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Original Article HEMATOLOGY

Survival outcomes of hypomethylating agents maintenance therapy in new diagnosed AML patients: Real experience data

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ABSTRACT

OBJECTIVE: Acute myeloid leukemia (AML) is a hematological malignancy that frequently affects elderly population. With introducing the hypomethylating agents (HMAs) in elderly AML treatment, survival rates and quality of life have improved. However, long-term management in elderly and frail patients is still a challenge. In the present study, we aimed to determine whether HMA maintenance therapy is required until disease progression in frail and elderly AML patients by examining with a real-life data.

METHODS: In a multicenter study, we analyzed non-promyelocytic elderly AML patients who were treated with first-line azacitidine or decitabine monotherapy in two different groups, retrospectively. While patients were treated with HMA until progression in the maintenance group, 6+3 cycles of azacitidine or decitabine were administered as a standard care of elderly AML patients in the non-maintenance group. Survival outcomes were compared between the groups.

RESULTS: HMA therapy was maintained until progression in 20 patients, and HMA therapy was terminated after 6+3 cycles in 21 patients. Patients received a median of 6 (1–14) HMA cycles during follow-up time. The median 7.5 months of overall survival were observed (2–17 months) in maintenance and 3 months (1–13 months) in non-maintenance groups (p=0.001).

CONCLUSION: Despite long-term exposure to HMA may appear as a risk factor for complications and toxicities in elderly and frail AML patients, the maintenance of therapy until disease progression provides a significant survival advantage. Therefore, we suggest that HMA therapy should continue until disease progression regardless the sort of HMA.

Keywords: Acute myeloid leukemia; azacitidine; decitabine; hypomethylating agents.

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Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy which is characterized by the expansion of abnormal clonal myeloid cells in the bone marrow (BM) and peripheral blood [1]. According to Surveillance, Epidemiology, and End Results Cancer Statistics, elderly population with the median age of 67 years is mostly affected [2]. The treatment of patients older than age 60 years is limited and unsatisfactory due to

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multiple comorbidities, age-related system dysfunctions, poor performance status, and intolerance of chemotherapy [3]. Despite the fact that low intensive therapies are considered a better therapeutic option for frail and elderly patients, unsatisfactory outcomes are reached in survival with a higher risk of relapse. The 2-and 5-year overall survival (OS) rates of elderly AML patients are approximately 10% and 2%, respectively [4–6]. Therefore, more effective, less toxic regimens, and long-term remission sustained strategies should be planned for this population. Hypomethylating agents (HMAs) therapy with either decitabine or azacitidine is recommended for elderly and unfit AML patients by National Comprehensive Cancer Network and European Leukemia Net (ELN) [7, 8].

Response rates and outcomes were compared between HMA and low-dose cytarabine (LDAC) regimens in two large randomized trials [9, 10]. In neither study, primary analysis of OS was revealed statistically significant. Furthermore, similar results were reported in a meta-analysis of 13 studies by Stone et al. [11]. The meta-analysis did not indicate any difference in complete remission (CR) rate (15%) between HMA and LDAC. In the analysis of 11 cohorts, relapse-free survival was found similar with the median 8.8 months. Furthermore, median OS was median 5.4 months versus 7.5 months, however, it was not statistically different.

Despite, the 1st year analysis demonstrates a survival advantage of HMA [10], up to 10 cycles of treatment are approved by the government but further cycles require an approval in Turkey. However, patients may continue HMA until progression or death with the approval procedures. In the present study, we aimed to demonstrate the response rates and survival outcomes of azacitidine or decitabine maintenance therapy until progression in frail and elderly AML patients by examining real-life data.

Highlight key points

- AML is a hematological malignancy that frequently affects the elderly population. Long-term management in elderly and frail AML patients is a challenge.
- Effective, less toxic regimens and long-term remission sustained strategies should be planned for this population.
- Despite long-term exposure to HMA may appear as a risk factor for complications and toxicities in older and frail AML patients, maintenance of HMA provides significant survival advantage.

