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ORIGINAL RESEARCH

Feasibility and Outcome of a Phase II Study of Intensive Induction Chemotherapy in 91 Elderly Patients with AML Evaluated Using a Simplified Multidimensional Geriatric Assessment

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ABSTRACT

Introduction: We prospectively tested in a phase II study high-dose aracytin and idarubicin plus amifostine as induction regimen in 149 patients with acute myeloid leukaemia (AML) aged ≥ 60 years, evaluated by a simplified multidimensional geriatric assessment (MGA).

Methods: Ninety-one fully or partially fit patients (61%) were allocated to intensive chemotherapy and 58 (39%) frail patients to best supportive care (BSC). Intensively treated patients, showing early death and complete response (CR) rate respectively of 5.5% and 73.6%, received 61 consolidations, followed by autologous transplant (ASCT), stem cell transplantation (SCT) or gemtuzumab ozogamicin, depending on mobilization outcome and donor availability.

Results: The 8-year overall survival (OS) of these patients was 20.4%, with median duration of 11.4 months significantly superior to the 1.5 months of BSC arm ($p < 0.001$). Hyperleukocytosis and cytogenetics were predictors of survival with a relative risk of 1.8 in patients with poor karyotype without hyperleukocytosis ($p = 0.02$) and 3 in those with hyperleukocytosis (≥ 50,000/μl) ($p = 0.002$).

Conclusion: MGA allowed tailored post-consolidation in 53.8% of patients after high-dose aracytin induction, with long-term survival doubling that reported in the literature after standard-dose cytarabine regimens.

Trial Registration: The study was registered with the Umin Clinical Trial Registry (www.umin.ac.jp/ctr), number R000014052.

Keywords: Acute myeloid leukaemia (AML); Autologous transplant (ASCT); Elderly; Gemtuzumab ozogamicin (GO); Multidimensional geriatric assessment (MGA); Oncology

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Key Summary Points

Why carry out this study?

This prospective phase II study evaluates the feasibility and efficacy of an intensive induction schedule, including high-dose aracytin plus idarubicin, preceded by amifostine, in a cohort of elderly patients with acute myeloid leukaemia, whose fitness was evaluated by simplified Balducci's multidimensional geriatric assessment. This subset of patients still represents an unmet medical need with 30–50% complete response rates and 5% 10-year overall survival probability.

This study aimed to demonstrate a survival advantage of 15% compared to the historical long-term data of 5%. Secondary end points were disease-free survival, event-free survival, induction treatment-related death, haematological and non-haematological toxicities.

What was learned from the study?

This approach with intensified dose aracytin plus idarubicin in elderly patients with acute myeloid leukaemia, selected using a simplified multidimensional geriatric assessment, is feasible in > 60% of patients.

The survival rate was more than double and complete response rate was 20% higher than those reported in the literature, with low induction death rate (5% vs 10–20% reported).

Multidimensional geriatric assessment identified frail patients ineligible for intensive therapy while fit and partially fit patients with acute myeloid leukaemia had similar tolerance and outcome apart from delay of polymorphonuclear neutrophil recovery > 1500/ml after induction (15 days in fit patients vs 21 days in partially fit patients, $p = 0.03$).

Multidimensional geriatric assessment represents an accurate tool to define eligibility for chemotherapy since French Decisional Index and Sorror haematopoietic cell transplantation co-morbidity index did not influence outcome and tolerance. Considering the very poor outcome of elderly patients, even in the new drugs era, this regimen represents an excellent backbone for future protocols, exploring new post-remission treatments in this unfavourable setting.

INTRODUCTION

The poor outcome of elderly patients with acute myeloid leukaemia (AML) is mainly due to the unfavourable (peculiar) biological properties of the disease and their frailty caused by comorbidities [1, 2] and the physiological process of ageing [3, 4]. Consequently, only a minority of (elderly) patients aged over 60 receive adequate intensive induction treatment and very few can be enrolled in prospective clinical trials; moreover, the adverse biological characteristics of the disease [5, 6] including the high incidence of primary multidrug resistance phenotype are responsible for the lower complete response (CR) rate observed in this subset than younger patients [7]. To improve both the efficacy and the tolerance of chemotherapy, different approaches have been tested in this setting: the benefits of anthracycline dose escalation seem restricted to patients younger than 65 years [8]; fludarabine-containing regimens demonstrated better extra-haematological tolerance and an encouraging response rate, but without long-term control of the disease in a non-transplant setting [9]. Intensification of the cytarabine dose has been tested in younger patients with encouraging results [10]. Recent guidelines from the National Comprehensive Cancer Network (NCCN) and Italian Society of Haematology (SIE) [11, 12], however, discourage this approach in an elderly population because of the high extra-haematological toxicity. Preliminary reports show the feasibility and safety of

