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Impact of age and induction therapy on outcome of 180 adult patients with acute myeloid leukemia; retrospective analysis and literature review

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ABSTRACT

The prognosis of acute myeloid leukemia (AML) remains poor. Among 180 patients, the median age was 53 (14-88) years. The overall 2-year disease free survival (DFS) was 28.6% (+/- 3.4), 47.7% (+/- 6.6%) for ≤ 40, 23.6% (+/- 5.8%) for 41–60 and 11.7% (+/- 4.2%) for ≥61 ($p < 0.0001$). The overall 2-year survival (OS) was 45.3% (+/- 3.8%), 78.6% (+/- 5.5%) for ≤40, 43.5% (+/- 6.9%) for 41–60 and 15.8% (+/- 4.8%) for ≥61 ($p < 0.0001$). Induction outcome of ≥61 was best in high dose chemotherapy (HDC) group ($p < 0.0001$). Only those ≤40 had durable DFS and OS. HDC appears to improve the outcome of older AML patients.

1. Introduction

The incidence of acute myeloid leukemia (AML) is increasing with some improvement in mortality rates over decades due the development on new anti-leukemia drugs and the improvement in management of chemotherapy and allogeneic stem cell transplant (allo-HSCT) complications [1]. The prognosis of AML, however, remains poor with an overall 5-year survival (OS) of 28.3%; while the OS is 40–50% in patients younger than 50 with de novo AML, the OS for elderly is only 5–10% [1–3].

AML prognosis depends on pretreatment factors such as age and cytogenetics upon diagnosis and post-treatment prognostic factors such as response to induction and more recently minimal residual disease [4–6].Approximately 65% of newly diagnosed AML will have an abnormal karyotype at the time of diagnosis, with older patients having higher incidence of high-risk cytogenetics compared to the young [7,8]. Age impact on the outcome of AML patients is not only related to cytogentics, but also performance status at diagnosis, with treatment related deaths up to 19% in patients above age 55 [9]. Older patients with AML are less likely to achieve complete remission (CR) after induction chemotherapy and they are more likely to experience disease relapse even if CR is attained [10]. Many elderly AML patients may not qualify for remission induction and an even fewer might qualify for consolidative allogeneic hematopoietic stem cell transplantation (SCT) [6].

In the present study we aimed to study the outcome of AML patients diagnosed at King Abdulaziz Medical City, Riyadh with emphasis on outcome in different age groups particularly the elderly.

2. Methodology

2.1. Patient selection

After due institutional review board approval, all patients ≥ 14 years of age with confirmed AML in the period of 2000–2018 were identified; and all records were retrospectively extracted.

2.2. Risk stratification

To determine the need for consolidative SCT, all patients were risk stratified at presentation based on their cytogenetic and molecular profile as per the updated European Leukemia Network (ELN) risk stratification [11].

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2.3. Induction chemotherapy

Patients received standard induction (SI) consistent of seven days of cytarabine at a dose of 200 mg/m^2 plus three days of idarubicin at a dose of 12 mg/m^2 twice per day (7 + 3) if they were younger than 65 and they are deemed fit to be able to tolerate high dose chemotherapy. Those with co-morbidities received reduced induction (RI) in the form of either five days of cytarabine at a dose of 100 mg/m^2 plus two days of idarubicin at a dose of 12 mg/m^2 twice per day (5 + 2) or intermediate dose cytarabine at a dose of 1500 mg/m^2 twice a day for three days for a total of six doses on days one, three and five. Patients with poor performance status, those with multiple comorbidities and those older than 70 years of age were treated with 5-azacitidine (AZA) or palliative therapy (PC) which could consist of supportive care with or without low doses of chemotherapy.

2.4. Response assessment and definitions

At count recovery or on day 28 post-chemotherapy, whichever comes first, a bone marrow aspiration and biopsy were performed to assess the disease response. Response criteria were defined as per the ELN 2017 criteria [11]. CR was defined as the presence of 5% or less bone marrow blasts, absence of circulating blasts and blasts with auer rods, absence of extramedullary disease, absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L (1000/μL); platelet count $\geq 100 \times 10^9$/L (100 000/μL). CR with incomplete hematologic recovery (CRi) was defined as bone marrow blasts $<5\%$; absence of circulating blasts and blasts with auer rods; absence of extramedullary disease except for residual neutropenia ($<1.0 \times 10^9$/L [1000/μL]) or thrombocytopenia ($<100 \times 10^9$/L [100 000/μL]). Primary refractory disease was defined as no CR or CRi after two courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause. Death in aplasia was defined as death occurring ≥ 7 d following completion of initial treatment while cytopenic. Disease relapse was defined as hematologic relapse (after CR, CRi): bone marrow blasts $\geq 5\%$, reappearance of blasts in the blood or development of extramedullary disease.

