Haematologica 1998; 83:126-131 original paper

Therapeutic options and treatment results for patients over 75 years of age with acute myeloid leukemia

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Abstract

Background and Objective. **Acute myeloid leukemia (AML) is a prevalent disease of the elderly. Given the progressive aging of the general population, the frequency of the disease will further increase, especially in very old individuals. In a cohort of 70 consecutive AML patients aged over 75 years, we investigated the clinico-hematological characteristics and treatment results.**

Design and Methods. **Seventy patients aged > 75 were diagnosed at our institutions as having AML between January 1987 and December 1996. This figure represents 8% of the whole AML patient population observed during the same period. These patients were studied concerning the main clinical and hematological features at presentation, therapeutic approach and clinical outcome.**

Results. **A myelodysplastic syndrome preceded the onset of AML in 10 patients (14%). Trilinear myelodysplasia was present in 28 patients (40%). Hypocellular leukemia was diagnosed in 12 cases (17%). An active infection was found in 12 patients (17%). Aggressive chemotherapy was given to 22 patients (31%), low-dose ARA-C (LDARA-C) to 7 patients (10%), while 41 (58%) were managed with supportive care and/or hydroxyurea (HU). Therapeutic choice was significantly influenced by performance status (p = .03), infections (p = .0001), severe co-morbid disease (p = .0001), and hypocellular AML diagnosis (p = .0001). Complete remission (CR) was obtained in 7/22 patients aggressively treated (32%), 0/7 in the LD-ARA-C group, and in one patient treated with HU. The median survival for the whole patient population was 18 weeks. There was no significant difference among the three treatment groups. However, patients achieving CR experienced significantly longer survival as did those with hypocellular leukemia.**

Interpretation and Conclusions. **In spite of a relevant selection at diagnosis, intensive chemotherapy is not appropriate for the majority of very old patients with AML. However, since a minority of patients takes substantial advantage from an aggressive approach, any effort should be made to preliminarily identify this subset at diagnosis.**

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Key words: acute myeloid leukemia, elderly patients, patient selection

More than half of all cases of acute myeloid leukemia (AML) are diagnosed in patients over 60 years of age and more than one third are over 70.[1-6] Furthermore, given the progressive aging of the general population, the frequency of the disease in the elderly is expected to further rise in the future, especially in very old individuals, i.e. those over 75. In this age subset, although clinical experience suggests that hematologists are rather reluctant to submit patients to intensive treatment programs, quantitative information concerning the rate of inclusion into chemotherapy trials as well as the clinical outcome is substantially lacking.[7-9] Since the proper management of these patients is likely to gain increasing clinical relevance in the future, it is important to provide data on the clinical characteristics and therapeutic results currently achieved in these extremely aged AML patients. Here we report our experience on a series of 70 consecutive patients over 75 years of age with AML observed at our institutions during the last decade.

Materials and Methods

Patient characteristics

Seventy patients aged > 75 were diagnosed at our institutions as having AML between January 1987 and December 1996. This figure represents 8% of the whole AML patient population observed during the same period. Diagnosis was based on conventional morphologic and cytochemical FAB criteria.[10] In 58 cases (83%), immunophenotypic studies, performed as previously described,[11] were also carried out. There were 41 males and 29 females. The median age was 79.6 years (range 76-86). Forty-six patients (66 %) were aged between 76 and 80, while 24 (34%) over 80. Main clinical and hematological characteristics at diagnosis are summarized in Table 1. Three patients were in performance status (PS) 1, 24 in PS 2, 31 in PS 3 and 12

Table 1. Clinical and hematological characteristics at diagnosis.

No.	70
Sex (M/F)	41/29
Median age (range)	79 (76-86)
Antecedent MDS	10 (14%)
TrMDS	28 (40%)
Hypocellular AML	12 (17%)
FAB M1-M2	30 (43%)
FAB M4-M5	40 (57%)
PS 1 (WHO)	3 (4.%)
PS 2	24 (34%)
PS 3	31 (44%)
PS 4	12 (17%)
Active documented infection	12 (17%)
Blasts in PB (x10^9/L)	19 (0.04-240)
Hemoglobin (g/dL)	8.5 (5.5-12.2)
Platelets (x10^9/L)	46 (9-580)
Serum albumin < 3 g/dL	18 (26%)
Serum creatinine > 2.5 g/dL	8 (6.4%)
Serum LDH (IU/L)	841(178-3581)