MATERIALS AND METHODS

Patients and Treatment Modalities

Retrospectively, we analyzed non-promyelocytic elderly AML patients who were treated with first-line HMA in two different centers between 2014 and 2020. Elderly, unfit patients with poor performance status and comorbidities who are not ineligible for intensive treatments were included in the study. While newly diagnosed AML patients with de novo AML or transformed from MDS were treated with first-line HMA including azacitidine or decitabine monotherapy which were included in the study, MDS transformed AML patients who had previous HMA treatment history were excluded from the study.

Azacitidine 75 mg/m^2 subcutaneous (sc) injection for 7 days every 4 weeks and decitabine 20 mg/m^2 subcutaneous (sc) injection for 5 days every 4 weeks were administered. While patients were treated with HMA until progression as the maintenance group, 6+3 cycles of azacitidine or decitabine were administered as the standard care of elderly AML in non- maintenance group. Patients randomized regardless type of AML (de novo or secondary AML) and laboratory characteristics of patients including leukocyte, hemoglobin, platelet count, and blast ratio at the time of diagnosis.

The patients were evaluated according to age, comorbidities, performance status, laboratory data, and cytogenetic risk profile by the physician of each center. Treatment modality, response to therapy, and overall were recorded. Data were collected from hospital database and by review of the patient's electronic medical records.

Response Assessment

BM biopsy was obtained from all patient's before 7th cycles of HMA due to response assessment. The hematologic response was determined according to the criteria of ELN recommendations [12]. The definition of CR was applied as BM blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 × 10^9 /L (1000/μL); and platelet count >100 × 10^9 /L (100,000/μL). OS was measured from randomization to death or to the last visit.

Ethical Approval

All procedures performed in the present study 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 com-

Table 1. Characteristics, laboratory, and treatment details of groups

	Total	Maintenance group (n=20)	Non-maintenance group (n=21)	p
Median age, years (range)	75 (59–84)	74 (59–84)	75 (62–82)	0.610
Median Hb, g/dl, (range)	8.8 (6.3–12.8)	8.75 (6.8–12.8)	8.9 (6.3–11.4)	0.958
Median leu/mm^3, (range)	3800 (540–152000)	1925 (174–66200)	5400 (570–152000)	**0.011***
Median plt (/mm^3) (range)	41000 (3000–146000)	42500 (3000–146000)	41000 (9000–102000)	0.506
Median blast counts, % (range)	40 (20–90)	38 (20–90)	40 (20–90)	0.547
Median LDH (U/L) (range)	372 (126–5753)	369 (150–824)	372 (126–5753)	0.774
Median cycle # (range)	4 (1–14)	6 (1–14)	3 (1–6)	<**0.001**
ECOG 0, 1, 2 (n)	18	11	7	**0.177**
ECOG 3, 4 (n)	23	9	14	
De novo AML (n)	17	12	5	**0.019****
MDS transformer AML (n)	24	8	16	
Azacitidine (n)	27	11	16	0.153
Decitabine (n)	14	9	5	
CR ratio %	22	12.2	9.8	0.645
Favorable risk (n)	4	0	4	
Intermediate risk (n)	22	15	7	**0.014****
Unfavorable risk (n)	15	5	10	

LDH: Lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; CR: Complete remission; *: Kolmogorov-Smirnov, p<0.005; **: Mantel-cox, p<0.005.

parable ethical standards. Approval for this study was granted by Local Ethics Committee (number: 25, Date: February 14, 2020).

Statistical Analysis

Statistical analyses were made using SPSS version 25.0 software (Chicago, IL, USA). All continuous variables were expressed as median (range) and categorical variables were expressed as number (percent). Categorical variables were compared using Chi-square test and Fisher's exact test if required. Survival analysis was performed by Kaplan–Meier estimates and groups were compared using log-rank test. Hazards were calculated using multivariate analysis performed with Cox-proportional hazards analysis. All P values were two tailed and assumed to be significant if <0.05.