high-dose cytarabine (HD-ARAC) and idarubicin in elderly patients with AML [13]. The clinical comparison between different kinds of anthracycline compounds yielded overlapping results [14], although a higher CR rate was recently observed with idarubicin in patients older than 50 [15]. We previously reported that a single high dose of idarubicin along with HD-ARAC and amifostine was feasible [13] in a preliminary series of 41 fit elderly patients with AML. Moreover Charlson Comorbidity Index, Autonomy Daily Life (ADL) scores and geriatric syndromes were shown to predict response, mortality and survival in elderly patients with AML [16–18]. On the basis of this background we planned to assess the real feasibility and effectiveness of a treatment tailored on a simplified Balducci's multidimensional geriatric assessment (MGA) [19], in a large cohort of 149 elderly patients with AML, evaluated according to a method previously tested in patients with diffuse large B cell lymphoma (DLBCL) [20].

METHODS

This phase II single-centre non-randomized study aimed to prospectively evaluate the feasibility and outcome of intensive induction chemotherapy in an unselected series of elderly patients, observed in real-life practice.

Between June 1999 and September 2010 we prospectively observed 149 consecutive patients with non-M3 AML over 59 years (range 60–89), who were evaluated using a simplified MGA, as reported elsewhere [17, 19] and in the supplementary material. Difficulties in performing tests, due to AML symptoms and cultural differences, might impair the results of tests for cognitive and instrumental abilities and we decided to evaluate only comorbidities, geriatric syndromes and physical functions. This allowed us to identify three groups of patients: (1) *fit* patients ($N = 70$, 47%) comprising those with ADL score = 6, no grade II comorbidities and geriatric syndromes; (2) *partially fit* patients ($N = 21$, 14%) with ADL = 6, < 3 grade II comorbidities, no geriatric syndromes who fulfilled all the other inclusion criteria (Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status ≤ 2, serum bilirubin < 1.5 ULN and creatinine below normal; ejection fraction $\geq 45\%$, absence of other malignancies) and received intensive chemotherapy; (3) *frail* patients ($N = 58$, 39%), with ADL < 6 or 1 grade III or > 2 grade II comorbidities or a geriatric syndrome not related to AML or aged > 85 years, were considered "a priori" eligible only for best supportive care (hydroxyurea or vinblastine and transfusion support). MGA was part of eligibility criteria: 42/58 frail patients met the inclusion criteria but were considered frail and so not enrolled. The main causes of frailty are reported in the supplementary material.

Secondary patients with AML and history of environmental, occupational or therapeutic exposure to haematotoxins or radiation or evolving from at least 6 months antecedent myelodysplasia or other myeloid stem cell disorders were also enrolled.

Cytogenetic risk was available in 81 patients, determined by applying the Southwest Oncology Group (SWOG)/ECOG classification [21].

Compliance with Ethics Guidelines

This research involved human participants. All patients gave written informed consent, according to the Declaration of Helsinki. Additionally, the Ethics Committee of Ospedali Riuniti di Ancona approved the protocol. The study was registered with the Umin Clinical Trial Registry (www.umin.ac.jp/ctr), number R000014052.

Induction Chemotherapy

Ninety-one eligible patients (61%), of the 149 screened by MGA, received intensive induction chemotherapy, the so-called Memorial, consisting of 3000 mg/m^2 per day of cytarabine by 3-h infusion for 5 days and 40 mg/m^2 of idarubicin given intravenously on day 3 for 20 min, preceded by 1000 mg of intravenously administered amifostine as described elsewhere [13].

In patients older than 70 years the idarubicin and cytarabine doses were reduced by 25%. Supportive care, timing of bone marrow

biopsies and response criteria were the same as previously reported [13].

Consolidation Chemotherapy and Post-Consolidation Strategy

Sixty-one patients received an HD-ARAC consolidation scheme reduced to 4 days with a further 25% reduction of the dose in patients older than 70 years ($N = 15$). PBSC (peripheral blood stem cell) collections were planned after consolidation therapy and filgrastim at 5 μg/kg per day was administered subcutaneously from day + 4 after the end of chemotherapy until the last leukapheresis. A minimum dose of $CD34^+$ cells collected ($> 3 \times 10^6$/kg) was required for a post-consolidation autologous transplant (ASCT); where the PBSC harvested was insufficient a second mobilization attempt was allowed, after a second course of chemotherapy, including a VP-16 plus cytosine–arabinoside (ARA-C) intermediate dose for 3 days, followed by granulocyte colony-stimulating factor (G-CSF). Poor mobilizers and patients ineligible for ASCT for other reasons received gemtuzumab ozogamicin (GO) consolidation of 3 monthly 3 mg/m^2 i.v. infusions followed by three further courses every 3 months as previously described [22]. Relapsed patients received a second-line chemotherapy at the clinician's discretion.

