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Research paper

Not type of induction therapy but consolidation with allogeneic hematopoietic cell transplantation determines outcome in older AML patients: A single center experience of 355 consecutive patients

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ABSTRACT

Therapeutic decision making is often challenging in older AML patients. We collected retrospective data of 355 consecutive AML patients (≥60 years) who were treated with intensive chemotherapy (IC) (n = 155), hypomethylating agents (HMA) (n = 83), or best supportive care (BSC) (n = 117) between 2002 and 2017. Overall survival (OS) and response rates after therapy were analyzed. Multivariate Cox regression was performed to analyze the impact of different treatment strategies on survival. The median OS was not significantly different between patients treated with IC or HMA (14.9 vs 10.9 months; HR = 1.32, p = 0.076)), despite a difference in complete remission rate (59% after IC vs 35% after HMA). Patients who received a allogeneic hematopoietic cell transplantation (allo HCT) after treatment with IC or HMA had a significant survival benefit compared to patient who didn't proceed to allo HCT (median OS 65 vs 8 months, respectively, p < 0.001). The type of induction therapy (i.e. IC or HMA) did not impact on survival after allo HCT (48 vs 65 months, respectively, p = 0.440). In conclusion, consolidation with an allo HCT provides a significant benefit for older AML patients independent of upfront treatment with IC or HMA. Our data suggest that more older patients should be considered for an allo HCT.

1. Introduction

Acute myeloid leukemia (AML) is a malignant disorder of the hematopoietic system characterized by maturation arrest and accumulation of myeloid blasts. AML mostly affects older individuals with a median age at diagnosis of 67 years [1–3]. The prognosis of the older age group (> 60 years) is worse compared to younger age groups, with cure rates < 10% and a median overall survival (OS) of 10 months after treatment with intensive chemotherapy (IC) [1,4]. In contrast to younger patients, the outcomes for the older patient-group (> 60 years) have not improved over the past decades [3,5]. The increased incidence of co-morbidities and unfavorable disease characteristics are factors contributing to the poor outcome of older AML patients [1,4,6,7].

In clinical practice the optimal management of AML in older patients is challenging [8]. Older patients are often considered not eligible for treatment with IC, due to poor performance status and/or inadequate organ function which can lead to excessive toxicity and treatment-related mortality [6,9,10]. Additionally, disease related factors such as cytogenetic abnormalities, which are more frequent in older patients, might render the disease less sensitive to chemotherapy [1,11,12].

Currently, there is no general consensus concerning standard approach for the upfront treatment of AML in older patients (> 60 years). A few prospective randomized trials have shown that various treatment options (azacitidine, decitabine, low dose cytarabine and gemtuzumab ozogamycin) are superior to best supportive care (BSC) [13–17]. Recently the hypomethylating agents (HMA) azacitidine and decitabine have become more frequently applied in the treatment of AML, since

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HMA therapy is generally well-tolerated by patients with low extramedullary toxicity [14,16–21]. In addition, HMAs have been shown to be effective in AML with adverse cytogenetics [14,18,22].

Moreover, the application of allogeneic hematopoietic cell transplantation (allo HCT) is increasing, but still only applied in a small and selected subset of older patients [23]. The choice for HMA or IC which may or may not be followed by allo HCT is not supported by prospective data but often based on physician's choice, patient- and disease-related factors as well as patient's personal preference.

To study the impact of HMAs and conventional care options, comprising either IC or BSC, and the impact of allo HCT in routine clinical practice, we retrospectively analyzed treatment results of 355 consecutive newly diagnosed AML patients of 60 years or older in the University Medical Center Groningen (UMCG), the Netherlands.

2. Material and methods

2.1. Patient inclusion and data collection

This single-center, retrospective database study was conducted with all consecutive patients aged 60 years or older at the time of AML diagnosis (according to WHO 2016 criteria, whenever possible) [24] who received any treatment (either BSC or IC or HMA) in the UMCG. Information on patient-, disease-, and treatment characteristics were collected by studying individual patient files. Genetic risk was defined according to the European LeukemiaNet (ELN) 2017 genetic risk stratification, if available with inclusion of molecular markers and if molecular markers were not available based on patient karyotype [25]. Baseline co-morbidity was quantified by the HCT-comorbidity index and performance score (PS) according to the WHO performance status grading system [26]. This study was approved by the medical ethical committee of the UMCG.

