZA or DAC in AML patients. In MDS group, the rate of patients who achieved remission was statistically significantly higher in patients who received DAC (p = 0,032). **Conclusion:** The advantage in terms of response for MDS and no survival difference between AZA and DAC for AML and MDS patients will be an important contribution to the literature.

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Keywords: hypomethylating agents (HMAs) • decitabine (DAC) • azacitidine (AZA) • acute myeloid leukemia (AML) • myelodysplastic syndrome (MDS)

Introduction

Myelodysplastic syndrome (MDS) is defined as a clonal hematopoietic stem cell disease, and it progresses with cytopenias as a result of infective hematopoiesis [1]. Progression to acute myeloid leukemia (AML) is observed at a rate of 30% [1]. Chronic myelomonocytic leukemia (CMML) is the clonal disease of the hematopoietic stem cell and is characterized by persistent, absolute monocytosis. As it has both myelodysplastic and myeloproliferative properties, it has been included in the group of myelodysplastic/myeloproliferative neoplasias, and diagnostic criteria have been determined by the WHO [2]. According to the International Prognostic Scoring System (IPSS) in patients diagnosed with MDS, chemotherapy and stem cell transplantation options are evaluated according to the low-, intermediate-, and high-risk groups. For MDS/CMML and AML patients, who are not suitable for high-dose chemotherapy, azacitidine (5- azacitidine, AZA) and decitabine (5-Aza-2′-deoxycytidine, DAC) are the treatment options in patients with lower toxicity [3, 4].

AZA and DAC are two separate cytidine analogs. As they act via DNA hypomethylation, they are referred to as the hypomethylating agents (HMAs). It is used in the treatment of various hematological malignancies such as MDS, CMML and AML and frequently preferred in patients who are not suitable for high-dose chemotherapy [5,6]. AZA and DAC, which are nucleoside analogs, act by inhibiting the DNA methyltransferase (DNMT) enzyme. DAC binds directly to DNA, while AZA binds to DNA and often to RNA, preventing RNA and protein synthesis. In the absence of DNMT, apoptosis of leukaemic cells is induced, and anti-leukaemic therapy is targeted [7].

A clear difference in efficacy between AZA and DAC has not been supported by clinical trials and appears to be considered as of similar efficacy. In our study, as an important contribution to the literature, we aimed to compare the efficiency of AZA and DAC on survival and response in patients with intermediate- or high-risk MDS, AML and intermediate- or high-risk CMML for whom high-dose chemotherapy is not an option.

Materials & Methods

One hundred and fourteen intermediate-to-high risk MDS, CMML and AML patients who were treated with HMAs in our hematology clinic between January 2005 and January 2020 were evaluated retrospectively. Demographic data such as age and gender, diagnoses, treatment options (AZA or DAC), overall survival (OS) and responses determined by bone marrow biopsy after 4 cycles of treatment were revealed.

Treatment preferences & response

The choice of AZA or DAC was the physicians' decision. Patients in AZA subgroup received 75 mg/m^2 AZA for 7 days, while patients in DAC subgroup received 20 mg/m^2 DAC for 5 days. Patients with a bone marrow blast below 5% after 4 cycles were determined as responding to treatment.

Exclusion criteria

A total of 12 (8 MDS, 4 AML) patients were excluded from the study because of missing patient data. A total of 18 patients (8 MDS, 10 AML) who died before completing 4 cycles of treatment or whose treatment was discontinued for any reason were also excluded from the study. The data of the remaining 84 patients (49 MDS, 35 AML) were statistically analyzed. CMML patients were included in the MDS group in the statistical analysis.

Statistical analysis

PASW 18.0 for Windows program was used for statistical analysis. Statistical significance was accepted as p-values $< 0,05$. Descriptive statistics were presented as numbers and percentages for categorical variables, mean, standard deviation, median, minimum, maximum, percentile 25 and percentile 75 for numerical variables. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Chi-square test was used for categorical variables when the condition was met in pairwise group comparisons; if not, Fisher Exact test was used. Mann–Whitney U test was used when the normal distribution condition was not met in pairwise group comparisons for numerical variables. The effect of drugs on mortality was analyzed by Cox regression analysis and the effect on response to treatment by logistic regression analysis.