in PS 4, as assessed according to WHO criteria. In 10 patients (14%) a previously diagnosed myelodysplastic syndrome (MDS) preceded the onset of AML (4 RAEB, 5 RAEB-t and 1 CMML, respectively). In 28 patients (40 %) morphological trilineage myelodysplasia (TrMDS), as defined according to the criteria of Brito-Bapapulle *et al.*,[12] was found. Twelve patients (17%) were diagnosed with acute hypocellular leukemia defined by markedly reduced bone marrow cellularity, pancytopenia and low count or absence of blast cells in the peripheral blood.[13-16] A decrease in serum albumin concentration (< 3 g/dL) was observed in 18 patients (27%), while a serum creatinine value > 2.5 mg/dL was found in 8 patients (11%). Nineteen patients (27%) presented severe antecedent disease requiring specific therapeutic intervention, while 12 (17%) had a documented active infection.

Table 2. Clinical and hematological characteristics at diagnosis by different therapeutic approach.

	Intensive induction	*LDARA-C*	*Supportive treatment*	*p value*
No.	22	7	41	
Age	78.8	80.1	79.6	.74
PS 1-2	15	2	13	
PS 3	7	4	17	.03
PS 4	0	1	11	
Severe co-morbid disease	0	0	19	< .0001
Active infection	0	0	12	< .0001
Hypocellular AML	0	0	12	< .001
Antecedent MDS	2	2	6	.43
TrMDS	5	5	18	.05
Blasts in PB (x10^9/L)	21	34	8	.15
Serum LDH (IU/L)	853	871	815	.24
Days of hospitalization	40	12	7	< .001

Therapeutic selection

Twenty-two out of 70 patients (31%) were selected for intensive induction therapy. Depending on the period of observation, i.e. before or after June 1991, induction treatment consisted of a combination of either daunorubicin (DNR) at the dose of 40 mg/sqm intravenously (iv) on day 1 plus cytosine-arabinoside (ARA-C) at the dose of 100 mg/sqm every 12h from day 1 to 5 in 9 cases, or of idarubicin (IDA) (10 mg/sqm iv) days 1 to 3 plus ARA-C in 13 patients, respectively. Post-remission treatment was given to all patients achieving CR. In patients treated with DNR, a second identical induction course was administered, while the group treated with IDA consolidation consisted of one course of IDA (10 mg/sqm on day 1), ARA-C (100 mg/sqm every 12h from day 1 to 5) and etoposide (100 mg/sqm from day 1 to 5). Nine patients were given DNR/ARA-C, 13 received IDA/ARA-C. Seven patients (10%) were treated with low-dose of ARA-C (LDARA-C) that is 10 mg/sqm every 12h for 15-21 days subcutaneously, and finally 41 patients (58%) were managed with supportive care only and/or with hydroxyurea in the case of leukocytosis higher than 30×10^9/L. The reasons of exclusion from aggressive treatment were: a) diagnosis of hypocellular leukemia in 12 patients (17%), that were also excluded from LDARA-C; b) severe renal failure in 7 (10%); c) preexisting co-morbid disease in 19 (27%); d) active infection in 12 (17%); e) PS 4 in 12 (17%). More than one of these features were simultaneously present in some patients. No well established criteria were adopted to assign patients to LDARA-C; possibility to administer the treatment in a outpatient setting, geographical reasons (distance from our institution) and personal physician attitude were usually the discriminant for selecting between LDARA-C and supportive care.

Age did not differ among the three groups (median 79.8 for intensive chemotherapy subset, 80.1 for LDARA-C patients, and 79.6 for patients receiving supportive treatment only, p = .84). On the contrary, PS was significantly different when the three groups were compared (p = .03). Table 2 summarizes main patient characteristics at diagnosis through different therapeutic approach. Statistical analysis was performed by using Student's t test or chi-square test. Survival curves were calculated according to the method of Kaplan and Meier,[17] differences between survival were evaluated by the log-rank test.

Results

The median overall survival (OS) of the entire patient population was 18 weeks and is depicted in Figure 1. Complete remission (CR) was obtained in

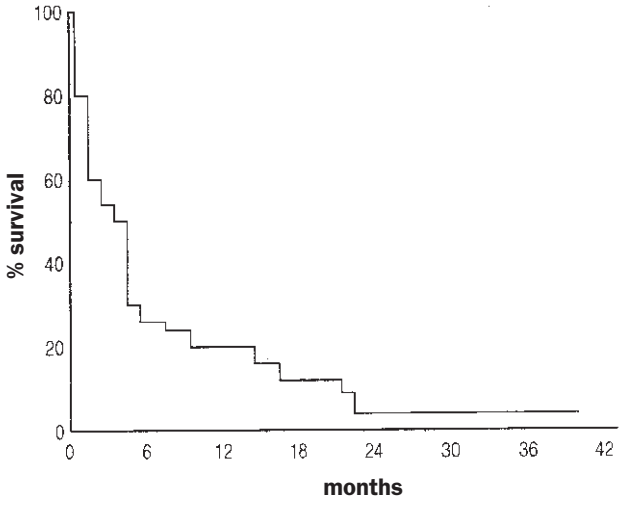

Figure 1. Survival of the whole patient population (median 18 weeks).