2.5. Consolidative therapy and allogeneic SCT

The consolidative therapy was decided based on whether the patient is a candidate for consolidative SCT, the disease characteristics (risk stratification), the response to induction therapy and the availability of a matched donor. SCT was recommended for all high and intermediate risk groups based on the ELN risk stratification if patient is eligible and donor available [11]. Matched related donor (MRD) was preferred over matched unrelated donor (MUD) over haploidentical donor.

2.6. Statistical analysis

Overall survival (OS) was calculated from the date of the start of induction chemotherapy until the date of death of any cause or last documented follow-up. Disease free survival (DFS) was calculated from the delivery of induction chemotherapy until death of any cause or evidence of disease relapse. Baseline patient, disease and treatment related variables were reported using descriptive statistics (counts, medians and percentages). Categorical and continuous variables were compared using Pearson's chi-squared and Wilcoxon / Kruskal-Wallis, respectively. Probability of OS and DFS was computed using the Kaplan-Meier method. Group comparisons were made using the log-rank test. Statistical analyses were performed using JMP Pro-Version 11 (SAS Institute, Cary, NC, USA) software and EZR on R commander.

3. Results

3.1. Patient characteristics

A total of 180 patients were identified through a query of our Oncology database. The median age at diagnosis was 53 (14-88) years and 103 (57%) were males. The age distribution was as follows; 58 (32%) were between 14–40 years, 57 (32%) between 41–60 years and the remaining 65 (36%) were over 60 years of age. Co-morbidities were present in 73 (41%) of patients including 8 (5%) of patients with 3 or more co-morbidities. The median Eastern Cooperative Oncology Group (ECOG) status was 1 (0–4). The World Health Organization (WHO) leukemia subtype was as follows; 91 (51%) with recurrent genetic abnormality, 31 (17%) AML with myelodysplasia related changes, 56 (31%) AML not otherwise specified (NOS) and 2 (1%) were therapy related disease. Risk stratification was as follows; 39 (22%) had favourable disease, 79 (43%) had intermediate disease, 50 (28%) had poor risk disease and there were 12 (7%) with unknown status due to various factors such as failed cytogenetics, dry aspirate and referral from another center.

With regards to induction therapy, 109 (60%) patients received SI, 32 (18%) received RI, 21 (12%) received AZA while 18 (10%) received PC. Median follow-up was 16.3 months (0.16–168.3) for all patients and 36.1 months (2.3–168.3) for alive patients. Outcome post induction was as follows; 112 (62%) achieved CR/CRi post first induction, 32 (18%) had primary refractory disease while 13 (7%) died in aplasia; and 62 (34%) underwent allogeneic SCT. The baseline characteristics and induction outcome of the whole cohort are detailed Table 1. The 2-year DFS for the entire cohort was 28.6% +/- 3.4 whereas the 2-year OS for the entire cohort was 45.3% +/- 3.8%.

Table 1
Baseline characteristics of the entire cohort.

Characteristic	*N* = 180
Age, median (range)	53 (14-88)
Age, n (%)	
14–40	58 (32)
41–60	57 (32)
≥ 61	65 (36)
Male, n (%)	103 (57)
Co-morbidities	
0	106 (59)
1–2	65 (36)
≥ 3	8 (5)
ECOG, median (range)	1 (0–4)
WHO Subtype, n (%)	
Recurrent Genetic Abnormality	91 (51)
AML with MDS	31 (17)
AML NOS	56 (31)
Therapy Related	2 (1)
Risk Stratification, n (%)	
Favorable	39 (22)
Intermediate	79 (43)
Poor	50 (28)
Unknown	12 (7)
Induction Type	
Standard Induction	109 (60)
Reduced Induction	32 (18)
5-AZA	21 (12)
Palliative	18 (10)
Induction Outcome, n (%)	
CR/CRi	112 (62)
Primary Refractory	32 (18)
Death in Aplasia	13 (7)
Unknown	23 (13)
Allogeneic SCT, n (%)	62 (34)

