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Treatment of elderly patients with AML: results of an individualized approach

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ABSTRACT

Background and Objective. **AML treatment in elderly patients must be individualized according to their characteristics. We report the results of a tailored treatment approach in all consecutive AML patients older than 60 years diagnosed at our institution during the last 2 years.**

Design and Methods. **Between December 1994 and December 1996, 43 AML patients over 60 years of age (median, 72; range 61-89) were managed according to their performance status (PS) and associated diseases. Twenty patients (46%) were eligible for intensive chemotherapy and received combination chemotherapy including an anthracycline (idarubicin or daunorubicin), ara-C and VP-16. After complete remission (CR), consolidation chemotherapy with mitoxantrone and intermediate- high-dose ara-C was given to 13 of the 15 patients in remission (65% of all patients candidates for intensive treatment). Twenty-three patients who were not eligible for intensive chemotherapy received palliative measures.**

Results. **Patients treated with one course of intensive chemotherapy had a CR rate of 70% (95% CI: 48-92%)(n = 14) with a mortality rate of 20% (n = 4) and a resistance of 10% (n = 2). An additional patient reached CR after rescue therapy. Median CR duration was 10.5 months. Median survival was 10.5 months. Patients above 70 years had a median survival of 5 months compared to the median not reached for those aged between 60 and 70 years (p = 0.03). This latter group had a probability of survival of 52±18% at 18 months. None of the patients treated with palliative measures achieved CR and the median survival in this group was only 1.5 months.**

Interpretation and Conclusions. **Patients with AML aged 70 years or less with good PS and without severe associated diseases should be intensively treated due to the high probability of achieving CR and an acceptable median-term survival. By contrast, results in patients 70 years or older and in those suitable only for palliative treatment because of a poor PS or severe associated diseases are very poor. Alternative treatment approaches for these patients should be investigated.**

Key words: leukemia, AML, elderly, treatment

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Acute myelogenous leukemia (AML) is predominantly a disease of the elderly. The median age of the patients at diagnosis is 60 years or older.[1] Although high complete remission rates and long disease-free survival can be obtained in younger adults with AML, treatment results in elderly patients are usually poor.[2-5] This is mainly due to the fact that elderly people are less able to tolerate intensive chemotherapy and frequently have associated diseases, this leading to an increased treatment-related mortality.[6,7] On the other hand, elderly patients generally present secondary AML following myeloproliferative disorders and myelodysplastic syndromes (MDS) more often.[8] In addition, there are some data supporting that leukemia in the elderly might be biologically different from that of adults. For this reason, it has been suggested that proliferating cells in the AML of the elderly could be less mature.[9] In addition, bad prognostic cytogenetic abnormalities are more frequently observed in older patients than in younger ones and the overexpression of MDR-related proteins has been reported to be particularly common in leukemias of the elderly.[10-12] All these characteristics confer less sensitivity to chemotherapy.

Which type of elderly patients with AML should receive intensive therapy is unclear.[4,13-17] At our institution, two alternatives have been employed (i.e., intensive treatment, palliative treatment) according to the performance status (PS) of the patients and the presence of associated diseases. We describe the clinical characteristics and evolution of all elderly patients with AML diagnosed at our center during the last two years and treated according to these two approaches.

Materials and Methods

Patients

Between December 1994 and December 1996, 43 AML patients older than 60 years were consecutively diagnosed at our institution. The median age was 72 years (range, 61 to 89); 23 patients were women and 20 were men. Distribution according to the revised French-American-British (FAB) crite-

ria[18] was as follows: M0 (1 case), M1 (7 cases), M2 (6 cases), M4 (3 cases), M5 (11 cases), M6 (1 case), unclassifiable (1 case), secondary to myelodysplasia (13 cases). At diagnosis, a major associated medical disorder (e.g., renal insufficiency, cardiac failure) was present in 10 patients (23%). Six patients (14%) had extramedullary infiltration. Thirty-one patients (72%) presented hemoglobin (Hb) levels below 100 g/L, 6 (14%) had hyperleukocytosis (more than 100×10^9/L leukocytes), and in 4 (9%) the platelet count was below 20×10^9/L. Serum LDH was high (over 450 IU/L) in 22 cases (51%), 10 (23%) patients had a serum creatinine level above 1.3 mg/dL, and 10 (23%) a serum bilirubin level higher than 1.0 mg/dL. Two patients (5%) presented disseminated intravascular coagulation.

