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Survival of elderly patients with acute myeloid leukemia

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A B S T R A C T

Background and Objectives. The prognosis of elderly patients with acute myelogenous leukemia (AML) is usually dismal, while the true survival of older patients not included in clinical trials is not known. We retrospectively evaluated the impact on survival of an aggressive versus a non-aggressive approach in 1005 patients aged >60 years registered in the database of the GIMEMA cooperative group.

Design and Methods. Group A patients (n=621) received aggressive treatment, while group B patients (n=384) underwent non-aggressive therapy. The groups were different for risk factor distribution: the patients in group B had a higher median age, worse performance status (PS) and a higher proportion of previous myelodysplastic disease.

Results. The overall median survival was 7 and 5 months in groups A and B, respectively (p <0.0001). At multivariate analysis the following factors were associated with a significantly shorter survival: age >71 years (RR=1.27; 95% CI=1.07-1.50), PS=2-4 (RR=1.44; 95% CI=1.24-1.68), white cell count >10,000 μL (RR=1.37; 95% CI=1.06-1.75), and heart dysfunction requiring treatment (RR=1.26; 95% CI=1.05-1.50). No difference in survival was associated with aggressive or non-aggressive treatment (RR=1.1; 95% CI=0.94-1.32). Patients aged <70 years, with no heart disease, but a white cell count >10,000/μL showed a significantly better survival when treated aggressively (median survival 7 vs 3 months, p = 0.011).

Interpretation and Conclusions. Despite an obvious selection of patients with a worse prognosis in group B, the difference in survival between the two groups was marginal. Multivariate analysis failed to demonstrate a significant survival benefit in aggressively treated patients. All these considerations indicate that elderly patients with AML are overall unlikely to benefit from aggressive treatment, so that this should be offered only to selected patients.

Key words: acute myeloid leukemia treatment, elderly, survival.

Acute myeloid leukemia (AML) is a relatively common disease in elderly people.[1-2] The outcome of AML has improved in younger patients, but remains highly unsatisfactory in the elderly.[3] This is due to both biological disease-related[4,5] and patient-related[6,7] differences between younger and older patients. To date, complete remission (CR) is achieved in less than 60% of elderly AML patients with standard chemotherapy; but fewer than 15% of elderly patients who achieve CR survive free of leukemia after 3 years.[8-10]

Several approaches have been attempted to improve these results (3-drug induction, new anthracyclines, high-dose Ara-C, use of growth factors, different post-remission strategies),[11-17] but none of them has led to a significant improvement over standard chemotherapy. Even recent trials, in which patients could have received more advanced and effective supportive care, did not achieve better results.[18-20]

With the current selection criteria, intensive standard chemotherapy can be offered only 40-50% of patients aged > 60 years: elderly patients not eligible for intensive chemotherapy are managed by conservative treatment, out of clinically controlled trials.[21-23] It is also conceivable that some elderly AML patients are never referred to hematology centers, being considered ineligible for aggressive treatment strategies. The true proportion and survival of elderly AML patients not eligible for clinical trials is not known. Cancer registry data are usually incomplete because of the limited geographic area coverage and lack of specificity in the diagnosis and follow-up.

The prognosis of elderly patients treated with conservative treatment is generally regarded as very poor compared to that of

patients receiving intensive therapy;[24] however, a comparison between the results of intensive standard chemotherapy and conservative management should be carefully evaluated, as these different approaches are obviously used in patients with very different prognostic factors at onset and even a truly randomized study between these 2 approaches could, of course, enroll only patients potentially eligible for aggressive treatment. The decision whether to consider an elderly AML patient eligible or not for an aggressive approach should also take into account factors other than age, such as performance status, co-morbidity, multidrug resistance (MDR) gene expression[3] and karyotype,[25-27] but in many instances this is still an open question.

In this study, we analyzed the overall survival of a large cohort of unselected elderly AML patients in order to elucidate the role of intensive versus conservative approaches and to identify a subgroup of patients in whom an aggressive approach could truly prove beneficial.