3.2. Outcome in different age groups

Patient, disease and therapy baseline was stratified by age and results as follows; Fifty-eight (32%) patients were 40 years old or younger, 57 (32%) patients were 41–60 years and 65 (36%) were older than age 60 at the time of diagnosis. Overall, baseline co-morbidities were higher in the older age groups ($p < 0.0001$) and a worse ECOG status ($p < 0.0001$). Incidence of higher risk disease was also more common with age ($p = 0.04$).

Treatment offered also differed based on underlying age. Among the young and middle age groups 100 (87%) received SI, 9 (8%) received RI while 6 (5%) received AZA or PC. Among the same group, 86 (75%) achieved CR/CRi at the end of induction and 59 (51%) underwent allogeneic SCT. Among those older than age 60, only 9 (14%) were deemed fit to receive SI, 23 (35%) received RI while 13 (20%) received AZA and 20 (31%) received PC. Overall, 25 (38%) achieved CR/CRi, 15 (23%) were primary refractory and only three (5%) underwent allogeneic SCT. The use of SI was significantly higher in the young and middle age groups than older at 91%, 82% and 14%, respectively ($p < 0.0001$). Furthermore, a significantly inferior induction outcome was noted in the latter group with lower incidence of CR/Cri and higher incidence of death in aplasia ($p = 0.0002$). Use of allogeneic SCT was also significantly varied among the three groups at 64%, 39% and 5% for the younger, middle age and older groups; respectively, ($p < 0.0001$). These results are shown in Table 2.

The 2-year DFS stratified by age groups was 47.7% +/- 6.6% for patients younger than 40 years, 23.6% +/- 5.8% for 41–60 years and 11.7% +/- 4.2% > 61 years ($p < 0.0001$). The 2-year DFS compared between different age groups was ≤ 40 vs. ≥ 61 HR 0.32 (0.2–0.49; < 0.0001); 41–60 vs. ≥ 61 HR 0.66 (0.44–0.97; 0.037); ≤ 40 vs. 41–60 HR 0.48 (0.3–0.75; 0.0014). The 2-year OS stratified by age groups was 78.6% +/- 5.5% for patients younger than 40 years, 43.5% +/- 6.9% for 41–60 years and 15.8% +/- 4.8% > 61years ($p < 0.0001$). The 2-year OS compared between different age groups was ≤ 40 vs. ≥ 61 HR 0.15 (0.087–0.27; < 0.0001); 40–60 vs. ≥ 61 HR 0.49 (0.32–0.76; 0.001); ≤ 40 vs. 40–60 HR 0.31 (0.17–0.55; < 0.0001). The 2-year DFS stratified by age groups is shown in Fig. 1.

Table 2
Baseline characteristics of the cohort stratified by age groups.

Characteristic / Age group	14–40 ($n = 58$)	41–60 ($n = 57$)	≥ 61 ($n = 65$)	P value
Male, n (%)	32 (55)	28 (49)	43 (66)	0.15
Co-morbidities				< 0.0001
0	54 (93)	35 (61)	17 (27)	
1–2	4 (7)	22 (39)	39 (61)	
≥ 3	0	0	8 (12)	
ECOG, median (range)	0 (0–1)	0 (0–3)	2 (0–4)	< 0.0001
WHO Subtype, n (%)				0.18
Recurrent Genetic Abnormality	34 (59)	26 (46)	31 (48)	
AML with MDS	6 (10)	10 (17)	15 (23)	
AML NOS	18 (31)	19 (33)	19 (29)	
Therapy Related	0	2 (4)	0	
Risk Stratification, n (%)				
Favorable	17 (29)	14 (25)	8 (12)	
Intermediate	29 (50)	23 (40)	27 (42)	
Poor	11 (19)	16 (28)	23 (35)	
Unknown	1 (2)	4 (7)	7 (11)	0.04
Treatment Type				< 0.0001
Standard Induction	53 (91)	47 (82)	9 (14)	
Reduced Induction	1 (2)	8 (14)	23 (35)	
5-AZA	0	1 (2)	13 (20)	
Palliative	4 (7)	1 (2)	20 (31)	
Induction Outcome, n (%)				0.0002
CR/CRi	45 (78)	41 (72)	25 (38)	
Primary Refractory	7 (12)	9 (16)	15 (23)	
Death in Aplasia	2 (3)	3 (5)	8 (12)	
Unknown	4 (7)	4 (7)	17 (26)	
Allogeneic SCT, n (%)	37 (64)	22 (39)	3 (5)	< 0.0001