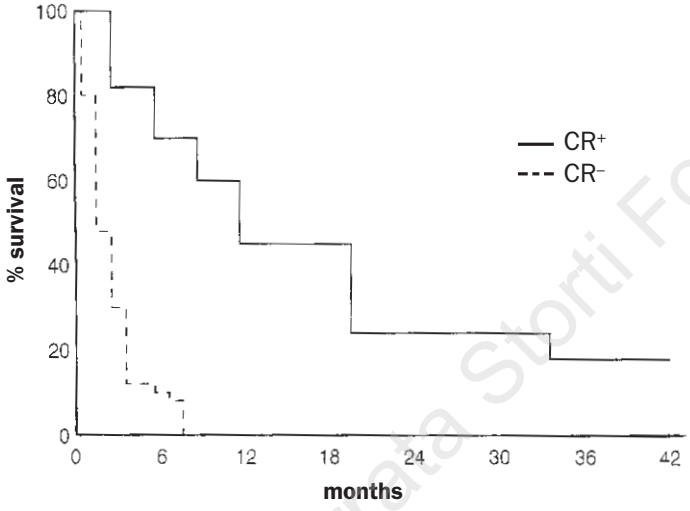

Figure 2. Survival according to CR achievement (p = .008).

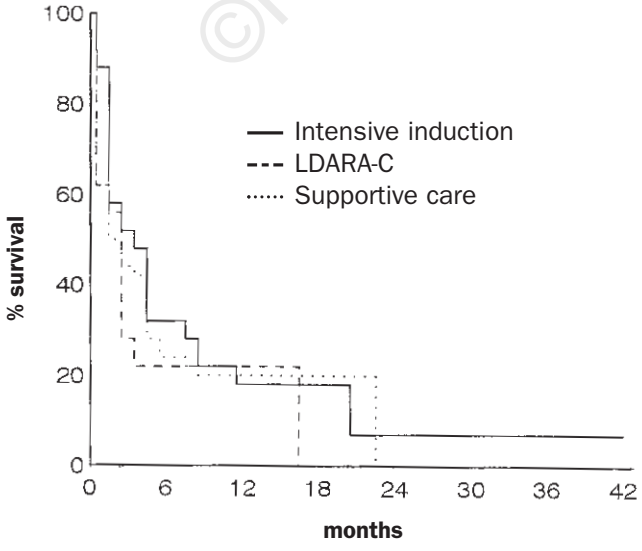

Figure 3. Survival by therapeutic approach (p = .21).

7 out of 22 patients receiving intensive induction (32%). The low number of patients who went into CR did not allow any comparison between patients receiving either DNR or IDA; however, all remitters experienced profound pancytopenia requiring intensive support in terms of both blood and platelet transfusions. Among the 15 patients who failed to achieve a CR, hypoplastic death (death occurring during marrow hypoplasia) occurred in 5 cases (22%). Infection was the cause of death in 3 patients, while two patients died of cerebral hemorrhage. Primary drug resistance (defined as remission induction therapy failing to produce significant bone marrow hypoplasia in patients surviving 15 or more days after therapy or leukemic regrowth following aplasia) occurred in 10 patients (45%).

Extrahematological toxicity of grade > 2 occurred in 18 out of 22 patients and consisted of 17 episodes of mucositis, 13 of infections, 2 of neurologic toxicity, 1 of acute fatal renal failure and 1 of severe cardiac arrhythmia. The median OS and disease free survival (DFS) for this group of patients were of 16 and 32 weeks, respectively. One patient is still alive and in first CR at 40 months from diagnosis. The median survival for patients achieving CR was 34 weeks; CR achievement had a significant impact on OS, as showed in Figure 2. It is worth noting that when we compared therapeutic choices of the current cohort to patients aged between 61 and 75 years concomitantly observed, we found that 93 out of 145 (64%) received an aggressive induction therapy. The difference is highly significant ($p = .0001$).