Response and Outcome Definitions

Response criteria and treatment outcomes were defined according to the recommendations of Cheson et al. [23]. Also see the supplementary material.

Statistical Methods

The primary end point was initially the improvement of the CR rate; the study was then amended including overall survival (OS) as primary end point, disease-free survival (DFS), event-free survival (EFS), induction treatment-related death (TRD), haematological and non-haematological toxicities as secondary end points. The initial sample size was 42 patients, calculated according to the Simon minimax design [24], predicting a 20% increase in the CR rate, in comparison with the current gold standard of 50% reported in the literature (beta and alpha errors of 0.20 and 0.05, respectively) [8, 25]. We then extended the sample size to 91 patients, in order to demonstrate a survival advantage of 15% compared to the historical long-term data of 5% [8, 18, 26, 27], with the same alpha and beta errors. The planned time of accrual was 11 years with 5 years follow-up.

In addition to the main prognostic factors, we evaluated the French Decisional Index (FDI) [28] and the haematopoietic cell transplantation co-morbidity index (HCT-CI) [29] as variables potentially influencing outcome (Table 1s in the supplementary material).

The two-sided Fisher's exact test was performed to analyse the influence of patient and disease characteristics (age > 70 years, cytogenetic risk, WBC count > 50,000/μl, ECOG/WHO performance status (PS), secondary AML, FDI and HCT-CI) on the response rate. The distribution of OS, DFS and EFS was estimated by the Kaplan–Meier method [30]. Log rank test was performed to compare survival probabilities by age group and disease characteristics. All factors identified at univariate analysis with a p value less than 0.1 were further analysed by Cox regression multivariate analysis. All test results are reported using two-sided p values for which 95% confidence interval (CI) hazard ratios were calculated.

SPSS 18.0 software was used to analyse the data.

RESULTS

Baseline Characteristics

The baseline characteristics of the three groups of patients are listed in Table 1. Frail patients were older, had a poorer PS score and significantly more secondary and poor prognostic karyotype AML than the fit and partially fit subgroup of patients. Partially fit patients had worse HCT-CI score (47.6% with score > 2) compared to fit patients (12.8% with score > 2) ($p = 0.0001$). All the other baseline

Table 1 Patients characteristics of the 91 intensively treated (70 fit and 21 partially fit) and 58 BSC (best supportive care) patients

	Intensive induction Fit/partially fit, *N* (%)	BSC *N* (%)	*p*		Intensive induction Fit/partially fit, *N* (%)	BSC *N* (%)	*p*
Gender			0.87	Performance status			0.003
Male	39/11 (55.7/55)	31 (53.4)		0–1	64/16 (91.4/76.2)	32 (55.6)	
Female	31/10 (44.3/47.6)	27 (46.6)		2	4/3 (5.7/14.3)	26 (44.4)	
Karyotype			0.05	3	2/2 (2.8/9.5)	0	
Favourable	5/0 (7.1/–)	0		FDI			0.49
Intermediate	31/12 (44.3/57.1)	11 (35.5)		0	40/12 (57.1/57.1)	4 (66.7)	
Unfavourable	25/8 (35.7/38.1)	20 (64.5)		> 0	30/9 (42.9/42.9)	2 (33.3)	
AML type			0.005	HCT-CI			
De novo AML	42/13 (60/62)	27 (46.5)		0–2	48/11 (68.6/55)	5 (55.6)	0.23
Secondary AML	28/8 (40/38)	31 (53.4)		> 2	9/10 (12.8/47.6)*	2 (44.4)	
Age			< 0.001	WBC count			0.45
< 70 years	41/11 (58.6–52.4)	10 (17.2)		< 50,000/μl	61/19 (87.2/90.5)	48 (82.4)	
> 69 years	29/10 (41.4/47.6)	48 (82.8)		≥ 50,000/μl	9/2 (12.8/9.5)	10 (17.6)	
Median (range)	68 (60–77)	78 (60–89)					

FDI French Decisional Index, *HCT-CI* haematopoietic cell transplant-comorbidity index
*$p < 0.0001$

characteristics were equally distributed between fit and partially fit patients.