Design and Methods

The Italian hospital-based registry of adult cases of acute leukemia has, since July 1992, been collecting simple epidemiological data on all patients with newly diagnosed acute leukemia observed within the GIMEMA cooperative group. The registration form is filled in at diagnosis, which is made according to FAB criteria, regardless of eligibility for treatment programs. The database is located at the Italian National Health Institute. Additional clinical and biological data on AML, type of treatment and results as well as hospital stay duration from diagnosis to death or last follow-up were subsequently requested from the centers for all the AML patients aged >60 years registered in the database: patients with acute promyelocytic leukemia were excluded from this study. The treatment programs adopted in the different centers are varied but have been grouped together into *aggressive* or *non-aggressive* type, as specified below.

Statistical methods

The differences between aggressive and non-aggressive treatment, with regard to patients' characteristics, were analyzed by χ^2 test for categorical variables and by Student's t test for continuous variables. The Kaplan - Meier method was used to estimate survival curves;[28] differences between survival were tested by the log-rank test. The Cox proportional hazard model was used for multivariate analysis of factors prognostic for mortality.[29]

Results

Between July 1992 to December 1998, 1005 eligible patients older than 60 years with a diagnosis of AML were enrolled in the GIMEMA registry by 43 Italian Hematology Centers. The GIMEMA centers and their representatives involved in the study are listed in the appendix. The median age of the whole population was 69 years. According to medical decision, based on clinical and biological parameters, 621 patients (61.8%) (group A) received intensive treatment based on anthracycline + Ara-C (370 patients), anthracycline + Ara-C + etoposide (199 patients), fludarabine-containing regimens (27 patients) or other different associations (25 patients). The remaining 384 patients (38.2%) (group B) were considered not eligible for intensive treatment and have been managed with conservative approaches (supportive care only in 104 patients, low-dose Ara-C ± other drugs in 125 patients, hydroxyurea ± other drugs in 110 patients, 5-azacytidine in 17 patients and other associations in 28 patients).

As expected, the median age was significantly lower in group A than in group B (67.7 versus 73.7 years, $p<0.0001$). Clinical and hematologic parameters at onset were compared between the two groups stratified according to age < 70 or >70 years, as shown in Table 1. The two groups were unbalanced for many relevant prognostic factors, such as a higher rate of poor performance status (PS), a greater cardiac co-morbidity (defined as heart disease other than hypertension, requiring a specific chronic therapy) and a higher proportion of patients with a previous myelodysplastic (MDS) phase among group B patients. No difference was found with regard to the other parameters shown in Table 1. The FAB subgroup distribution was also homogeneous among the two groups. Median WBC count at diagnosis was 18.0 and 13.3×10^9/L in groups A and B, respectively ($p = 0.04$).

The crude overall survival results of group A and group B patients are shown in Figure 1. The median survival was 7 (0-85) and 5 (0-253) months, respectively ($p < 0.001$). The survival rate at 12 months was 31.6% and 21.3%, respectively. The mean follow-up duration was 8.6 months (range 0-125). Eighty-six patients were lost to follow-up at the time of analysis.

Analyzing the impact of the type of treatment on the crude survival of patients divided into two age groups, 60-70 years and >70 years (Figure 2), revealed a significant difference only among the younger population of patients. In patients >70 years, despite the unbalanced distribution of risk factors, no significant differences in survival were observed between those treated aggressively or non-aggressively: the median

Table 1. Distribution of risk factors among the 2 groups, stratified according to age.

Risk factor	*Aggressive*	*Age ≤ 70 years Non-aggressive*	*p*
PS 2-4	46.3%	60.4%	0.003
Heart disease	13.5%	36.6%	<0.001
Previous MDS	3.0%	13.2%	<0.001
Liver disease	6.4%	16.9%	<0.001
Renal disease	4.4%	10.5%	0.014
Fever	33.3%	33.6%	0.958
Infection	15.3%	18.8%	0.322
Hemorrhage	15.8%	22.5%	0.080

Risk factor	*Aggressive*	*Age ≥ 71 years Non-aggressive*	*p*
PS 2-4	54.7%	65.0%	0.039
Heart disease	25.0%	44.0%	<0.001
Previous MDS	5.0%	8.7%	0.161
Liver disease	10.7%	9.5%	0.725
Renal disease	12.5%	6.9%	0.079
Fever	37.3%	29.9%	0.123
Infection	20.3%	16.7%	0.383
Hemorrhage	25.0%	21.2%	0.412

PS: performance status (WHO); MDS: myelodysplasia;
AML in patients > 60 years: aggressive versus non-aggressive treatment.