2.2. Treatment

The treatment options included in this study were; IC, HMA (either azacitidine or decitabine), and BSC. Treatment was allocated based on physician's choice, inclusion in a clinical trial, and patient's preference. IC was administered to patients according to HOVON or EORTC studies, which all contained standard dose cytarabine and an anthracycline (HOVON 42, 43, 81, 97, 102, 103, 132, 135; EORTC-AML-21) [27,28]. Patients diagnosed with acute promyelocytic leukemia (APL) were excluded from the analysis. The hypomethylating agent azacitidine was available in the Netherlands from December 2008 in a compassionate named patient program. It was administered following the approved schedule of 75 mg/m^2 for 7 consecutive days every 28 days. The hypomethylating agent decitabine was available in the Netherlands since 2012 for AML therapy, for patients considered 'unfit' to receive standard induction chemotherapy. Decitabine was administered to all patients in a dose of 20 mg/m^2 for 10 days every 28 days, applied according to Blum et al. [22]. Based on these favorable data on the 10-day decitabine schedule compared to the 5-day schedule, our center uses the 10-day schedule. BSC consisted of transfusions, antibiotics, and hospital admissions if needed. Treatment was reviewed or discontinued in case of disease progression, unacceptable toxicity, or patient decision to withdraw consent. Additional consolidation with an allo HCT was also recorded.

2.3. Assessment of efficacy and response criteria

Response to treatment was evaluated after every treatment cycle of IC and for HMA by assessing blood counts and by bone marrow aspirate if available. Morphologic response to treatment was scored according to the ELN 2017 recommendations on diagnosis and management of AML in adults [25]. Relapse of disease was defined as recurrence of ≥5% blasts in bone marrow or blasts in peripheral blood or development of extramedullary disease after a previous state of complete remission (CR).

OS was measured from date of diagnosis to death from any cause. Patients who remained alive were censored on the date of last visit to the hospital. Event-free survival (EFS) was measured from the date of marrow evaluation which confirmed CR/CRi (CRi; complete remission with incomplete hematologic recovery) until the date of relapse, death, or censoring. Additionally the overall, and 1-year relapse rates were determined as well as the early death rate within 7 and 28 days.

2.4. Statistical analysis

Descriptive statistics are given for all treatment groups to characterize the cohort. Differences between treatment groups in response rates were compared using Pearson's Chi-Square test or Fisher's exact test for categorical variables and Mann-Whitney U test or Kruskal-Wallis test for quantitative variables. Survival curves were estimated using the Kaplan-Meier method. The log-rank test was performed to test for differences in survival distribution. Univariate and multivariate Cox proportional regression analyses were performed to evaluate the effect of treatment strategy and several patient-related and disease-related factors on OS and estimate related hazard ratios (HR) and 95% confidence intervals (CI). In addition to the univariate and multivariate analyses a 1:1 patient matched cohort was selected to minimize the effect of treatment selection bias and observed confounding bias. Patients were matched on cytogenetic risk group and age group (60–69 or ≥70 years) at diagnosis. Survival analysis based on treatment strategy was performed for the matched cohort. For all analyses a P-value of < 0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics Version 23.

3. Results

3.1. Study population and baseline characteristics

Four-hundred-sixty-five patients were included in the database. One-hundred-ten patients were excluded from further analyses because they received treatment in another hospital (77 patients), were aged younger than 60 years at time of diagnosis (9 patients), were assigned an incorrect diagnosis (myelodysplastic syndromes (MDS) instead of AML) (1 patient) or diagnosed with APL (23 patients). Three-hundred-fifty-five consecutive patients of 60 years or older diagnosed with AML and treated in the UMCG between January 2002 and July 2017 were included in the analyses (Fig. 1).

Of these 355 patients 155 (44%) were treated with IC, 83 (23%) were treated with HMAs, and 117 (33%) patients received BSC. The median age at diagnosis was 69 years. The majority of patients was diagnosed with *de novo* AML (62.8%). Most patients had an intermediate cytogenetic risk (41.1%), closely followed by unfavorable risk (39.1%). Almost 20% of patients had an favorable cytogenetic risk. Fifty-eight patients could not be classified based on cytogenetic risk due to missing data. Hyperleukocytosis (white blood cell count $> 100 \times 10^9$/L) was present in 6% of patients at diagnosis. Baseline patient- and disease characteristics of the different treatment groups are shown in Table 1.