Toxicity

Haematological and extra-haematological toxicities were assessed in 91 and 61 patients after induction and consolidation respectively and are reported in Table 2 separately in fit and partially fit patients. After induction we observed five (5.5%) TRDs: one patient died of pneumonitis, two of febrile neutropenia and two of microbiologically documented infections; we observed six TRDs during consolidation therapy (9.2%): five from infectious episodes and one death while in aplasia.

We did not observe excess toxicity in partially fit patients apart from longer polymorphonuclear neutrophil (PMN) recovery > 1500/μl after induction (15 days in fit patients vs 21 days in partially fit patients, $p = 0.03$) which did not translate into longer duration of hospitalization or higher incidence of grade III–IV infection or neutropenic fever.

The median time required to achieve a neutrophil count > 1500/μl was similar after consolidation: 14 days in fit vs 17.5 days respectively in the two groups.

Platelet recovery, transfusional need, extra-haematological toxicity, median duration of fever > 38 °C, i.v. antibiotic therapy,

Table 2 Haematological, extra-haematological toxicity and transfusional need after 91 induction and 61 consolidation courses in fit and partially fit patients

	Induction		Consolidation	
	Fit (n = 70)	**Partially fit (n = 21)**	**Fit (n = 47)**	**Partially fit (n = 14)**
Toxicity-related death, *N* (%)	4 (5.7)	1 (4.7)	6 (12.7)	0
Neutrophil > 1500/μl, median day of recovery (range)	15 (9–33)	21 (12–72)*	14 (9–53)	17.5 (13–23)
Platelet > 20,000/μl, median day of recovery (range)	16.5 (12–26)	19 (12–36)	15 (8–49)	16.5 (12–32)
Platelet > 100,000/μl, median day of recovery (range)	17 (11–52)	21.5 (13–43)	29 (12–68)	25.5 (15–50)
Red blood cell transfusions, median (range)	11 (3–32)	10 (4–47)	6 (0–24)	4 (2–10)
Platelet transfusions, median (range)	6 (0–22)	6 (2–19)	5 (0–24)	3 (1–12)
Grade III–IV mucositis incidence, *N* (%)	2 (2.9)	2 (9.5)	7 (15)	1 (4.7)
Grade III–IV hepatic toxicity incidence, *N* (%)	7 (10)	1 (4.7)	8 (17)	2 (14.3)
Grade III–IV cardiac toxicity incidence, *N* (%)	1 (1.4)	–	2 (4.2)	1 (7)
Grade III–IV neurologic toxicity incidence, *N* (%)	1 (1.4)	–	3 (6.4)	–
Grade III–V infections/febrile neutropenia, *N* (%)	33 (47)/ 14(20)	10 (47)/9 (42)	30 (63.8)/ 4(8.5)	6 (28.6)/1 (7)
Duration of fever, median (range)	5.5 (0–27)	4 (0–11)	2 (0–15)	2.5 (0–11)
Duration of antibiotic, median (range)	16 (0–66)	18 (0–34)	10 (0–32)	9 (0–21)
Duration of hospitalization, median (range)	30 (15–56)	32 (24–61)	24 (14–61)	24 (16–40)

*p = 0.03

hospitalization after induction and consolidation therapy were similar between the two groups.

Details of febrile episodes are reported in the supplementary material.

Response

We observed 67 CRs (76.1%) in the 88 patients whose response was assessable (3 patients who died during aplasia were too early for evaluation); 21 had a resistant disease. Consistent with the intention to treat (ITT) criterion, the CR rate was 73.6%.

Fit patients along MGA criteria had 71.4% CR rate similar to that of partially fit patients (81%) (Table 2s in the supplementary material).

Patients with unfavourable cytogenetics achieved a 63.6% CR rate, significantly lower than the 85.1% observed in patients with favourable- and intermediate-risk cytogenetic AML (p = 0.03); in the 35 patients with antecedent secondary AML, the CR rate was 65.7%. The CR rate in the 39 patients with FDI > 0 was 66.7%. Cytogenetic risk, gender, secondary disease diagnosis and FDI entered the multivariate analysis: poor-risk cytogenetics was the only factor able to significantly predict a lower CR rate (RR of 3.26; 95% CI 1.18–9.53).

Among the 67 patients in CR, 61 (91%) received at least one consolidation course.

Early relapse ($n = 3$), death in CR ($n = 1$) or ineligibility due to poor PS ($n = 2$) ruled out the possibility of first consolidation therapy. After consolidation we observed six toxicity-related deaths and two early relapses, while there was a severe deterioration in the PS of four patients who were consequently forced to drop out of the protocol. Forty-nine patients, therefore, underwent PBSC mobilization; 24 of them (49%) achieved successful mobilization. Lastly, 22 patients received ASCT; among the 24 patients failing PBSC mobilization, 23 received post-consolidation therapy based on GO and 4 underwent allogeneic transplant because of high risk of the disease.