3.3. Outcome in elderly AML

Given the heterogeneity in therapy delivered most seen in the elderly group, we stratified them based on therapy. We observed a significant difference in the following variables; median age was youngest in the SI and oldest in the AZA / PC groups ($p < 0.0001$), ECOG highest in the AZA / PC groups ($p = 0.04$) and induction outcome was best in the SI / RI groups ($p < 0.0001$). The 2-year DFS stratified by type of induction was as follows: standard vs. reduced HR 0.43 (0.28–0.67; 0.0002); palliative vs. 5-AZA HR 0.48 (0.24–0.96; 0.04); standard vs. palliative HR 0.56 (0.32–1; 0.051). The 2-year OS stratified by type of induction was as follows: standard vs. reduced HR 0.37 (0.22–0.6; < 0.0001); palliative vs. 5-AZA 0.42 (0.2–0.86; 0.018); standard vs. palliative 0.39 (0.21–0.71; 0.0024). Allogeneic SCT was offered to 3 patients only, all of whom received SI. These results are shown in Table 3.

The 2-year DFS in patients > 60 years old stratified by therapy were as follows; SI 22.2% +/- 7.9%, RI 17.4% +/- 7.9%, AZA 0% and PC 7.7% +/- 7.4 ($p = 0.032$). The 2-year OS were as follows; SI 22.2% +/- 17.7%, RI 22.9% +/- 8.9%, AZA 0% and PC 9.6% +/- 8.9%. These results are shown in Fig. 2.

4. Discussion

AML is a common malignancy among adult patients with an estimated total of 21,450 newly diagnosed cases and 10,920 deaths in the United States alone in 2019 [1]. For over 3 decades, the backbone of induction therapy consisted of anthracycline and cytarabine combination which was originally reported in 1973 [12,13]. However, recent advances in descriptive mutational classification have led to the development of multiple new AML targeted therapies. During 2017 and 2018 alone the US Food and Drug Administration (FDA) approved one combination drug (CPX-351) and seven new drugs to treat AML (glasdegib, midostaurin, venetoclax, enasiderib, giltretinib, gemtuuzumab ozogamicin and ivosidenib) [14]. However, experience with those agents remains limited as we need further studies to optimize their use with other drugs including chemotherapy. The 5-year overall survival has improved for AML patients due to a number of factors including improvements in supportive care. This has not equated among different age groups [1,15–17]. For instance, the 5- and 10-year survival for adolescents and young adult patients (15–34 years) is 52.3% and 47.9%. Yet, they are only 36.6% and 33.6% for middle age (35–54 years), 19.9% and 17.9% for (55–64 years) age group and only 9.2% and 4.5% for elderly (65–74 years) [17].

In the present study, the median age at diagnosis was 53 (14-88) years much younger compared to the United Kingdom which was reported by Roman et al. where median age at diagnosis of all 5231 myeloid subtypes combined being 72.4 years (IQR 61.5–80.2 years) and older than in India as reported by Phillips et al.: the median age among 380 newly diagnosed AML patients was 40 years (range: 1–79; 12_3% were ≤ 15 years, 16_3% were ≥ 60 years old) and there were 244 (64_2%) males [18,19]. A recent study reporting the outcome of 135 newly diagnosed AML patients in the Western Region of Saudi Arabia median age of 42 years (range 14–67) relatively younger than our cohort. The age distribution was as follows; 58 (32%) were between 14–40 years, 57 (32%) between 41–60 years and the remaining 65 (36%) were over 60 years of age. Our cohort has more elderly patients compared to what was reported by Alabdulwahab et al. where 65 (48.1%) patients were < 42 years, and only 11 (8.2%) > 60 years [20].