Eligibility criteria

Eligibility criteria for intensive chemotherapy were as follows:

a) age 60 or older with newly diagnosed AML as defined by FAB criteria; b) ECOG performance status ≤ 2; c) normal cardiac function with left ventricular ejection fraction ≥ 50%, measured by echocardiography or radionuclide cardioangiography; d) normal or minimal impairment of renal (creatinine < 2 mg/dL) and liver (bilirubin < 2 mg/dL) functions, except if objective data presented that the abnormality was due to the leukemia; e) negative HIV, HBV and HCV serology tests.

Neither the age nor the antecedent of myelodysplasia limited the option to treat with intensive chemotherapy. A total of 20 patients (46%) fulfilled those criteria and were therefore treated with intensive chemotherapy. The remaining 23 patients (54%) received a palliative treatment because of the following reasons: a) PS > 2 (n = 15); b) abnormal cardiac function (n = 6); abnormal renal function not related to leukemia (n = 2). Clinical characteristics of all patients included in this study are shown in Table 1.

Table 1. Patient characteristics.

	Intensive treatment	*Palliative treatment*
No. of patients	20	23
Age 66 (61-78)	75 (63-89)	
>70 years	6	19
Male/female	12/8	8/15
FAB subtype		
De novo		
M0-M2	8	6
M3	0	0
M4-M5	6	8
M6-M7	0	1
Unclassifiable	1	0
Secondary to MDS	5	8
Extramedullary infiltration	2	4
Leukocyte counts (x10^9/L)	5 (0.3-178)	14 (1.4-225)
Hemoglobin (g/L)	79 (46-130)	80 (36-110)
Platelet counts (x10^9/L)	72 (9-197)	57 (15-216)
LDH (IU/L)	499 (213-1944)	537 (162-2741)
DIC 1	1	
Percentage marrow blasts	65 (30-100)	60 (30-100)
Cytogenetics		
Performed	19	17
Abnormal	8	5

Age, leukocytes, hemoglobin, platelets, LDH and marrow blasts are shown as their median values with extremes in parentheses. Abbreviations: MDS: myelodyplastic syndrome, DIC: disseminated intravascular coagulation.

Treatment

Remission induction chemotherapy consisted of combinations including an anthracycline (idarubicin 10 mg/m^2 or daunorubicin 60 mg/m^2) i.v. for 3 days, ara-C by 100 mg/m^2 in continuous i.v. infusion for 7 or 10 days and VP-16 at a dose of 100 mg/m^2 i.v. × 3 or 5 days. Consolidation chemotherapy was a single course of mitoxantrone (12 mg/m^2 i.v. × 3 days) and ara-C in total doses ranging from 1.2 to 9.6 g/m^2 i.v. during two hours. No maintenance chemotherapy was administered.

Patients were nursed in conventional rooms. Oral antibiotics were prophylactically prescribed during neutropenia. Sustained fever (≥ 38°C) was treated with broad-spectrum antibiotics. Red cell transfusions were given to maintain the hematocrit above 25%. Platelet transfusions were given to maintain platelet counts over 20×10^9/L.

Twenty-three patients non-eligible for intensive treatment were managed with palliative therapy, including blood transfusions and 6-mercaptopurine (50 to 150 mg per day, administered orally as long as required if increasing leukocyte counts were observed). In this group patients were managed as long as possible on an out-patients basis.

Response criteria

Complete remission (CR) was defined as normocellular bone marrow containing less than 5% blasts, together with peripheral blood showing Hb more than 100 g/L and neutrophils above 1×10^9/L and, when applicable, absence of extramedullary leukemia. All those patients who responded completely had a second bone marrow aspirate performed before consolidation therapy to verify the remission status. Death during induction included patients dying with hypoplastic marrow or in remission succumbing to complications of chemotherapy. Any of the following were considered as major complications of intensive treatment: toxic rash affecting more than 50% of the body surface, life-threatening

Table 2. Response to intensive treatment.

	Nº (%)	*(95% CI)*
Total of patients	20	
Complete remission	15 (75)	(54-96)
One course of induction	14	
After salvage therapy	1	
Failure	5	
*Resistant disease**	1	
Death during induction	4	

Abbreviations. CI = confidence interval.
**Initial resistance in two patients, one of them subsequently achieved CR after salvage therapy.*

Table 3. Major complications of intensive treatment.

	Induction Nº (%)	*Consolidation Nº (%)*
Toxicity		
Mucocutaneous	2	0
Liver	1	0
Renal	1	0
CNS	0	1
Hemorrhage	1*	0
Infection	9	8
Septicemia	5	6
Fungal	2*	0
GRAM+ bacteria	1	1*
GRAM– bacteria	2*	5
Pneumonia	2*	1
Cellulitis	2	0
Esophageal candidiasis	0	1
Total episodes	14	9
Nº patients complicated	12/20 (60)	9/13 (69)

**Treatment-related death in five patients. Abbreviations: CNS = central nervous system.*

hemorrhage or infection, any CNS symptomatology, and two-fold elevation over the upper normal creatinine or bilirubin serum levels.