OS, DFS and EFS

With a median follow-up of 70 months (range 24–124) 20 patients are still alive; 17 are still in conventional care regimens (CCR) while 3 relapsed, but achieved a second CR after salvage treatment. One is still in second CR, and the other two eventually relapsed after retreatment with GO. The 8-year OS, DFS and EFS were respectively 20.4% (11.1–34.8%), 22.9% (14.5–34.2%) and 17.9% (11.3–27.2) (Fig. 1a). Median OS, DFS, EFS were 11.4 and 7.8 and 7 months respectively. The OS of patients identified as frail was significantly lower since all died within 18 months with a median OS of 1.5 months ($p < 0.001$, Fig. 1b), while similar survival was observed in fit and partially fit patients (Table 3s in the supplementary material).

The 8-year OS was significantly reduced in patients with a secondary disease vs those with de novo AML (10.4% vs 27.1%; $p = 0.04$), reduced in those with unfavourable-risk cytogenetics vs other risk groups (11.4% vs 30.3% $p = 0.01$) and reduced in patients with a WBC count > 50,000/µl vs < 50,000/µl (0% at 33 months vs 23.4%, $p = 0.009$). Similar results were observed for DFS and EFS. Furthermore, patients older than 69 years showed both a lower DFS (10% vs 33.3%, $p = 0.04$) and EFS (7.7% vs 26.2%, $p = 0.05$) than younger patients.

Multivariate analysis confirmed the prognostic value of cytogenetic risk and hyperleukocytosis (Table 3). Patients with poor karyotype had a 2.1 relative risk of dying or a 1.89 relative risk of dying or relapse when compared with patients with intermediate- and

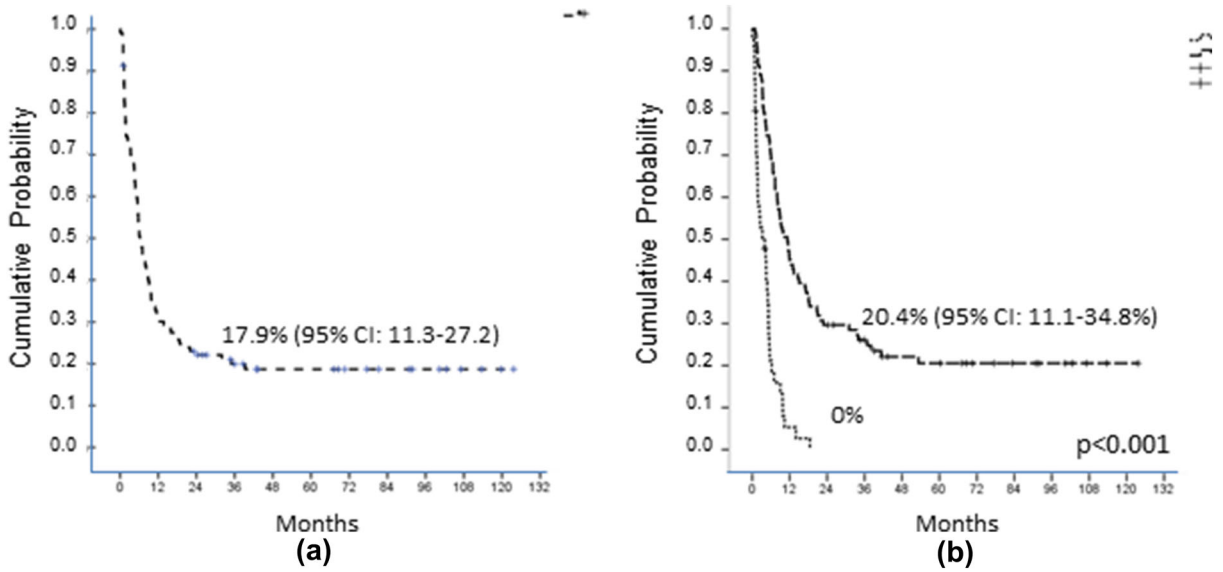

Fig. 1 **a** EFS in 91 fit and partially fit patients with AML receiving intensive treatment (Memorial induction). **b** OS in 149 patients with AML, 91 fit and partially fit receiving Memorial induction and 58 frail receiving best supportive care (BSC)