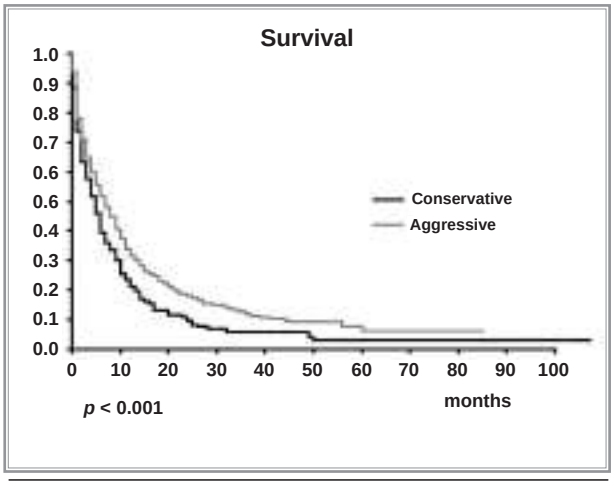

Figure 1. Crude overall survival estimate (Kaplan - Meier) on the whole population of patients treated *aggressively* or *conservatively*.

survivals were 4 (0-67) and 4 (0-53) months, respectively ($p = 0.398$). Another subgroup analysis was done, comparing differently treated subgroups survival within the aggressive and non-aggressive treatments: no statistical differences in survival were found in group A among patients who received anthracycline + Ara-C vs anthracycline + Ara-C + etoposide vs fludarabine-containing regimens, nor were any differences found in group B among patients who received supportive care only vs low-dose Ara-C ± other drugs vs hydroxyurea ± other drugs (Figure 3).

Thirty-eight patients (32 in group A and 6 in group B) survived > 3 years and have been analyzed: these patients did not differ from the general population as concerns clinical characteristics at onset (gender, PS, median age, previous MDS, concomitant diseases), with the exception of a lower incidence of heart disease (2 out 38 patients, 5.1%). Whether some parameters at diagnosis could predict mortality was analyzed by a multivariate Cox model. As shown in Table 2, age > 70 years, PS ≥ 2, WBC >10×10^9/L, and pres-