Results

Of the 84 patients included in the study, 37 were females (44%) and 56 were males (56%). There were 35 (41,7%) patients with AML, 39 (46,4%) patients with MDS and 10 (11,9%) patients with CMML. In total, 50 patients (59,5%) received AZA, and 34 (40,5%) received DAC. A total of 64 patients (76,2%) were unresponsive to treatment, while 20 patients (23,8%) had remission. Looking at the last situation, 44 patients were alive (52,4%), while 40 patients (47,6%) were exitus. (Table 1).

Statistical analysis of AML patients

No statistically significant difference was found in the analysis performed between the patients received AZA or DAC in AML patients ($p \geq 0,05$, for all) (Table 2). When the effect of DAC on mortality compared to AZA was examined, no statistically significant result was obtained ($p \geq 0,05$, for both) (Table 3). There was no statistically significant difference between the response groups ($p \geq 0,05$, for all) (Table 4). When the effect of DAC on remission was examined, it was not a statistically significant factor ($p \geq 0,05$, for all) (Table 5).

Statistical analysis of MDS/CMML patients

The rate of patients who achieved remission was statistically significantly higher in patients who received DAC ($p = 0,032$) (Table 6). When the effect of DAC on mortality compared to AZA was examined, no statistically significant result was obtained ($p \geq 0,05$, for all.) (Table 7). In the remission subgroup, the decrease in age and the increase in the follow-up duration were statistically significant compared to failure subgroup ($p = 0,002$; $p = 0,008$, respectively) (Table 8). When the effect of DAC on remission compared to AZA was examined, it was a statistically significant factor that increased remission ($p = 0,036$) (Table 9).

Discussion

Various studies conducted with HMAs have been compared with low-dose chemotherapeutics such as best supportive care and low-dose ARA-C therapy, and their superiority to these treatments in patients who are not eligible for

Table 1. Demographic features, DAC and AZA usage, diagnoses, responses and last status.

	n	%
Gender		
Female	37	44,0
Male	47	56,0
DAC and AZA distribution		
AZA	50	59,5
DAC	34	40,5
Diagnoses		
AML	35	41,7
MDS	39	46,4
CMML	10	11,9
Responses		
Failure	64	76,2
Remission	20	23,8
Last status		
Alive	44	52,4
Exitus	40	47,6

AML: Acute myeloid leukemia; AZA: Azacitidine; CMML: Chronic myelomonocytic leukemia; DAC: Decitabin; MDS: Myelodysplastic syndrome.

Table 2. Comparison of AZA and DAC in AML patients.

		n	All patients	n	AZA	n	DAC	p-value
Gender, n (%)	Female	35	16 (45,7)	21	7 (33,3)	14	9 (64,3)	0,072†
	Male		19 (54,3)		14 (66,7)		5 (35,7)	
Median age, years (range)		35	71 (50–82)	21	70 (50–82)	14	73 (62–82)	0,362§
Response, n (%)	Failure	35	31 (88,6)	21	20 (95,2)	14	11 (78,6)	0,129‡
	Remission		4 (11,4)		1 (4,8)		3 (21,4)	
Last status, n (%)	Exitus	35	18 (51,4)	21	12 (57,1)	14	6 (42,9)	0,407†
	Alive		17 (48,6)		9 (42,9)		8 (57,1)	
Median total cycles of treatment (range)		35	2 (1–6)	21	2 (1–6)	14	2 (1–6)	0,901§
Median total dose (range)		35	525 (100–3150)	21	750 (375–3150)	14	200 (100–600)	
Median dose per cycle (range)		35	375 (100–525)	21	525 (375–525)	14	100	
Median follow-up duration, months (range)		35	9 (1–60)	21	10 (1–60)	14	6 (2–40)	0,710§

†Chi-Square;
‡Fisher exact test;
§Mann–Mann U.
AZA: Azacitidine; DAC: Decitabine.