Table 3 Multivariate analysis of factors influencing CR and OS

	CR		OS		DFS		EFS	
	RR	***p***	**RR**	***p***	**RR**	***p***	**RR**	***p***
Cytogenetic risk		0.03		0.005		0.012		
Favourable/intermediate	1		1		1			
Unfavourable	3.26 (1.18–9.53)		2.1 (1.25–3.5)		1.89 (1.15–3.1)			
Hyperleukocytosis	–	–		0.001		0.0001		< 0.0001
< 50,000/μl			1		1		1	
> 50,000/μl			3.5 (1.7–7.26)		3.45 (1.68–7.1)		5.1 (2.2–11.79)	
Prognostic score	–	–		0.005		< 0.0001		
0 (no risk factor)			1		1			
1 (unfavourable cytogenetics without hyperleukocytosis)			1.8 (1.1–3)	0.02	1.91 (1.5–3.17)	0.012		
> 1 (hyperleukocytosis ± unfavourable cytogenetics)			3 (1.5–5.9)	0.002	4.45 (2.16–9.2)	<0.0001		
Age								0.048
< 70 years							1	
> 69 years							1.72 (1–2.94)	

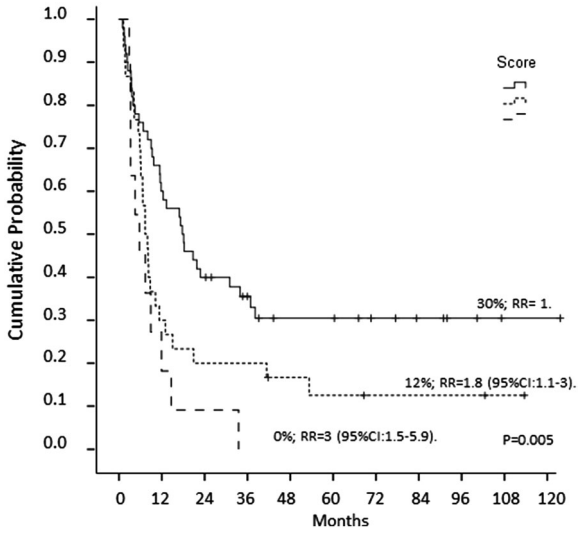

Fig. 2 OS in 91 elderly patients with AML by prognostic score. Score = 0: WBC < 50,000/ml, favourable/intermediate cytogenetics. Score = 1: WBC < 50,000/ml, unfavourable cytogenetics. Score > 1: WBC > 50,000/ml ± unfavourable cytogenetics

low-risk cytogenetics. Hyperleukocytosis (≥ 50,000/μl) at the time of diagnosis significantly lowered OS and EFS, with relative risks respectively of 3.53 and 3.45. We tested a prognostic score assuming that the presence of unfavourable karyotype and hyperleukocytosis accounts for a score of 1 and 2, respectively. We therefore identified three groups of patients: one with no risk factor (score = 0) and 30% 8-year OS, RR of dying of 1; one with unfavourable karyotype alone (score = 1) 1.8 RR of dying (95% CI 1.1–3, $p = 0.02$) and 12% 8-year OS; one with hyperleukcytosis alone or with unfavourable karyotype (score > 1) with 3 RR of dying (95% CI 1.5–5.9, $p = 0.002$) and 0% 3-year OS (Table 3, Fig. 2).

DISCUSSION

The cure rate for AML in the elderly is very low and the outcome for these patients is generally poor. Unfortunately, very few prospective trials in this setting address the outcome of an unselected population of elderly patients with AML, as only a minority of them are enrolled in clinical trials [3, 31].

On the basis of our previous encouraging experience in the setting of aggressive lymphoma [16], we describe a simplified MGA as a tool for selection of elderly patients with AML eligible for intensive treatment, which identified 39% of the patients with AML referred to our centre as frail and suitable only for BSC while 61% satisfied the inclusion criteria for receiving intensive treatment.

As induction therapy we adopted the same schedule previously used, with encouraging results in the setting of relapsed/refractory acute lymphoblastic leukaemia, including HD-ARA-C plus single high-dose idarubicin [32], modified by incorporating amifostine, in order to reduce both haematological and extra-haematological toxicity [33–35]. Even though HD-ARA-C is not generally recommended as induction treatment, in the young and elderly alike [36], some studies [37] suggest that escalation of HD-ARA-C in combination with idarubicin could be effective both in induction and in consolidation treatment [10, 37, 38].