RESULTS

Totally 41 newly diagnosed AML patients, who were treated with a HMA monotherapy, were analyzed retrospectively. De novo AML patients were evaluated 41.5% and secondary AML were 58.5%. None of the patients had extramedullary disease. While 20 patients were maintained with same HMA until progression, 6+3 cycles of HMA treatment were administered in 21 patients. According to performance status, 56.1% of the patients had Eastern Cooperative Oncology Group (ECOG) score erative Oncology Group (ng to performance status, 56.1% of the patients had atments analysis, and poor prognostic classification, rates of 4.8%, 70.9%, and 24.3% were evaluated, respectively. Azacitidine monotherapy was selected as the first-line treatment in 65.9% of patients and decitabine was in 34.1%. Patients received a median of 6 (1–14) HMA treatment cycles. Treatment was delayed if febrile neutropenia and hemorrhage with Grade 4 thrombocytopenia occurred. Nonetheless, treatment was not terminated in any patient due to side effects. The laboratory, patient characteristics, and treatment are summarized in Table 1.

No statistically significant difference was found between the groups in respect of the ECOG performance score (PS), age, and initial BM blast count. Furthermore, groups were found well balanced according to HMA in treatment selection (p=0.153). CR ratio (12.2% vs. 9.8% p=0.645) was found similar in two groups. However, the ratio of secondary AML patients was found statistically

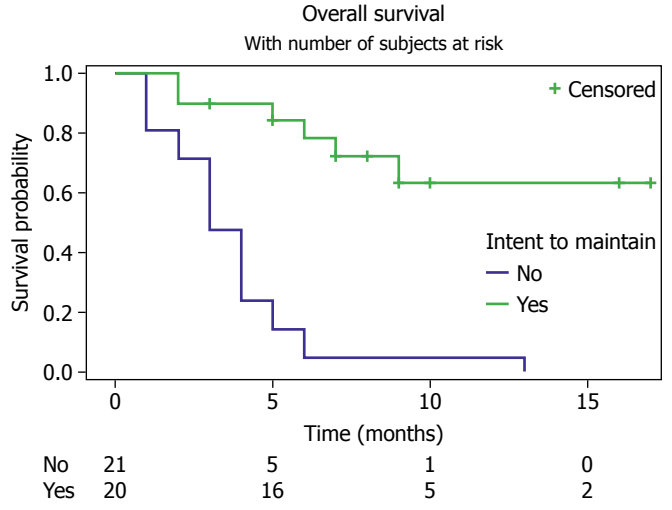

FIGURE 1. Kaplan–Meier estimates of overall survival between the HMA maintenance and non-maintenance groups.

higher in non-maintained group (p=0.019). Groups were defined statistically different when they were compared regarding to prognostic risk profile (p=0.014). Half of non-maintenance patients (n=10) were presented with unfavorable risk profile. In the maintenance group, there were no patient presented with favorable risk profile and ¾ of patients (n=15) had intermediate risk profile.

The first 60-day mortality rate was revealed similar in both groups (10% vs. 28.6%, resp., p=0.238). The median 7.5 months OS was observed (2–17 months) in maintenance and 3 months (1–13 months) in non-maintenance groups (p=0.001).

Survival parameters are detailed in Figure 1.

DISCUSSION

Either decitabine or azacitidine is widely used as single HMA in AML treatment over decades. However, in the literature, the comparison between randomized trials of AML patients treated with azacitidine and decitabine is not available. When compared the clinical benefit indirectly with prior systematical analyzes, the remarkable superiority was not demonstrated in safety and efficacy between two HMAs in AML patients [13]. Therefore, the selection of agent is made by considering the clinicians experience with the agent and patients' medical characteristics. Despite low CR rates are achieved with HMAs, a continuation of the therapy is recommended until disease progression is allowed by their limited toxicities and patients' preference [14].