3.2. Response to treatment

Any response (CR, CRi, PR (partial remission), MLFS (morphologic leukemia free state)) was achieved in 117 (76%) of patients who received IC, in 36 (43%) of patients who received HMA, and in 2 patients (1.7%) in the BSC group. The odds ratio for patients in the IC group to obtain a response was 3.89 (2.21–6.84) compared to the HMA group ($p < 0.001$). The CR rates for patients treated with IC and HMA were 59% and 35%, respectively ($p < 0.001$). However, when specifically looking at CR rates in patients treated with decitabine the rates were

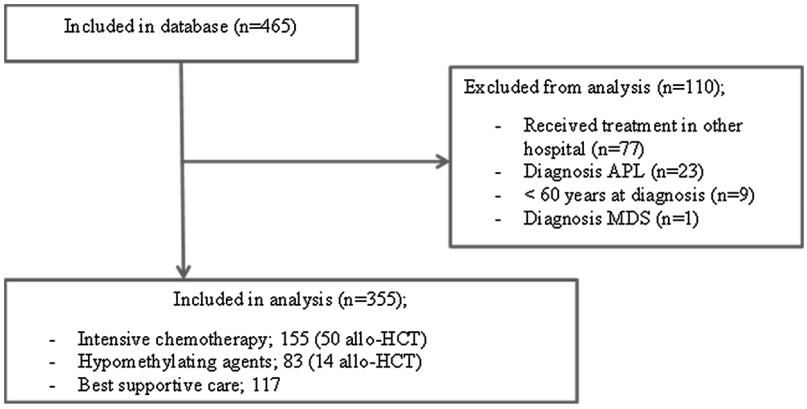

Fig. 1. Flowchart of the study population.

comparable to those in the IC group (50% vs 59%, p = 0.334). EFS was also comparable in the IC and HMA treatment groups, at 320 days versus 341 days (p = 0.863). The overall- and 1-year relapse rates did not differ significantly between IC and HMA (44% vs 39%; p = 0.785 and 24% vs 19%; p = 0.853, respectively). Remarkably, within the HMA group most patients treated with decitabine relapsed within 1 year of diagnosis, whereas most patients treated with azacitidine relapsed after 1 year from diagnosis. The responses in the various treatment arms are shown in Table 2.

3.3. Allogeneic hematopoietic cell transplantation

In this cohort 68 patients out of 355 (19%) were consolidated with an allo HCT after non-myeloablative conditioning (n = 67) or myeloablative conditioning (n = 1). Fifty-nine patients received an allo HCT after a single first-line treatment; 45 out of 155 (29%) after IC and 14 out of 83 (17%) after HMA. Additionally 4 patients received allo HCT after HMA and IC treatment and 5 patients received a transplantation after a relapse. In the IC treatment group 44 of the 45 patients were in CR/CRi when they received the transplant. In the HMA treatment group all 14 patients had received decitabine as first line therapy and 11 patients were in CR/CRi when they received the transplant. Baseline characteristics of patients who received an allo HCT are shown in supplementary Table 1.

3.4. Overall survival by treatment strategy

The median OS of all 355 patients was 8.0 months. Patients treated with either of IC or HMA had a superior survival compared to patients who only received BSC (14.9 vs. 10.9 vs 2.3 months, respectively (p < 0.001)) (HR = 0.28 (0.20 − 0.40), p < 0.001) (Fig. 2a). There was no significant difference in OS between patients treated with IC or HMA (14.9 vs 10.9 months, p = 0.075) (HR = 1.32 (0.97–1.80), p = 0.076) (Fig. 2a). After correction for the factors age at diagnosis, cytogenetic risk, WBC count at diagnosis, PS, and co-morbidity score in multivariate Cox regression analysis, the HR remained stable at 1.39

Table 1
Patient characteristics.