As suggested by our previous pilot experience [13], our schedule was feasible in this large series of patients with AML (both fit and partially fit, selected by the MGA) and was characterized by an excellent tolerability profile, with a 5% induction death achieving an outstanding 73.6% CR rate, according to the ITT criterion. Conversely, in the same subset of patients recent prospective studies also show an average CR rate of 50% with a 15% TRD and a long-term survival of 10% which is the half of that reported in our study [39]. Patients with poor cytogenetic AML have the worst prognosis in the over 60s with a 26% CR rate in Grimwade et al.'s MRC analysis of 1065 elderly patients, and even if a direct comparison is not possible our CR rate doubled this result with 63.6% CR rate [6].

Induction schedules including updosing daunorubicin [8] or administering a low or fractionated dose of GO [40] failed to give similar results. The HOVON/SAKK/AMLSG randomized trial exploring the updosing of daunorubicin to 90 mg/m^2 in combination with standard-dose ARA-C produced a 64% double induction CR rate with an 11% 30-day mortality and a survival and response benefit only in the

elderly up to 65 years. Furthermore, updosing daunorubicin failed to produce any survival benefit in patients with poor-risk cytogenetic AML.

To the best of our knowledge the best experience with high dose aracytin (2 g/m^2 per day for 6 days) combined with standard-dose daunorubicin produced a 69% CR rate and 10% toxicity-related deaths [41] in the elderly setting with a median OS of 15.3 months, higher than that reported in our study (11.4 months). However our patients had higher transplant rate than that of Arellano et al.'s (28.9% vs 10%), and consequently transplant mortality might have reduced first-year survival. Comparison between the long-term outcomes is unfortunately impossible because of the lack of long-term survival probability in Arellano et al.'s study.

Other studies exploring HD-ARAC feasibility and efficacy in similar settings included fludarabine ± gemtuzumab and idarubicin with a similar toxicity profile but lower CR rate than our and Arellano et al.'s studies, probably because of a 33% higher dose of cytarabine used in the latter compared to FLAG-like schemes [42–44] (Clavio, Candoni, Ferrara).

A retrospective analysis of experiences at M. D. Anderson Cancer Center (MDACC) described outcomes of 446 patients with AML aged ≥ 70 years receiving various intensive cytarabine-based regimens (up to 2 g/m^2 daily) including fludarabine, idarubicin or other drugs. They reported a CR of 45% with a median OS of 4.6 months and early 8-week mortality rates of 36% [45]. The presence of at least one of the factors age > 80 years, PS ≥ 2 (ECOG/WHO), complex karyotype (≥ 3 abnormalities) and creatinine level > 1.3 mg/dl predicted high 8-week mortality rate, which was reduced when low air flow room facilities were available with a hazard ratio of 0.35.

In our population the presence of a previous haematological disease and an FDI score > 1 negatively affected the response, but the unfavourable-risk cytogenetics was the only negative predicting response factor. However, it should be underlined that in those patients with unfavourable karyotype, secondary AML or FDI > 1 the CR rate was equally good: 63.6%, 65.7% and 66.7%, respectively. In a similar setting, clofarabine achieved a lower CR rate, ranging from 40% to 30% in fit and partially fit elderly patients, respectively [46, 47].

Hypomethylating agents might represent an interesting and attractive alternative option, with better quality of life, in comparison to conventional chemotherapy. A multicentre randomized study evaluated azacitidine (AZA) efficacy and safety vs CCR in 488 patients with AML, aged ≥ 65 years, with > 30% bone marrow blasts [48]. The study demonstrated a 1-year survival superiority of AZA over CCR with median OS of 12.1 months, comparable to ours, but a shorter median follow-up of 24 months. Similar efficacy was also observed in the extremely poor prognosis setting of unfavourable cytogenetic AML with median OS of 6.4 months in the AZA arm, compared to 7.3 months observed in our study. Unfortunately, the difference between the median RFS and OS (9.3 vs 10.6 months) was 1 month in the azacitidine arm and we did not find studies demonstrating clinical efficacy of new drugs in patients failing to respond to hypomethylating agents, who still represent an unmet medical need. A recent phase III study showed similar but inferior results after decitabine, another hypomethylating agent, with median OS of 7.7 months (3.1 months in poor cytogenetic risk setting) [49].

We also prospectively tested the feasibility in the real-life setting of an intensive program in a population of elderly patients with AML selected by MGA: overall 54% of patients (49/91) completed the program: according to the ITT criteria the 8-year overall survival was 20.4%, with a median OS of 11.4 months These data compare well to the results reported by the EORTC and CETLAM groups where the post-consolidation strategy was represented by ASCT [50, 51]. In less than half of the patients receiving consolidation chemotherapy who failed PBSC mobilization, not eligible for ASCT, we offered an alternative post-consolidation in the form of GO therapy with a very encouraging outcome [20]. One shortcoming of the study is its lack of molecular data on NPM and FLT3 status, even though their prognostic role in

elderly patients setting is still controversial [52, 53].