This study reflects the survival outcomes of HMAs maintenance in elderly AML patients with the median age of 75 years. In seven large studies with HMAs [9, 10, 15–19], incidence of population (>75 years old) was reported 38–53% and up to 13% of them had poor performance with Eastern Cooperative Oncology Group (ECOG) score more than 2. However, in daily practice, clinicians may experience higher rates of older, frail AML patients with poor performance status more than reported.

In our study, while median 7.5 months of OS were determined in the HMA maintenance group, 3 months were defined in the non-maintenance group. When the groups were compared, statistically significant OS was achieved in patients with maintenance of HMA therapy. In the literature, Kadia et al. [20] showed median 8.6 months of OS in AML patients treated with decitabine. In another study with azacitidine, AML001, median 10.4 months of OS were demonstrated [9]. Whereas these former studies include more fit or younger AML patients, the present study includes frail and older population with higher ECOG PS, especially. In this cohort, more than half (56%) of the patients have ECOG PS of more than 3 which were included, who were mostly excluded from prior studies, conversely. DACO-16 study declared a median 7.7 months of OS with decitabine treatment, and it is a similar survival result with our real-life data [10]. DACO study describes similar age distribution with the median age of 73 years and 3/4 of patients had <2 ECOG PS. Therefore, we consider that poor performance status may influence the survival outcomes in our cohort.

We observed that both two centers participating the study tend to provide intensive treatments for old and fit patients. HMAs are administered only for older patients who are not eligible for intensive therapy due to poor performance status. This may explain the inclusion of more frail and elderly patients in our study than the other studies.

In the present study, higher leukocyte account was observed in the non-maintenance group with median count of 5400/mm^3. Prior studies showed the association between high leukocyte count and worse prognosis [21–25]. However, these studies demonstrated the association with higher leukocyte count than our cohort. Furthermore, another study with AML patients who received supportive HMA showed no relationship between the leukocyte count at the time of diagnosis and response [26]. Therefore, difference in leukocyte counts between groups was ignored in our cohort.

The secondary AML patients have poor prognosis than de novo AML patients have, as well-known [27]. Patients with de novo AML were more likely to achieve CR than patients with secondary AML [28]. Similarly, in the present study, no difference was revealed between the two groups in terms of therapy response. Since the patients were randomized regardless of type of AML, count of secondary AML patients was found higher in the non-maintenance group than the maintenance group. This may be major limitation of study besides the retrospective design and lack of genetic risk stratification due to technical inadequacy.

Conclusion

Despite long-term exposure to HMA may appear as a risk factor for complications and toxicities in older and frail AML patients, maintenance of HMA provides significant survival advantage. Therefore, we suggest that HMA therapy should continue until disease progression regardless the sort of HMA.

Ethics Committee Approval: The Mugla Sitki Kocman University Clinical Research Ethics Committee granted approval for this study (date: 14.02.2020, number: 25).