	All (n = 355)	IC (n = 155)	HMA (n = 83)		BSC (n = 117)
			Aza (n = 51)	Dec (n = 32)	
Gender					
- Male (n)	216 (60.8%)	90 (58.1%)	34 (66.7%)	18 (56.3%)	74 (63.2%)
- Female (n)	139 (39.2%)	65 (41.9%)	17 (33.3%)	14 (43.8%)	43 (36.8%)
Age at diagnosis (median in years, range)	69 (60–96)	67 (60–76)	71 (60–83)	69 (61–79)	73 (60–96)
Performance score ≥2 (n)	151 (42.5%)	62 (40%)	12 (23.5%)	5 (15.6%)	72 (61.5%)
Co-morbidity score					
- < 3	246 (69.3%)	117 (75.5%)	34 (66.7%)	23 (71.9%)	72 (61.5%)
- ≥ 3	109 (30.7%)	38 (24.5%)	17 (33.3%)	9 (28.1%)	45 (38.5%)
AML Classification (n)					
- De novo	223 (62.8%)	106 (68.4%)	26 (51.0%)	18 (56.3%)	73 (62.4%)
- Therapy related	48 (13.5%)	18 (11.6%)	10 (19.6%)	2 (6.3%)	18 (15.4%)
- Prior MDS/other hematologic disease	84 (23.7%)	31 (20.0%)	15 (29.4%)	12 (37.5%)	24 (22.2%)
Cytogenetic risk (ELN 2017) (n)					
- Favorable	59 (19.9%)	34 (23.6%)	4 (8.3%)	8 (26.7%)	13 (17.3%)
- Intermediate	122 (41.1%)	61 (42.4%)	22 (45.8%)	7 (23.3%)	32 (42.7%)
- Unfavorable	116 (39.1%)	49 (34.0%)	22 (45.8%)	15 (50.0%)	30 (40.0%)
- *Missing*	58	11	3	2	42
Molecular markers[a] (positive) (n)					
- CBFB-MYH11	4/306 (1.3%)	2/141 (1.4%)	0/48	1/32 (3.1%)	1/85 (1.2%)
- RUNX1-RUNX1T1	8/305 (2.6%)	4/140 (2.9%)	0/48	2/32 (6.3%)	2/85 (2.4%)
- FLT3-ITD	44/278 (15.8%)	32/139 (23.0%)	0/38	1/27 (3.7%)	11/74 (14.9%)
- Mutated NPM1	49/262 (18.7%)	30/133 (22.6%)	5/40 (12.5%)	4/27 (14.8%)	10/62 (16.1%)
- Increased EVI1 expression	39/196 (19.9%)	17/103 (16.5%)	12/34 (35.3%)	6/25 (24.0%)	4/34 (11.8%)
- Biallelic mutated CEBPA	5/195 (2.6%)	3/102 (2.9%)	0/35	0/25	2/33 (6.1%)
White blood cells ($x10^9$) (median, range)	4.7 (0.4–467.1)	5.3 (0.4–467.1)	2.8 (0.4–56.4)	3.6 (0.5–135.4)	7.3 (0.5–281.2)
WBC > 100×10^9 (n)	21 (5.9%)	13 (8.4%)	0	1 (3.1%)	7 (6.0%)
LDH (U/L) (median, range)	316 (115–4632)	314 (130–3282)	256 (115–1757)	390 (173–4632)	366 (116–3405)

[a] Data on presence of molecular markers wasn't available for all patients.

Table 2
Response to upfront therapy.

	IC (n = 155)	HMA (n = 83)		BSC (n = 117)	P-value	
		Aza (n = 51)	Dec (n = 32)		Overall	IC vs HMA
Median OS (months)	14.9	8.8	10.9	2.3	< 0.001[#]	*NS*
- *alloHCT patients censored*	13.8	8.8	10.3	2.3	< 0.001[#]	
3-year survival	34 (21.9%)	9 (17.9%)	2 (6.3%)	2 (1.7%)	< 0.001[*]	*NS*
Response to therapy						
- Overall	117 (75.6%)	18 (35.3%)	18 (56.3%)	2 (1.7%)	< 0.001[*]	< 0.001[*]
- CR	92 (59.4%)	13 (25.5%)	16 (50.0%)	0	< 0.001[*]	< 0.001[*]
- CRi	13 (8.4%)	0	1 (3.1%)	0	0.002[*]	0.025[*]
- PR	10 (6.5%)	4 (7.8%)	1 (3.1%)	2 (1.7%)	*NS*	*NS*
- MLFS	2 (1.3%)	1 (2.0%)	0	0	*NS*	*NS*
- No response	38 (24.4%)	33 (64.7%)	14 (43.8%)	115 (98.3%)		
Event free survival (in responders) median (days), range	320 (3–5311)	521 (120–1714)	227 (49–1273)	–	*NS*	*NS*
Relapse rate						
- Overall1	40 (43.5%)	8 (61.5%)	6 (37.5%)	–	*NS*	*NS*
- 1-year[a,b]	22 (23.9%)	2 (15.4%)	5 (31.3%)	–	*NS*	*NS*
Early deaths						
- ≤ 7 days[c]	1 (0.9%)	0	0	16 (13.7%)	< 0.001[*]	*NS*
- ≤ 28 days[c]	10 (8.7%)	1 (2.0%)	0	42 (35.9%)	< 0.001[*]	*NS*
Allogeneic HCT (n)					< 0.001[*]	*NS*
- Yes, upfront	45 (29.0%)	0	14 (43.8%)	0 (0%)		
- Yes, relapse	5 (3.2%)	0	0	0		
- No	105 (67.7%)	51 (100%)	18 (56.3%)	111 (100%)		
Follow-up time (median in months, range)	12.3 (0.1–175.8)	8.8 (0.85–64.9)	9.2 (0.9–43.0)	2.3 (0–39.9)	< 0.001[^]	*NS*

[a] Percentages calculated with CR numbers (# relapsed/# CR).
[b] Calculated from date of diagnosis.
[c] Death within 7 or 28 days after diagnosis.
[#] Estimated with log-rank test.
[*] Estimated with Pearson's chi-square test.
[^] Estimated with Kruskal-Wallis test.