Poor-risk cytogenetics and hyperleukocytosis were the only factors predicting OS. All patients with a WBC count > 50,000/μl died within 3 years and only 11.4% of patients with AML with poor cytogenetics were still alive at 8 years. FDI did not have any prognostic influence on survival and 15% (6/39) of patients with a score > 0, defined by Malfuson as not eligible for intensive treatment with intention to cure [28], were actually cured by this HD-ARA-C-based protocol. The presence of previous haematological malignancies was not a prognostic factor for poor OS in multivariate analysis, even though only 10.4% of patients were alive at 8 years.

The majority of scores predicting response and survival in elderly patients with AML include cytogenetics and leukocytosis, but the assessment of an accurate comorbidity score might help the evaluation of the risk–benefit balance of intensive treatment. CCI [14] and HCT-CI [54] are respectively associated with remission rate and survival in two recent retrospective studies, the latter performed in a younger population of median age 40 years. We prospectively selected elderly patients with AML by simplified MGA with comprehensive evaluation of physical functions and comorbidities.

HCT-CI was > 2 in 47.6% of partially fit vs 12.8% of fit patients. These patients showed 65% CR rate and 21.1% 8-year OS, statistically similar to the 82.2% CR rate and the 22% 8-year OS observed in patients with HCT-CI < 3. These results could be explained by the fact that the diagnosis of previous cancer accounts for 3 in HCT-CI, overestimating the score in some of the patients with previous history of cured neoplasia. Furthermore spirometry and DLCO (carbon monoxide diffusing capacity of the lung) normal values reported by Sorror et al. are rarely found in the elderly population, also producing an increasing of HCT-CI in this setting. The Sorror score might therefore underestimate eligibility for intensive treatment of elderly patients with AML. Balducci MGA instead computes active comorbidities, ADL and geriatric syndromes, thereby producing a reliable measure of patient fitness. We previously published data on MGA tailored treatment in elderly patients with non-Hodgkin lymphoma, who received reduced dosages if partially fit. The initial AML study, performed in 42 patients, showed feasibility of intensive treatment even in partially fit elderly patients, probably owing to the use of the cytoprotector agent amifostine. We have therefore reduced the dosages only in patients over 70 as previously described. Partially fit patients showed 81% CR rate and 28.6% 8-year OS similar to 71.4% CR rate and 18.2% 8-year OS observed in fit patients. These results confirm treatment feasibility in partially fit patients. As expected, the 58 patients with AML identified as frail by the MGA, receiving BSC, achieved a median OS of 1.5 months.

Study Limitations

This is not a retrospective case–control study and we can only compare our results to those reported in the literature in similar settings with standard-dose ARA-C, GO, fludarabine, intensified daunorubicine-containing regimens. We reduced dosages of chemotherapy drugs only in patients over 70 and not in younger partially fit patients.

CONCLUSION

This approach with aggressive induction in elderly patients with AML selected using the simplified MGA is feasible in > 60% of elderly patients with AML and was highly effective in terms of the CR rate, without relevant treatment-related mortality. Despite the delay of PMN recovery > 1500/μl after induction in the partially fit patients with AML (15 days in fit patients vs 21 days in partially fit patients, $p = 0.03$) we did not observe longer duration of hospitalization, higher incidence of grade III–IV infection, neutropenic fever and induction death rate, suggesting the optimal tolerance of this schedule in comparison to fit patients. Moreover, > 50% of the patients in CR were able to receive an effective consolidation regimen, with an encouraging outcome: indeed, the survival rate was more than double that

reported in the literature in a similar setting [17, 38, 55, 56]. This regimen might therefore provide an excellent backbone for future protocols, exploring new post-remission treatments in this unfavourable setting.

MGA assessment might guide the enrollment in intensive treatment protocols, reducing the bias of patients selection in and between clinical trials. Simplified Balducci MGA was shown to be a reliable measure of functional status and comorbidities when compared to HCT-CI score in this monocentric study. Its reliability and reproducibility should be validated in larger multicentre studies.

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Compliance with Ethics Guidelines. This research involved human participants. All patients gave written informed consent, according to the Declaration of Helsinki. Additionally, the Ethics Committee of Ospedali Riuniti di Ancona approved the protocol. The study was registered with the Umin Clinical Trial Registry (www.umin.ac.jp/ctr), number R000014052.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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