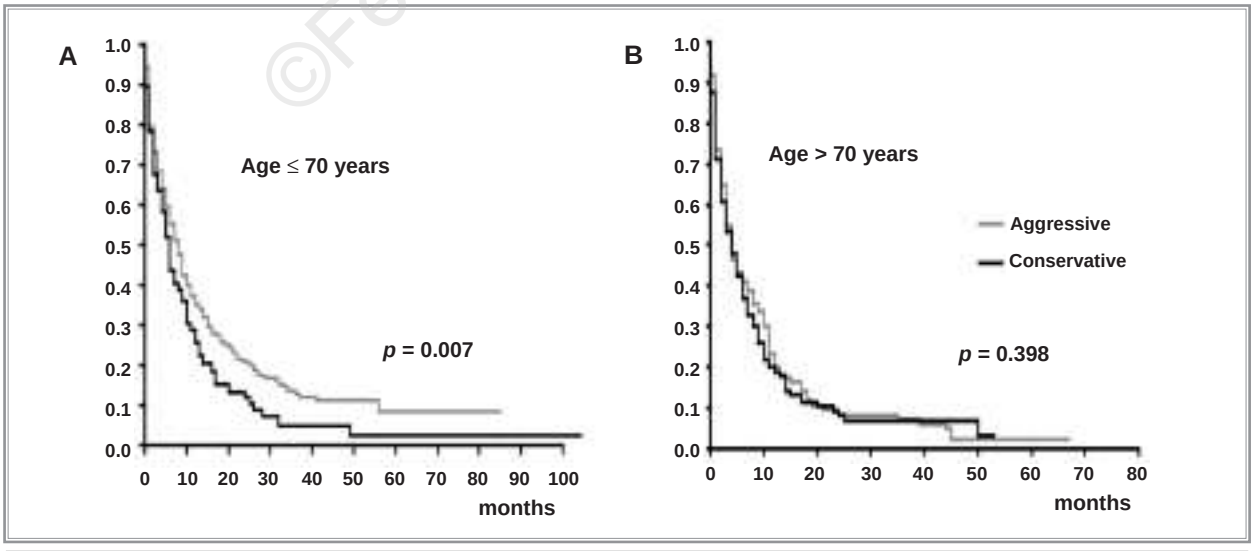

Figure 2. Crude overall survival estimate (Kaplan - Meier) analyzed separately in patients aged 60 – 70 years (A) and > 70 years (B).

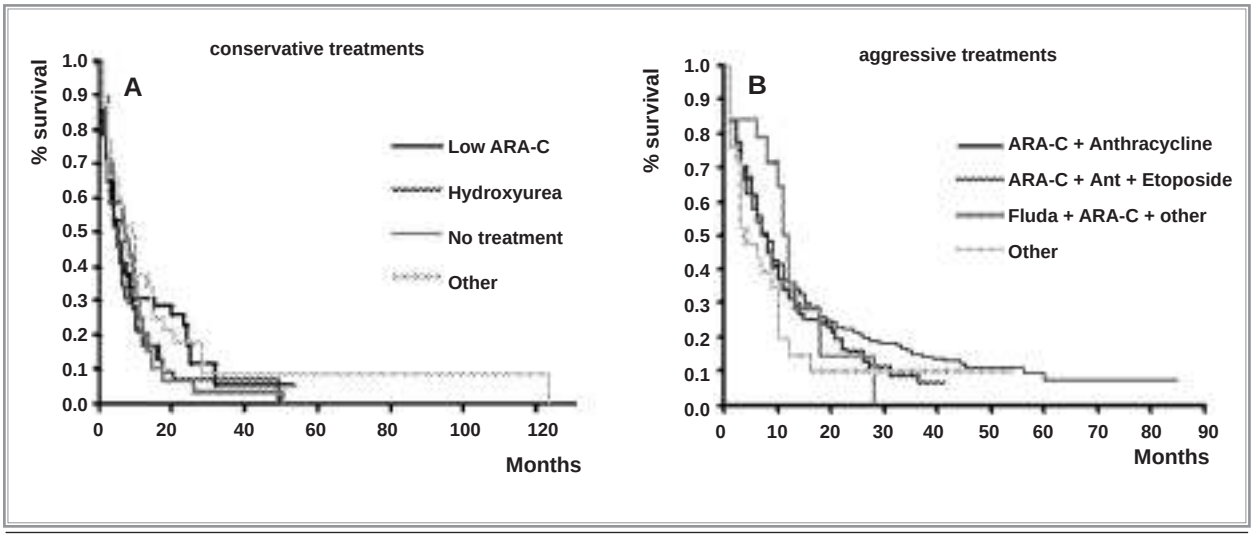

Figure 3. Crude overall survival estimate (Kaplan-Meier) analyzed separately in different *aggressive* treatment approaches (A) and in different *conservative* approaches (B).

Table 2. Mortality prognostic factors: relative risk (RR) by multivariate Cox model analysis.

		RR	*(95% CI)*
Age	< 70	1.0	
	70	1.27	(1.07–1.50)
PS (WHO)	0–1	1.0	
	2–4	1.44	(1.24–1 .68)
WBC	$< 10\times10^9$/L	1.0	
	$> 10\times10^9$/L	1.37	(1.06–1.75)
Treatment	Aggressive	1.0	
	Non-aggressive	1.11	(0.94–1.32)
Heart disease	No	1.0	
	Yes	1.26	(1.05–1.50)

PS: performance status (WHO); WBC: white blood cell count.

Table 3. Kaplan-Meier survival rate according to risk factor combinations at presentation.