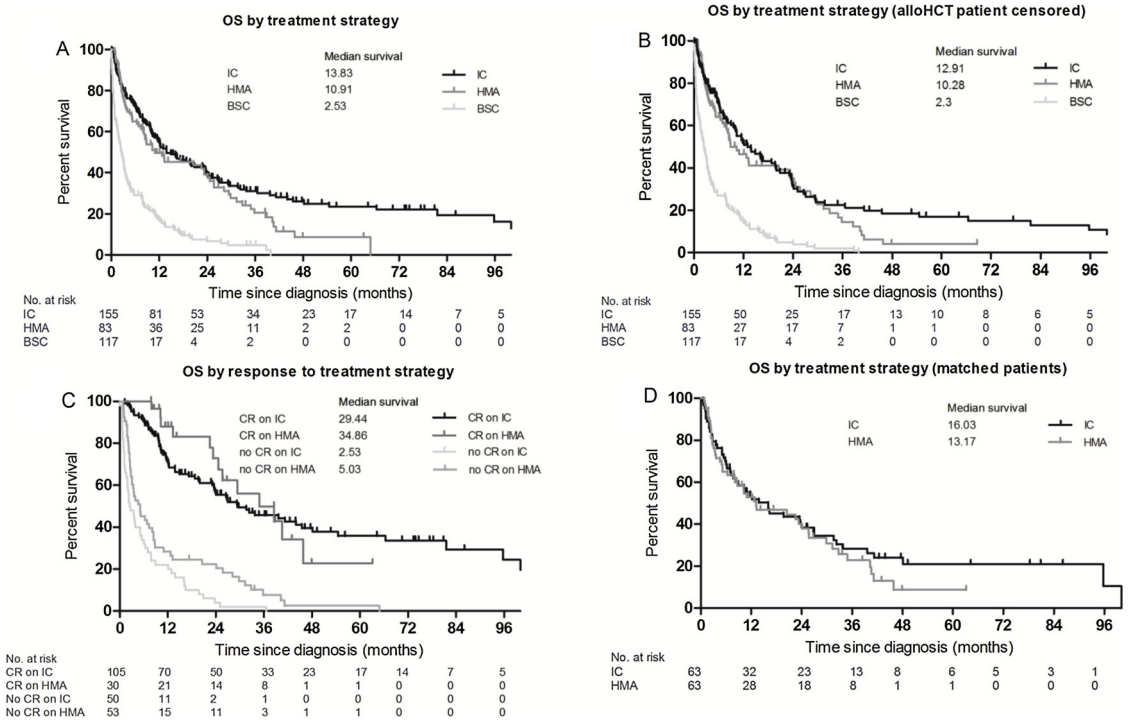

Fig. 2. OS by treatment strategy. (A) OS of all patients included in the analysis separated by treatment strategy (HMA, BSC, IC). Survival is significantly different between HMA and BSC, and IC and BSC, but not between HMA and IC ($p < 0.001$, $p < 0.001$, $p = 0.075$, respectively). (B) OS of all patients included in the analysis with patients who received an allo HCT censored on date of transplantation. Survival is significantly different between HMA and BSC, and IC and BSC, but not between HMA and IC ($p < 0.001$, $p < 0.001$, $p = 0.166$, respectively). (C) OS by response to different treatment strategies. Patients achieving CR had increased survival compared to patients not reaching CR in both groups ($p < 0.001$ and $p < 0.001$). In patients achieving CR there was no significant difference in survival between patients treated with IC or HMA ($p = 0.772$), however in patients not reaching CR there was a significant difference in survival ($p = 0.009$) between these 2 treatment groups. (D) OS in patients matched for age and cytogenetic risk and separated by treatment strategy ($p = 0.411$).

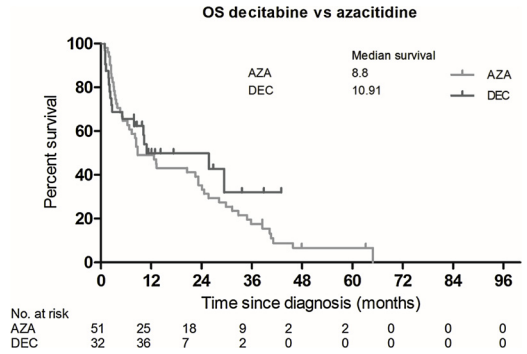

Fig. 3. OS by HMA drug: azacitidine vs decitabine (p = 0.408).