In the present analysis, 109 (60%) patients achieved CR/CRi at end of induction. The percentage of patients who achieved CR/CRi was similar in patients younger than age 40 and those 41–60: 45(78%) vs. 41(72%); compared to only 25 (38%) in patients older than age 60. Nonetheless, the long term outcome of the middle age group patients is

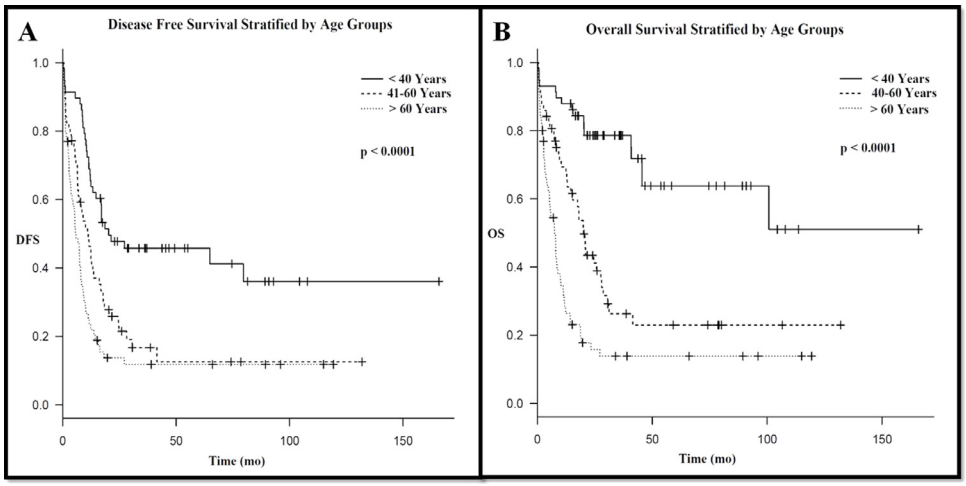

Fig. 1. Two-year disease-free survival and overall survival stratified by age groups. The 2-year DFS was 47.7% +/- 6.6% for patients younger than 40 years, 23.6% +/- 5.8% for 41-60 years and 11.7% +/- 4.2% > 61 years (p< 0.0001). The 2-year OS stratified by age groups was 78.6% +/- 5.5% for patients younger than 40 years, 43.5% +/- 6.9% for 41-60 years and 15.8% +/- 4.8% > 61 years (p< 0.0001)

Table 3
Baseline characteristics of patients ≥61 years stratified by type of therapy.

Characteristic / Treatment group	Standard induction (n = 9)	Reduced induction (n = 23)	5-AZA (n = 20)	Palliative (n = 13)	P value
Male, n (%)	9 (100)	15 (65)	13 (65)	6 (46)	0.02
Age, median (range)	62 (61–69)	68 (62–76)	74 (61–88)	70 (63–88)	< 0.0001
Co-morbidities					0.3
0	5 (56)	6 (26)	4 (21)	2 (15)	
1–2	4 (44)	13 (57)	13 (68)	9 (69)	
≥ 3	0	4 (17)	2 (11)	2 (15)	
ECOG, median (range)	1 (0–2)	1 (0–4)	3 (0–4)	3 (1-4)	0.0006
WHO Subtype, n (%)					0.04
Recurrent Genetic Abnormality	6 (67)	12 (52)	8 (40)	5 (38.5)	
AML with MDS	1 (11)	1 (4)	8 (40)	5 (38.5)	
AML NOS	2 (22)	10 (44)	4 (20)	3 (23)	
Risk Stratification, n (%)					0.08
Favorable	0	4 (17)	1 (5)	3 (23)	
Intermediate	3 (33.3)	11 (48)	10 (50)	3 (23)	
Poor	3 (33.3)	6 (26)	9 (45)	5 (39)	
Unknown	3 (33.3)	2 (9)	0	2 (15)	
Induction Outcome, n (%)					< 0.0001
CR/CRi	6 (67)	16 (69)	1 (5)	2 (15)	
Resistant Disease	3 (33)	2 (9)	8 (40)	2 (15)	
Death in Aplasia	0	3 (13)	3 (15)	2 (15)	
Unknown	0	2 (9)	8 (40)	8 (54)	
Allogeneic SCT, n (%)	3 (33)	0	0	0	0.005