Statistical methods

Results were analyzed as of July 1997. Patients who are still alive have been controlled for a median of 12 months. Survival analysis was calculated according to the Kaplan-Meier method[19] and curves were compared by the log-rank test.[20]

Results

Response to treatment

Intensive therapy. Fourteen of the 20 (70%) patients treated with one course of intensive chemotherapy achieved CR (Table 2). CR rate was 71% in patients with 70 years or less and 67% in those older than 70 (p: NS). Two patients (10%) presented primary resistance to chemotherapy; one of them attaining CR after salvage therapy with mitoxantrone and intermediate-dose ara-C while the other was managed with palliative treatment, because of severe toxicity during induction, and died 5 months later. Four of the five patients with AML which evolved after MDS achieved CR (the sixth died due to sepsis whilst neutropenic). Twelve patients (60%) developed major toxicity to induction treatment (Table 3). Four patients (20%) suffered from a life-threatening fungal infection (mainly by *Aspergillus spp.*). Liver and kidney toxicities were reversible and did not compromise ulterior treatment. Four patients (20%) died during induction (cerebral hemorrhage [n = 1], opportunistic infections [n = 3]).

Thirteen of the 15 patients complete responders received consolidation therapy; the remaining 2 patients were excluded due to excessive toxicity during induction. The interval between CR and the beginning of consolidation was 22 days (range, 8-47). Complications related to treatment are summarized in Table 3. Nine patients (69%) had major complications during consolidation therapy which required hospital admission, and 4 (31%) were managed on an out-patients basis. One patient (8%) died of sepsis (*Streptococcus viridans*) during bone marrow hypoplasia following consolidation and 12 remained alive in CR after hematological recovery. Median hospital stay of the patients who completed the intensive treatment, including admissions for treatment of complications, was 55 days (range, 33-79).

Palliative therapy. In most patients, treatment with 6-mercaptopurine had to be administered soon after diagnosis due to the progressive disease. No patient achieved CR.

Duration of remission

Actuarial median duration of CR was 10.5 months. Six patients were alive during continuous first CR for a period ranging between 4.5 and 25 months (median, 8.5). Eight patients relapsed between 3 and 19 months (median, 9) after CR achievement. One patient died in CR due to sepsis following consolidation treatment. Three of the four patients who responded completely with preceding MDS relapsed at 3, 5 and 19 months from remission, respectively. The estimated probability of being free of disease at 18 months was 30±16%. There was a significant difference in remission duration according to age: patients above 70 years had a median remission duration of 5 months vs 11 months for those between 60 and 70 years of age (p = 0.03). Other factors such as the patient's sex, number of circulating blasts, serum level of LDH, karyotype or history of preceding MDS were not associated with the duration of remission.

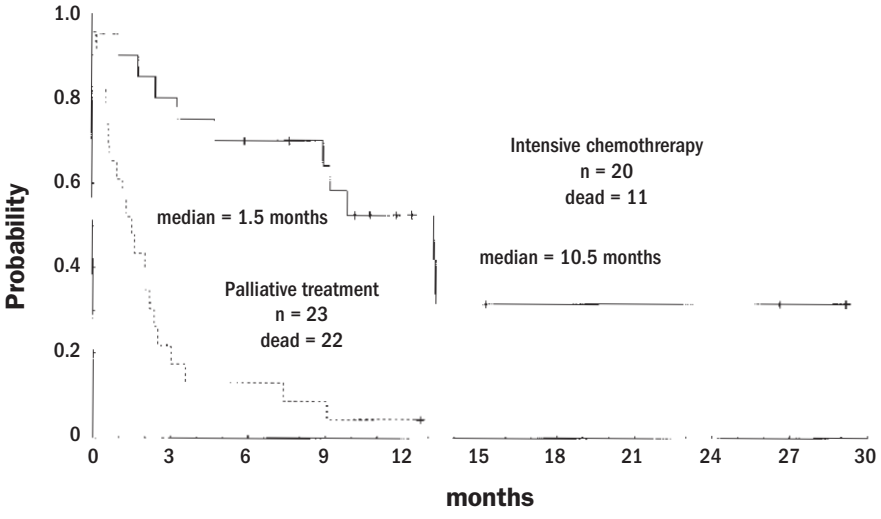

Figure 1. Overall survival by treatment modalities.