(0.95–2.02)(p = 0.086). Additionally, the 3-year survival rate was comparable with 22% and 13% for the IC group and HMA group, respectively (p = 0.103). Censoring patients who received an allo HCT at date of transplantation did not have a large effect on OS after IC or HMA treatment (Fig. 2b). A separate analysis including patients diagnosed and treated from 2010 onwards, when HMA became available, also showed no difference in OS between patients treated with IC or HMA (supplementary Fig. 1). Within the HMA treatment group the median OS was not significantly different between patients treated with azacitidine or decitabine (8.8 versus 10.9 months, p = 0.408) (Fig. 3). The multivariate model yielded a HR of 1.02 (0.52–2.00), p = 0.960) after correcting for cytogenetic risk, PS, co-morbidity score, WBC count at diagnosis, and age at diagnosis.

3.5. Relation between CR and OS

Obtaining CR had a major impact on survival in patients treated with IC or HMA compared with patients who did not obtain a CR (in the IC group; 29.4 vs 2.4 months, p < 0.001 – in the HMA group; 34.9 vs 5.0 months, p < 0.001) (Fig. 2c). OS was comparable between patients achieving CR after treatment with IC or HMA (29.4 vs 34.9 months, respectively (p = 0.772)). However patients not obtaining a CR had a superior survival when treated with HMA compared to IC (5.0 vs 2.4 months, p = 0.009).

3.6. Matched cohort

To minimize the effect of treatment selection bias based on age or cytogenetic risk we created a cohort of patients matched 1:1 on age (60–69 or ≥70 years) and cytogenetic risk (favorable, intermediate or adverse). Sixty-three matched pairs were found. Again, there was no significant difference in median OS between the treatments groups IC and HMA (16.0 vs 13.2 months, p = 0.411) (Fig. 2d). Other risk factors known to influence survival were comparable between both groups (Supplementary Table 2).

3.7. Impact of receiving an allo HCT on survival

The median OS of patients who underwent an allo HCT after treatment with IC or HMA was 65 months, whilst patients who did not proceed to allo HCT had a median OS of 8 months (p < 0.001) (Fig. 4a). Analysis of the subset of patients who obtained a CR after induction therapy with IC or HMA showed a significantly better survival for patients who proceeded to allo HCT compared to patients who were not consolidated with an allo HCT (*median not reached* vs. 25 months, respectively (p < 0.001) (Fig. 4b).

The median OS in transplanted patients who received IC as induction therapy was comparable to survival after induction therapy with HMA (48 vs 65 months, respectively (p = 0.440) (Fig. 4c). The number of patients consolidated with an allo HCT changed over time and had increased in the last few years (Fig. 5).

3.8. Predictors for OS

To assess which factors influenced survival other than upfront treatment strategy (IC or HMA), we performed a multivariate regression analysis. First, we determined which factors were associated with OS in univariate analyses. Consolidation with an allo HCT and favorable cytogenetic risk were associated with increased OS. Initial treatment strategy was not a significant predictor of OS. A higher performance score, older age, adverse cytogenetic risk, and increased WBC counts were associated with decreased OS. Predictors for OS with p < 0.10 were selected for the multivariate analysis. Multivariate analysis confirmed consolidation with allo HCT as a strong independent predictor of OS. Upfront treatment strategy (IC or HMA) was not an independent predictor of OS (Table 3).

4. Discussion

This study presents a retrospective, single-institution experience with treatment of AML in older patients (≥60 years). Data from 355 patients treated with IC, HMA or BSC were analyzed. Patients who were treated with either IC or HMA showed a significant survival advantage compared with patients treated with BSC only, with a median OS of 14.9 and 10.9, respectively, versus 2.3 months. Median survival was comparable after treatment with IC or HMA (14.9 vs. 10.9 months (p = 0.075)). Although numbers were low, the survival in the HMA treatment group was comparable between patients treated with azacitidine or decitabine (8.8 vs 10.9 months, p = 0.408). After censoring those patients who received an allo HCT, the survival of patients who received either IC or HMA was even more comparable; the HR for survival was comparable (i.e. 1.38 vs. 1.20) (though with a wide confidence interval (0.80–1.80) due to relative low numbers). Patients achieving CR after treatment with IC or HMA also had a comparable survival. In contrast, patients that did not achieve CR had a significantly better survival when treated with HMA compared to IC (5.0 vs 2.4 months, p = 0.009). Consolidation with allo HCT led to a significant survival benefit in patients who had obtained CR compared to patients who did not proceed to allo HCT after reaching CR (p < 0.001), independent of first line treatment (either IC or HMA). OS in patients treated with IC or HMA prior to allo HCT was comparable (48 vs 65 months, respectively (p = 0.440)). Multivariate analysis confirmed that, considering treatment related factors (IC or HMA; allo vs no allo), consolidation with allo HCT and not the type of induction treatment was the major independent predictor for survival.