Table 3. The effect of DAC on mortality in AML patients.

			%95 CI HR	
	p-value	HR	Lower	Upper
Treatment (DAC)	0,617	0,775	0,286	2,102

DAC: Decitabine; HR: Hazard ratio.

high-dose chemotherapy has been studied. In study "AZA-001" (in AML cases and extensive randomized Phase III trials), best supportive care was found to be superior to low-dose cytarabine or intensive chemotherapy in high-risk MDS patients who were not suitable for stem cell transplantation. In this study, AZA was considered advantageous in terms of overall survival and AML transformation [8].

Although DAC is an active treatment for MDS, it has been found to be not effective on overall survival in a study by Lübbert *et al.*, DAC activity has been proven in elderly patients with high to intermediate risk, and its effect on survival has been demonstrated. However, in the study of Kantarjian *et al.*, the effect on survival was not found to

Table 4. Evaluation between response subgroups in AML patients.

		n	All patients	n	Failure	n	Remission	p-value
Gender, n (%)	Female	35	16 (45,7)	31	14 (45,2)	4	2 (50)	1,000†
	Male		19 (54,3)		17 (54,8)		2 (50)	
Median age, years (range)		35	71 (50–82)	31	71 (50–82)	4	74 (65–76)	0,678‡
Treatment, n (%)	AZA	35	21 (60)	31	20 (64,5)	4	1 (25)	0,279†
	DAC		14 (40)		11 (35,5)		3 (75)	
Last status, n (%)	Exitus	35	18 (51,4)	31	16 (51,6)	4	2 (50)	1,000†
	Alive		17 (48,6)		15 (48,4)		2 (50)	
Median follow-up duration, months (range)		35	9 (1–60)	31	6 (1–60)	4	13,5 (6–24)	0,499‡

†Fisher exact test;
‡Mann–Mann U.
AZA: Azacitidine; DAC: Decitabine.

Table 5. The effect of DAC on remission in AML patients.

			%95 CI OR	
	p-value	OR	Lower	Upper
Treatment (DAC)	0,369	0,634	0,235	1,713

DAC: Decitabine; OR: Odds ratio.

Table 6. Comparison of AZA and DAC in MDS patients.

		n	All patients	n	AZA	n	DAC	p-value
Gender, n (%)	Female	49	21 (42,9)	29	11 (37,9)	20	10 (50)	0,401†
	Male		28 (57,1)		18 (62,1)		10 (50)	
Median age, years (range)		49	66 (47–83)	29	65 (47–83)	20	66 (50–80)	0,527§
Response, n (%)	Failure	49	33 (67,3)	29	23 (79,3)	20	10 (50)	**0,032**†
	Remission		16 (32,7)		6 (20,7)		10 (50)	
Last status, n (%)	Exitus	49	22 (44,9)	29	14 (48,3)	20	8 (40)	0,567†
	Alive		27 (55,1)		15 (51,7)		12 (60)	
Median total cycles of treatment (range)		49	4 (1–15)	29	4 (1–15)	20	4,5 (1–7)	0,490§
Median total dose (range)		49	1050 (100–5775)	29	2100 (225–5775)	20	550 (100–1500)	
Median dose per cycle (range)		49	375 (100–525)	29	525 (225–525)	20	100 (100–525)	
Median follow-up duration, months (range)		49	21 (2–120)	29	21 (2–120)	20	21 (3–72)	0,721§

†Chi-Square;
§Mann–Mann U.
Boldface values indicate statistical significance.
AZA: Azacitidine; DAC: Decitabine.

Table 7. The effect of DAC on mortality in MDS patients.

			%95 CI HR	
	p-value	HR	Lower	Upper
Treatment (DAC)	0,698	0,858	0,396	1,859

DAC: Decitabine; HR: Hazard ratio.

be superior compared with best supportive care and low-dose cytarabine [5]. In our study, the rate of patients with MDS who achieved remission was statistically significantly higher in patients who received DAC (p = 0,032); but there was no statistically significant difference between AZA and DAC subgroups in terms of mortality.