Survival

Intensive therapy. Actuarial median survival of the 20 patients was 10.5 months (range, < 1 to 29+) (Figure 1). Median survival has not been reached in 14 patients aged between 60 and 70 years, with an estimated probability of survival at 18 months of 52±18%. Nine patients were alive while 5 died (three due to treatment complications and two because of relapsed leukemia). By contrast, six patients older than 70 had a median survival of 5 months (range, 2.5-13) with an estimated probability of 0% at 18 months. All six patients from this group died, two during chemotherapy, one because of resistant disease and three after a relapse. Median survival in patients with preceding MDS was 12 months (range, 3 to 29+). The median survival after leukemia relapse was 2 months, ranging from < 1 to 8 months. Age was the only statistically significant variable predicting survival.

Palliative therapy. Only 3 of the 23 (13%) patients of this group were alive 6 months after diagnosis and 22 had died at the end of the study. Median survival was 1.5 months (range, 2 to 272 days) (Figure 1). The main cause of death was disease progression (78%); other causes of death were pneumonia (13%) and hemorrhage (9%).

Discussion

In most studies dealing with treatment of AML in elderly patients it is concluded that the prognosis of these patients is poor and that treatment decisions should be made on an individualized basis.[15,21-23] According to this concept, during the last two years we have treated all AML patients above 60 years of age seen at our institution with palliative measures or combination chemotherapy according to their general status and whether or not severe associated diseases were present. Patients with good PS and no associated diseases were candidates to receive intensive treatment as given in younger patients. In 46% of the patients from this series fulfilling criteria for intensive therapy, a remarkably high proportion of CR (70%) was obtained with a single course of treatment. The CR rate obtained in this series is higher than that reported in other similar studies (28 to 59%).[24] This is most likely due to patient selection criteria since in our series only patients in good status were given intensive therapy. On the other hand, all but one of the patients received idarubicin, a drug which has been reported to be associated with a high percentage of CR with one course of treatment.[25,26] In fact, if all elderly patients with AML which were seen during the study period are analyzed together, the CR rate was only 35% (95% CI: 20 to 50%). Early deaths ocurred in 25% of the patients intensively treated. Again, this figure is similar to that found in other series (12-44%)[24] and slightly superior, but not dramatically higher, than that observed in most series of younger adults with AML (16-22%).[27-29]

Whether or not a better prophylaxis of infectious complications (e.g., by using colony-growth factors) could improve these results is doubtful.[30] Thus, in three randomized trials[31-33] and other controlled phase III study[34] evaluating the effect of colony-stimulating-factors in this setting, the reduction of the duration of neutropenia by 2-7 days showed no consistent benefit in terms of decreasing the incidence of severe infections, days of hospitalization or death rate. Only one of the 4 studies showed a survival advantage of the elderly patients with AML receiving GM-CSF compared to those given placebo.[31]

It is worth noting that four of five patients inten-

sively treated for AML evolving after MDS achieved CR. This is in agreement with other reports and emphasizes the role of intensive treatment in such patients provided their PS is good and no severe associated diseases are present.[35]

As far as prognostic factors are concerned, age was the only variable of statistical significance associated with survival in patients given intensive treatment. Patients older than 70 years had a shorter survival than those aged between 60 and 70 years, although the value of this observation is somewhat hampered by the small number of patients in each group. Other factors like abnormal karyotype, high number of circulating blasts, elevated LDH and history of preceding MDS that have been related to an adverse outcome in several reports[21,36,37-39] did not influence the CR rate, disease-free survival or survival in our series. Although the number of patients is small, the correlation between age and treatment outcome is worth emphasizing. Thus, patients above 70 years had a very poor outcome; after diagnosis, they spent 30% of their remaining life in the hospital and none survived longer than 13 months. By contrast, much better results were obtained in patients between 60 and 70 years.

In conclusion, intensive combination chemotherapy can be safely given to patients with AML up to the age of 70 provided their general status is good and no severe associated diseases are present. By contrast, treatment results in patients older than 70 seem to be very poor even if their PS and general condition is good.

Contributions and Acknowledgments

J.C. Boluda had the initial idea of performing this study. Contributed along with J. Sierra and B. Nomdedeu to the study design, collected and analyzed the data and prepared the first draft of the paper. J. Sierra designed the study along with B. Nomdedeu, helped J.C. Boluda in data analysis and in preparing the manuscript. J. Esteve was the senior medical attendant during the study period, informed the patients and their relatives about the purpose of the study and helped J.C. Boluda in data analysis. B. Nomdedeu made the first study design upon approval by Prof. E. Montserrat. Afterwards he prepared the final version of the protocol with J. Sierra and the cooperation of J.C. Boluda. E. Montserrat approved the protocol, revised its development, and corrected the different versions of the manuscript.

The order of the authors has been established according to the usual manner which implies that the first author is the idea promoter and the last one the senior member of the research group.

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Disclosures

Conflict of interest: none.

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