This study confirms the very poor prognosis of elderly AML patients who do not receive anti-leukemic treatment but only BSC. Our data, obtained from consecutive patients treated in a single center, confirm that treatment (either IC or HMA) improves survival rates significantly. This is in line with published reports from prospective studies showing superior survival after treatment with either azacitidine or decitabine compared with conventional care regimens or with gemtuzumab ozogamycin and low dose cytarabine compared with BSC [7,13–17]. Both analyses of all patients who received treatment (IC: n = 155 and HMA: n = 83) and a matched pair analysis of 63 pairs confirmed the comparable survival of older patients after treatment with IC and HMA, in accordance with previous reports [19,21]. Also in line with reports, the comparable survival between IC and HMA was reached despite a lower CR rate after treatment with HMA compared with IC [14,17,19,21]. This applies in particular to azacitidine. Despite the fact that the CR rates between azacitidine and decitabine treatment differed significantly, this did not translate into a significant difference in survival. This observation underlines the observation done by others that azacitidine impacts on OS, also when no CR has been obtained [14,17]. A prospective randomized study performed by the EORTC and GIMEMA study groups, with an up-front randomization between IC and

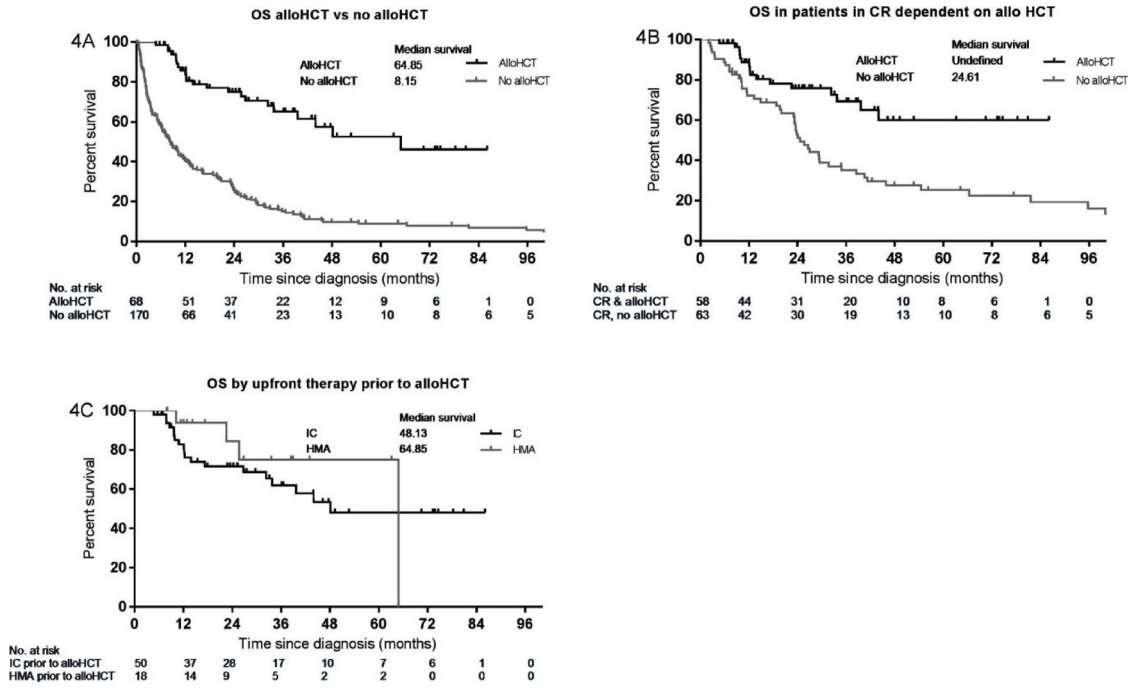

Fig. 4. OS after receiving allo HCT. (A) OS in patients who received an allo HCT and patients who didn't receive an allo HCT, independent of upfront treatment strategy ($p < 0.001$). (B) OS in patients that obtained CR, separated by consolidation with an allo HCT, independent of upfront treatment strategy ($p = 0.005$). (C) OS by upfront therapy prior to allo HCT ($p = 0.440$).