	Prognostic Groups	*Aggressive treatment Median survival (months)*	*Non-aggressive treatment Median survival (months)*	*p*
Age	≤ 70			
PS (WHO)	0 – 1	10	10	NS
WBC	$<10\times10^9$/L	(0–65)	(0–29)	
Heart disease	No	(n=144)	(n=31)	
Age	≤ 70	8	3	
WBC	$>10\times10^9$/L	(0–54)	(0–14)	0.010
Heart disease	No	(n=103)	(n=18)	

PS: performance status (WHO); WBC: white blood cell count; NS: not significant.

ence of heart disease requiring treatment, were independently and significantly correlated to a shorter survival. Conversely, the type of treatment (aggressive or non-aggressive) was not signifcantly correlated with survival.

Different combinations of risk factors were then tested with the aim of identifying a subgroup of patients in whom an aggressive approach could enable a significant survival advantage. The subgroup of patients characterized by the best combination of prognostic factors (age < 70 years, PS <2, WBC $<10\times10^9$/L, absence of heart disease) showed a relatively good median duration of survival, but surprisingly they had no advantage from *aggressive* induction treatment (Table 3). In contrast, patients aged <70 years, absence of heart disease, but WBC$>10\times10^9$/L represented the group in whom an *aggressive* approach produced a significantly better survival (Table 3).

The duration of hospitalization (considered as an indicator of the patients' quality of life) was almost twice as long in group A as in group B patients (median duration 41 versus 22 days, respectively; $p < 0.0001$).

Discussion

The true prognosis of elderly patients with AML is hardly depicted by the results of the many clinical trials available;[8,11-16,21-24,30-32] an important selection bias is almost invariably present in all studies, so that very old or high-risk patients are usually excluded. Nevertheless, this kind of information is now assuming growing importance in a modern health policy evaluation. This study was designed with the aim of analyzing the survival of the whole population of elderly AML patients

referred to the GIMEMA hematology hospitals in Italy. From this overview, which overcomes enrollment in clinical trials, the proportion of patients treated only with supportive care, with or without mild chemotherapy, is very substantial. A reliable analysis of the role of an aggressive induction treatment on the elderly AML patient population should take into account this finding. Many variables may influence the decision to offer supportive care instead of intensive treatment approach. Neuss *et al.*[33] showed, in their single institution study, that many of these variables are socio-economic rather than clinical, but in our multicenter study this aspect is difficult to examine.

When considering the results of this comparison between aggressive and non-aggressive treatment it is important to consider that the study is retrospective and non-randomized; therefore, there is an obvious selection of lower risk patients in the *aggressively treated* group. Nevertheless, the median survival advantage in this group, though highly significant in view of the number of patients analyzed, is only 2 months. Furthermore, if we analyze the survival results in patients older than 70 years, despite the disparity of risk factor distribution, no difference can be demonstrated.

When the disparity between the two populations was investigated by multivariate analysis, surprisingly the aggressive approach was not independently correlated with a better survival in the overall population.

A first conclusion that emerges from this analysis is that the overall prognosis of elderly patients with AML is very poor: only 28% of the patients survive more than one year after diagnosis: these data do not differ from those of many other published studies. However, it is worth noting that in our study these results are minimally influenced by the treatment strategy adopted.

The second endpoint of this study was to define the characteristics of a sub-population of patients in whom aggressive induction treatment could allow a better survival. We first analyzed the population of patients characterized by the association of the best prognostic factors. This population did indeed show a better median survival (10 months), but surprisingly this was identical for patients treated aggressively or non-aggressively. Thus, this association of clinical features (age < 70 years, PS 0-1, WBC < 10×10^9/L, absence of heart disease) identifies a population of patients with a better prognosis of a relatively good survival even when managed only with supportive care and/or mild chemotherapy. However, in the younger patients with no heart disease but with a high WBC count, aggressive induction treatment significantly prolonged survival. The conclusion is that when age and clinical conditions allow, aggressive treatment is advisable in patients presenting with a high WBC count.

The impossibility, in this setting, of considering other risk factors such as the cytogenetic and multidrug resistance (MDR) profile, which have been proven to be relevant in elderly patients with AML, prevents us from further subdividing the case series into biologically-based subgroups. These parameters, as documented by different studies,[4,25-26] need to be carefully considered in the treatment decision process. Although the duration of hospital stay can be considered only a rough indicator of quality of life, we observed a significant difference in this objective and easily measurable datum between the 2 groups of patients.