The effectiveness of DAC and AZA has been demonstrated; however, the clinical choice between them is controversial. The only comparative study was revealed by meta-analysis by Xie *et al.* [9]. In this study, DAC and AZA efficacy, toxicity and survival rates were compared only in cases diagnosed with MDS. Partial response,

Table 8. Evaluation of response subgroups in MDS patients.

		n	All patients	n	Failure	n	Remission	p-value
Gender, n (%)	Female	49	21 (42,9)	33	13 (39,4)	16	8 (50)	0,482†
	Male		28 (57,1)		20 (60,6)		8 (50)	
Median age, years (range)		49	66 (47–83)	33	69 (50–83)	16	62 (47–76)	**0,002**§
Response, n (%)	AZA	49	29 (59,2)	33	23 (69,7)	16	6 (37,5)	**0,032**†
	DAC		20 (40,8)		10 (30,3)		10 (62,5)	
Last status, n (%)	Exitus	49	22 (44,9)	33	17 (51,5)	16	5 (31,3)	0,181†
	Alive		27 (55,1)		16 (48,5)		11 (68,8)	
Total cycles of treatment (range)		49	4 (1–15)	33	4 (1–11)	16	6 (4–15)	
Median total dose (range)		49	1050 (100–5775)	33	1050 (100–5775)	16	650 (400–4725)	0,724§
Median dose per cycle (range)		49	375 (100–525)	33	375 (100–525)	16	100 (100–525)	
Median follow-up duration, months (range)		49	21 (2–120)	33	13 (2–120)	16	30 (8–72)	**0,008**§

†Chi-Square;
§Mann–Mann U.
Boldface values indicate statistical significance.

Table 9. The effect of DAC on remission in MDS patients.

			%95 CI OR	
	p-value	OR	Lower	Upper
Treatment (DAC)	**0,036**	3,833	1,093	13,450

Boldface values indicate statistical significance.
DAC: Decitabine; OR: Odds ratio.

hematological recovery and overall response rates were higher for AZA than DAC. There was no difference between these two drugs in terms of complete response, erythrocyte transfusion independence or hematological toxicity. Compared with the best supportive care, AZA was found to be significantly effective in OS and AML transformation; DAC was not effective. Therefore, it is seen that AZA is predominantly preferred in the MDS group.

We see that a study comparing DAC and AZA for AML or CMML is not in the literature. There are studies on effectivity for individual HMAs and treatment activities in AML or CMML. In a cohort by Stahl *et al.*, the treatment efficacy of HMAs in elderly relapse-refractory AML patients was evaluated. A total of 655 patients from 12 centers were evaluated. Fifty-seven percent of them received AZA, while 43% of them received DAC. Both complete response (CR) and the statistical contribution to OS have been demonstrated, but no assessment has been made between drugs [10].

In another multicenter study conducted by Bocchia *et al.*, a total of 306 advanced-age AML patients who received only DAC and were not suitable for intensive treatment were examined (median age: 75 years). The efficacy of decitabine as a first-line therapy for AML in advanced-age patients has been statistically demonstrated, and poor cytogenetic factors and high initial white blood cell count have been identified as negative predictors [11]. In a meta-analysis and review article published by He *et al.*[12] DAC efficacy in advanced-age AML cases was revealed by examining a total of 9 separate studies. Seven-hundred-and-eighteen patients were included in the analysis; there was no significant difference between age, cytogenetic risk, AML type and bone marrow blast percentage and DAC treatment response. With this meta-analysis, DAC has been described as an effective treatment in advanced AML cases. In another study conducted by Park *et al.*, DAC efficacy was demonstrated in advanced-age AML cases that are not suitable for conventional chemotherapy [12]. In our study, no statistically significant difference was found between AZA and DAC subgroups in AML patients, in terms of response or mortality.