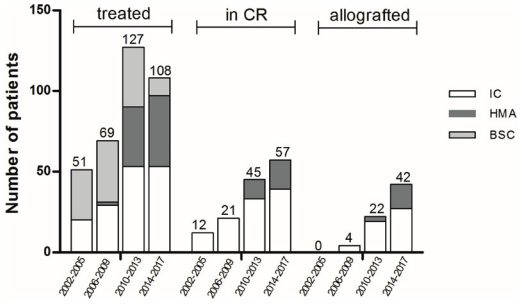

Fig. 5. Changes in treatment strategies over time in the study cohort. Of note; patients diagnosed January 2002 and July 2017 were included.

decitabine (10 day schedule) is currently in recruitment phase and should give more insight in the value of both treatment strategies in general and for molecular subgroups (AML1301; NCT 02172872).

Allogeneic HCT is the most potent curative option for AML patients [29]. Paradoxically, those patients who potentially could benefit most from an allo HCT (i.e. older patients with a dismal prognosis), are actually rarely receiving an allo HCT. For example, data from the Swedish cancer registry revealed that only about 10% of patients aged 60–65 years received an allo HCT [23]. In our cohort 18% of all patients, 27% of treated patients and 53% of patients in CR received an allogeneic graft. Indeed, in accordance with published data, those patients who received an allogeneic graft had a significantly better survival compared with those who did not receive an allograft [30,31]. Strikingly, the percentage of older patients receiving an allograft is rapidly increasing during the last years. Additionally, we show that, allo HCT, but not type of induction treatment, is an independent predictor for survival. Our data suggest that those patients who respond to treatment, either with IC or HMA, should be considered for further consolidation with allo HCT.

The retrospective character of this study is a limitation. Treatment selection is an important but difficult bias to analyze. As stated earlier treatment selection was based on physician's choice, inclusion in a clinical trial, and patient preference. We accounted for bias in patient- and disease characteristics by using multivariate analysis and matched pair analysis. Another bias includes the time factor because of the rapidly increasing number of older patients receiving an allo HCT. Moreover, patient numbers in the subgroup analyses are small and p-values should therefore be interpreted with caution. Relapse and treatment thereof were not included in the manuscript in which we

Table 3
Univariate and multivariate analyses for predictors of OS.

Univariate analysis	HR (95% CI)	*P-value*
Upfront treatment strategy		
- IC	Ref.	
- HMA	1.324 (0.971–1.805)	0.076
Consolidation with allo HCT	0.225 (0.145–0.349)	< 0.001
Age *(continuous)*	1.047 (1.016–1.079)	0.003
Performance score *(continuous)*	1.214 (1.019–1.445)	0.030
Comorbidity score *(continuous)*	1.092 (0.998–1.194)	0.055
WBC count *(continuous)*	1.003 (1.000–1.006)	0.030
Cytogenetic risk		
- Favorable	Ref.	
Intermediate	1.747 (1.094–2.790)	0.020
- Favorable	Ref.	
Adverse	2.375 (1.477–3.820)	< 0.001
- Intermediate	Ref.	
Adverse	1.360	0.072
Multivariate analysis		
Treatment strategy		
- IC	Ref.	
- HMA	1.270 (0.895–1.801)	0.181
Consolidation with allo HCT	0.198 (0.125–0.311)	< 0.001
Performance score *(continuous)*	1.289 (1.060–1.569)	0.011
WBC count *(continuous)*	1.006 (1.003–1.009)	< 0.001
Cytogenetic risk		
- Favorable	Ref.	
Intermediate	3.127 (1.851-5.282)	< 0.001
- Favorable	Ref.	
Adverse	4.777 (2.785-8.194)	< 0.001
- Intermediate	Ref.	
Adverse	1.559 (1.111-2.189)	0.010

focused on the effect of upfront treatment strategy for survival outcome. We are aware that relapse occurs up to 40% of patients and has a significant influence on survival outcome, however discussion of this issue and potential salvage therapeutic approaches in older patients fall beyond the scope of this article. The real life representation of clinical practice is a valuable strength of this analysis. Still, deciding on the optimal treatment strategy for older patients diagnosed with AML remains clinically challenging and prospective studies are warranted to provide a better insight into which patients benefit most from which therapy. In conclusion this study shows that consolidation with an allo HCT provides a large survival benefit for older AML patients, which is independent of upfront treatment strategy.

Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.03.004.

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