more comparable to that of elderly group despite the fact that two thirds of them presented with favorable or intermediate risk score, 82% received SI, and 39% underwent allo-HSCT. The 2-year DFS for those 41–60 was much lower compared with patients younger than 40 years, 23.6% +/- 5.8% vs. 47.7% +/- 6.6%. The DFS compared among the three age groups was as follows: ≤ 40 vs. ≥ 61 HR 0.32 (0.2–0.49; < 0.0001); 40–60 vs. ≥ 61 HR 0.66 (0.44–0.97; 0.037); ≤ 40 vs. 40–60 HR 0.48 (0.3–0.75; 0.0014). The 2-year OS for those 41–60 was 43.5%

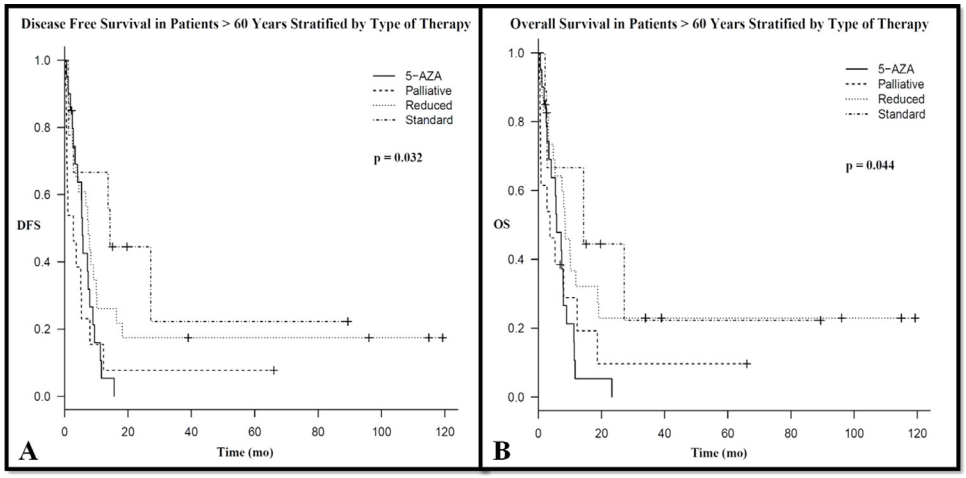

Fig. 2. Two-year disease-free survival and overall survival in patients older than 60 years old stratified by therapy. The 2-year DFS was 22.2% +/- 7.9% for standard induction (SI), 17.4% +/- 7.9% for reduced induction (RI), 0% for azacytidine and 7.7% +/- 7.4 for palliative care (PC) (p = 0.032). The 2-year OS were as follows; 22.2% +/- 17.7% for SI, 22.9% +/- 8.9% for RI, 0% for AZA and 9.6% +/- 8.9% for PC.

+/- 6.9% compared to 78.6% +/- 5.5% for patients younger than 40 years. The OS compared among the three age groups was as follows: ≤ 40 vs ≥ 61 HR 0.15 (0.087–0.27; < 0.0001); ≤ 40–60 vs. ≥ 61 HR 0.49 (0.32–0.76; 0.001);

≤ 40 vs. 40–60 HR 0.31 (0.17–0.55; < 0.0001). Some of the factors that might have contributed to this group's worse outcome include a higher incidence of poor risk disease (28% vs. 19%), AML/MDS (17% vs. 10%), and a lower proportion of SI (82% vs. 91%).

Historically, half of AML patients older than age 60 receive intensive induction therapies worldwide [21,22]. In the present cohort, 49% of patients older than age 60 received intensive chemotherapy (SI and RI) with 40% achieving CR/CRi. Elderly AML outcome improves when more intensive induction is delivered compared to a palliative approach; even among octogenarians [23,24]. However the response rate to intensive induction is different patients older than 60 compared to the young, with CR rates of 40–60% vs. 60–85% [25]. We observed improved outcomes in elderly patients receiving more intensive therapy with 68% achieving CR/CRi with significant improvement in DFS, standard vs. reduced HR 0.43 (0.28–0.67; 0.0002); palliative vs. 5-AZA HR 0.48 (0.24–0.96; 0.04); standard vs. palliative HR 0.56 (0.32–1; 0.051). Elderly patients who received more intensive therapies also had better OS: standard vs. reduced HR 0.37 (0.22–0.6; < 0.0001); palliative vs. 5-AZA 0.42 (0.2–0.86; 0.018); standard vs. palliative 0.39 (0.21–0.71; 0.0024) This highlights the importance of accurate evaluation of performance status and co-morbidities to identify patients eligible to receive more effective therapies. This can be accomplished by using models to predict adverse outcome with intensive remission induction regimen in elderly AML patients [26,27].