In the treatment of CMML, the use of HMA is often preferred in cases that do not respond to hydroxyurea. CMML is a complex clonal hematological disorder classified among MDS/myeloproliferative neoplasms. The prognosis is poor, and there is a lack of effective treatment. In a study of 43 patients treated with DAC, the overall response rate after six cycles was 47,6%, complete remission 16,6%, bone marrow response 19% and partial response 2,4%. After an average follow up of 51,5 months (range: 44,4–57,2), the median OS was 17 months,

and responders showed significantly longer survival than non-responders. DAC appears to be an effective and well-tolerated treatment for high-risk CMML patients [2].

Venetoclax is a selective B-cell lymphoma-2 (BCL-2) inhibitor, which is approved to treat elderly patients with newly diagnosed AML and high-risk MDS in combination with either low-dose cytarabine (ARA-C) or HMAs. In a study from 2020 [13], overall response in relapsed/refractory MDS patients who received venetoclax plus HMAs was 59%, and allogeneic stem cell transplantation was associated with long-term survival after treatment with the HMA–venetoclax combination. In another study [14], CR ratios in AML patients treated with venetoclax plus AZA and venetoclax plus DAC were 71% and 74%, respectively. Venetoclax-based treatment results were evaluated in another study containing real-life data from Turkey [15]. Six (10%) of the 60 patients were diagnosed with high-risk MDS, and the remaining were diagnosed with AML; the best objective response rate was 35% in the entire cohort. On the basis of all these findings, there is a need for comparison with large patient groups receiving HMAs plus venetoclax.

There are some important limitations for our study. The most important point is the limited number of patients. Statistical analysis has become difficult especially when subgroups are formed. It should also be emphasized that new analyzes should be performed including patients receiving new regimens containing BCL-2 inhibitor combinations.

Conclusion

In conclusion, no statistically significant difference was found in this study between AZA and DAC subgroups in AML patients, in terms of response or mortality. In MDS patients, statistically significant superiority was demonstrated in the DAC subgroup in terms of achieving remission. In the remission subgroup, the decrease in age and the increase in follow-up duration were statistically significant compared to the failed subgroup. The advantage in terms of response for MDS and no survival difference demonstrated between AZA and DAC for AML and MDS patients will be an important contribution to the literature.

Future Perspective

Proving the superiority of DAC in achieving remission in MDS patients seems to be a very important literature contribution. Reinforcing and improving this effect with a combination of BCL-2 inhibitor will be very beneficial for future treatment plans.

Summary points

- Myelodysplastic syndrome (MDS) is defined as a clonal hematopoietic stem cell disease and progresses with cytopenias as a result of infective hematopoiesis.
- Progression to acute myeloid leukemia (AML) is observed at a rate of 30%.
- For MDS and AML patients who are not suitable for high-dose chemotherapy, azacitidine (5-azacitidine [AZA]) and decitabine (5-aza-2′-deoxideidisin [DAC]) are the treatment options in patients with lower toxicity.
- Our aim was to compare the efficiency of AZA and DAC on survival and response in patients with intermediate- or high-risk MDS, AML and intermediate- or high-risk chronic myelomonocytic leukemia who have no chance of high-dose chemotherapy.
- The rate of patients with MDS who achieved remission was statistically significantly higher in patients who received DAC ($p = 0,032$); but there was no statistical significant difference between AZA and DAC subgroups in terms of mortality.
- No statistically significant difference was found between AZA and DAC subgroups in AML patients, in terms of response or mortality.
- The advantage in terms of response for MDS and no survival difference between AZA and DAC for AML and MDS patients will be an important contribution to the literature.
- In the light of all these findings, there is also a need for comparison with large patient groups receiving HMAs plus BCL-2 inhibitors.

Author contributions

All authors contributed to the editing of the manuscript. I Serin wrote the manuscript and made the accompanying figure.

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Ethical conduct of research

Our study was approved by the ethics committee of the University of Health Sciences Istanbul Training and Research Hospital on 15/02/2019 with the decision no. 1706. An informed consent was obtained from all patients to publish the study results.

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