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REFERENCES

1. Arber DA. The 2016 WHO classification of acute myeloid leukemia: What the practicing clinician needs to know. Semin Hematol 2019;56:90–5. [CrossRef]
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30. [CrossRef]
3. Wahlin A, Markevärn B, Golovleva I, Nilsson M. Prognostic significance of risk group stratification in elderly patients with acute myeloid leukaemia. Br J Haematol 2001;115:25–33. [CrossRef]
4. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. Arch Intern Med 2002;162:1597–603. [CrossRef]
5. Löwenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N Engl J Med 1999;341:1051–62. [CrossRef]
6. Daly MC, Paquette IM. Surveillance, Epidemiology, and End Results (SEER) and SEER-medicare databases: use in clinical research for improving colorectal cancer outcomes. Clin Colon Rectal Surg 2019;32:61–8. [CrossRef]
7. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al; European LeukemiaNet. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010;115:453–74. [CrossRef]
8. Tallman MS, Wang ES, Altman JK, Appelbaum FR, Bhatt VR, Bixby D, et al. Acute myeloid leukemia, version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:721–49. [CrossRef]
9. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015;126:291–9. [CrossRef]
10. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012;30:2670–7. [CrossRef]
11. Stone A, Zukerman T, Flaishon L, Yakar RB, Rowe JM. Efficacy outcomes in the treatment of older or medically unfit patients with acute myeloid leukaemia: A systematic review and meta-analysis. Leuk Res 2019;82:36–42. [CrossRef]
12. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424–47. [CrossRef]
13. Wen B, You W, Yang S, Du X. Indirect comparison of azacitidine and decitabine for the therapy of elderly patients with acute myeloid leukemia: a systematic review and network meta-analysis. Exp Hematol Oncol 2020;9:3. [CrossRef]
14. Gardin C, Dombret H. Hypomethylating agents as a therapy for AML. Curr Hematol Malig Rep 2017;12:1–10. [CrossRef]
15. Craddock CF, Houlton AE, Quek LS, Ferguson P, Gbandi E, Roberts C, et al. Outcome of azacitidine therapy in acute myeloid leukemia is not improved by concurrent vorinostat therapy but is predicted by a diagnostic molecular signature. Clin Cancer Res 2017;23:6430–40.
16. Passweg JR, Pabst T, Blum S, Bargetzi M, Li Q, Heim D, et al; Swiss Group for Clinical Cancer Research (SAKK). Azacytidine for acute myeloid leukemia in elderly or frail patients: a phase II trial (SAKK 30/07). Leuk Lymphoma 2014;55:87–91. [CrossRef]
17. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. J Clin Oncol 2010;28:556–61. [CrossRef]
18. Lübbert M, Rüter BH, Claus R, Schmoor C, Schmid M, Germing U, et al. A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy. Haematologica 2012;97:393–401. [CrossRef]
19. Lübbert M, Grishina O, Schmoor C, Schlenk RF, Jost E, Krauter J, et al. Results of the Randomized Phase II Study Decider (AMLSG 14-09) Comparing Decitabine (DAC) with or without Valproic Acid (VPA) and with or without All-Trans Retinoic Acid (ATRA) Add-on in Newly Diagnosed Elderly Non-Fit AML Patients. Blood 2016;128:589.
20. Kadia TM, Thomas XG, Dmoszynska A, Wierzbowska A, Minden M, Arthur C, et al. Decitabine improves outcomes in older patients with acute myeloid leukemia and higher blast counts. Am J Hematol 2015;90:E139–41. [CrossRef]
21. Padilha SL, Souza EJ, Matos MC, Domino NR. Acute myeloid leukemia: survival analysis of patients at a university hospital of Paraná.

Rev Bras Hematol Hemoter 2015;37:21–7. [CrossRef]
22. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. Blood 2015;125:3246–52. [CrossRef]
23. Liersch R, Müller-Tidow C, Berdel WE, Krug U. Prognostic factors for acute myeloid leukaemia in adults-biological significance and clinical use. Br J Haematol 2014;165:17–38. [CrossRef]
24. Kuo KH, Callum JL, Panzarella T, Jacks LM, Brandwein J, Crump M, et al. A retrospective observational study of leucoreductive strategies to manage patients with acute myeloid leukaemia presenting with hyperleucocytosis. Br J Haematol 2015;168:384–94. [CrossRef]
25. Yıldız A, Maral S, Albayrak M, Pala Ç, Cömert P, Öztürk Afacan HB et al. Are the conventional risk factors still valid for acute myeloid leukemia patients? Konuralp Tıp Dergisi 2020;12:5–11. [CrossRef]
26. Delaunay J, Mazur G, Minden M, Wierzbowska A, Jones MM, Berrak E, et al. Relationship between baseline white blood cell count and renal and hepatic function in older patients with acute myeloid leukemia. Leuk Res Rep 2013;3:17–20. [CrossRef]
27. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391–405.
28. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, Nørgaard M, Andersen MK, Dufva IH, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. J Clin Oncol 2015;33:3641–9. [CrossRef]