Cure should remain the goal following successful remission induction whenever feasible in elderly AML patients. Such consolidation can be achieved using allo-SCT most commonly using reduced intensity conditioning (RIC) [28]. Nonetheless, elderly AML patients are rarely offered allogeneic SCT due to concerns related to transplant related toxicity with only about 8% of them undergo allogeneic SCT in US [22]. In the present study; only 5% of the elderly group underwent consolidative allogeneic SCT.

The introduction of sequencing technologies had shown major differences in the cytogenetic and mutational profile of AML in the elderly [29,30]. The methylation patterns in such patients is similar to those seen in MDS patients [31]. These unique features may help scientist design more targeted therapies for such patient population. The BCL-2 inhibitor venetoclax combined with azacitidine or decitabine have resulted in an overall response rate of 59–65% with a median OS of 17.5 months with no additional adverse events compared to azacitidine or decitabine alone [32]. The addition of gemtuzumab ozogamicin (GO) to induction chemotherapy had been shown to reduce the relapse risk and to improve the survival of favorable and intermediate risk AML patients both young and old [33]. GO combined to azacitidine was shown to be of benefit in older AML patients with poor risk [34]. In the present cohort, only few elderly patients received venetoclax.and none received GO.

The isocitrate dehydrogenase-1 and 2 (*IDH1* and *IDH2*) small molecular inhibitors ivosidenib and enasidenib are being studied as single agents or in combination with hypomethylating agents for remission induction in newly diagnosed AML with patients harboring *IDH1* or *IDH2* mutations. If combination therapy is proven to be of benefit, these drugs can will be a great plus to elderly AML induction therapy armamentariumIn frontline setting two studies have shown an improved outcome with the addition of FLT3 inhibitors (sunitnib and quizartinib) to chemotherapy in elderly patients with FLT3-ITD-mutated AML [35,36].

Although more than half of the patients achieved CR at the end of induction, only patients younger than 40 had durable DFS and OS. Middle age group AML patients do much worse compared to the young and special intervention need to be implemented to improve the outcome of this age group. More options are available than ever before for treating newly diagnosed AML, including the elderly. Several gene mutations are associated with specific prognosis and ma guide treatment decisions such as: *c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASLX1* and *TP53* and all newly diagnosed AML patients should be tested for those [37]. For more comprehensive assessment, multiplex gene panel and next generation sequencing (NGS) should be considered [38]. It is preferred that *FLT3-ITD* and *FLT3-TKD* mutation status is known early to allow the introduction of *FLT3* inhibitor on day 8 of induction chemotherapy.

The panoply of the new molecularly targeted therapies especially when introduced early in the disease course will insure delivery of personalized/précised therapy to the majority of AML patients in general and the middle and old age ones in particular.. Older fit patients should not be denied curative therapies merely based on age.

CRediT authorship contribution statement

Khadega A. Abuelgasim: Conceptualization, Methodology, Data curation, Writing - original draft. **Bandar Albuhayri:** Conceptualization, Data curation, Writing - original draft. **Rayan Munshi:** Conceptualization, Data curation, Writing - original draft. **Areej Al Mugairi:** Conceptualization, Data curation, Writing - review & editing. **Bader Alahmari:** Conceptualization, Writing - review & editing. **Giamal Gmati:** Writing - review & editing. **Hind Salama:** Writing - review & editing. **Mohsen Alzahrani:** Writing - review & editing. **Ayman Alhejazi:** Supervision, Writing - review & editing. **Ahmed Alaskar:** Supervision, Writing - review & editing. **Moussab Damlaj:** Conceptualization, Supervision, Formal analysis, Writing - review & editing.

Declaration of Competing Interests

The authors declare no conflict of interest.

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