In conclusion, from the analysis of a large population of elderly AML patients in Italy the survival advantage deriving from aggressive induction treatment appears to be very limited, except for a small subgroup of patients. The longer duration of hospital stay in patients treated aggressively indicates higher health care expenses and a generally lower quality of life for these patients. Quality of life needs to be taken into careful consideration when proposing aggressive treatment to an elderly patient with AML, although the treatment could be associated with a small survival benefit.

AP, AM and FM conceived the idea for the study, AP, RL and LP wrote the manuscript, MET was responsible for the statistical analysis; MC, RC, MC, LDP, EDB, RI, FM, MCP, FR, AS and GV were responsible for data referred from the most representative GIMEMA centres; co-ordinators from GIMEMA centers contributing with a minor proportion of cases are listed in the appendix. The authors reported no potential conflicts of interest. We thank Professor Robin Foà for his assistance and critical review of this manuscript, and Doctor Giuseppe Gentile for his contribution to the design of the study.

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Appendix

GIMEMA centers and their representatives involved in the study.

Alessandria - Ospedale SS. Antonio e Biagio: A. Levis, B. Allione; Ancona - Ospedale di Torrette: P. Leoni, A. Olivieri; Avellino - Osp. S.G. Moscati: E. Volpe, N. Cantore; Bologna - Policlinico 'S. Orsola': M. Baccarani, P. Piccaluga; Bolzano - Ospedale Generale Regionale: P. Coser, P.Fabris; Cagliari - Ospedale Oncologico: G. Broccia, F. Adamo; Catania – Ospedale: R. Giustolisi, F. Di Raimondo; Catanzaro - Ospedale Regionale: Antonio Peta, C. Alberti – Ferrara - Arcispedale S. Anna: G. Castoldi, G. Scapoli; Cremona - Istituti Ospitalieri: P. Bodini, S. Morandi; Foggia - Ospedali Riuniti: M. Monaco, S. Cavotta; Genova - Università: R. Ghio, E. Balleari; Genova - Ospedale S. Martino: G. Santini, R. Cerri; Latina – Ospedale:

A. De Blasio; Milano - Medicina Interna-Università: G. Lambertenghi. Montefiascone – Ospedale: M. Montanaro, C. Andrizzi; Napoli - Università Federico II: B. Rotoli, A. Camera; Nuoro - Ospedale San Francesco: A. Gabbas, A. Calvisi; Palermo - Università degli Studi: G. Mariani, E. Mitra; Palermo - Istituto Clinica Medica: P. Citarrella, S. Miceli; Palermo – Ospedale: S. Mirto, F. Fabiano; Parma - Università degli Studi: V. Rizzoli, M. Prugnola; Pavia - IRCCS San Matteo: E. Ascari, R. Invernizzi; Perugia - Policlinico Monteluce: M. Martelli, A. Tabilio; Pesaro - CTMO Ospedale: G. Visani, G. Sparaventi; Pescara - Ospedale dello Spirito Santo: G. Fioritoni, M. Sborgia; Pordenone - Az.Ospedaliera: V. Zagonel; Potenza - Ospedale S.Carlo: F. Ricciuti, M. Pizzuti; Reggio Calabria - Azienda Ospedaliera: F. Nobile, B. Martino; Reggio Emilia - Arcispedale Santa Maria Nuova: L. Gugliotta, P. Avanzino; Roma Università "La Sapienza" – F. Mandelli, A. Pulsoni, R. Latagliata; Roma Università Cattolica: G. Leone, L. Pagano. Roma Università "Tor Vergata": S. Amadori, A. Venditti; Roma - Ospeale S. Camillo: I. Maiolino, L. Pacilli; S. Giovanni Rotondo - Casa Sollievo della Sofferenza: A. M. Carella, L. Melillo; Torino - Ospedale San Giovanni Battista: A. Boccadoro, D. Ferrero; Torino – Molinette: E. Gallo, F. Marmont; Vicenza - ULSS N.6: F. Rodeghiero, E. Di Bona.

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