No patient treated with LDARA-C achieved CR. One died early in induction, 1 had a partial response and 5 of them were refractory. Five out of 7 patients were managed as outpatients. Median OS for LD-ARA-C patients was 16 weeks. Among patients receiving support only one patient achieved CR while in treatment with hydroxyurea; the median survival for this group was 20 weeks. No patient with hypocellular variety received any kind of chemotherapy and median survival was 8 months, which is significantly better compared to the remaining patient population ($p = .01$). In Figure 3 survival for different therapeutic approach is shown; the difference is not statistically significant ($p = .21$). Patients receiving aggressive induction had a median hospitalization of 39 days (range 3-83), while those treated with LDARA-C or supportive therapy were hospitalized for a median of 12 and 7 days, respectively (range 2-28). The difference is highly statistically significant ($p = .0001$).

Discussion

The incidence of AML in elderly patients is increasing due to either the progressive aging of the general population or to an improved referral of elderly individuals to hematological departments for diagnostic work-up.[9,18] Furthermore, one should also consider that an undetermined number of these patients may not be referred to hematological institutions because of decisions made by either the general practitioner, or the family members (extremely advanced age, critical co-morbid disease, very low life expectancy).

In this study, we performed a critical analysis on a series of 70 consecutive AML patients aged more than 75 years observed at two different institutions in the South of Italy during the last decade. Typical features of elderly AML were found as concerns the clinico-hematological characteristics at diagnosis, i.e. high incidence of preceding MDS as well as frequent trilinear dysplastic abnormalities also in apparently *de novo* cases, suggesting that in some patients a subclinical undiagnosed MDS could have preceded the onset of AML. In addition, 12 patients (17%) presented with hypocellular AML, a variety almost exclusively seen in individuals older than 50 years.[13-16] All these patients showed markedly hypocellular bone marrow and profound peripheral pancytopenia with low blast count. Although some authors have suggested that aggressive treatment or LDARA-C may be of benefit in selected patients with hypocellular AML,[14,19] in very elderly patients the clinical behavior of this AML variety strictly resembles that of MDS rather than of typical AML (smoldering acute leukemia). In our series, no patient with hypocellular variety received any kind of chemotherapy and median survival was of 8 months, which is significantly better as compared to the remaining patient population. Finally, a considerable number of patients presented with various degrees of hypoalbuminemia and renal failure. The latter in 7 cases (10%) was a main reason of exclusion from any aggressive treatment.

Twenty-two of 70 patients (31%) were selected for aggressive induction treatment. There was no difference as concerns the median age of patients who received intensive chemotherapy as compared to those managed with LDARA-C or support and this is not surprising if we consider the restricted age range of our patient population (76-86 years). On the contrary, PS did significantly differ between the two groups, 68% of patients aggressively treated being in PS 1-2, as opposed to 27% of the remaining patients. The presence of co-morbid disease requiring specific treatment and/or of documented infection was the additional main criteria in addressing the therapeutic option. Finally, ill-defined criteria such as possibility to administer the treatment in a outpatient setting, geographical reasons (distance from our institution) and personal physician attitude were usually discriminant for selecting between LDARA-C and supportive care. Thus, as usually happens in the management of AML in the elderly,[20-22] during the process of clinical

decision making, a relevant selection was operated as concerns inclusion into chemotherapy trials, although these had been specifically developed for elderly AML patients. This may account for the relatively low rate of induction death (22%) observed in this study as compared to other series dealing with very elderly patients.[18] Nonetheless, the CR rate was low (32%), mainly due to the relevant percentage of refractory cases (45%), confirming that the unsatisfactory therapeutical results usually obtained in AML of the elderly, apart from the impaired patient capacity to withstand the side effects of chemotherapy, are also due to adverse biologic characteristics of leukemic cells.[7-9, 23-25]

Conflicting results in terms of survival advantage have emerged in randomized trials when intensive chemotherapy has been compared to attenuated approaches including *watch and wait* policy or LDARA-C,[26-27] as well as when growth factors have been given in combination with chemotherapy.[28-30] In our series, patients did not receive growth factors and, overall, those aggressively treated did not fare better than ones managed with a less intensive approach, in spite of a relevant selection at diagnosis. However, patients achieving CR had a significantly longer survival and one patient is still alive and in first CR at the time of writing at 40 months from diagnosis.

In conclusion, while these results seem to indicate that aggressive chemotherapy leading to bone marrow aplasia is not an appropriate therapeutic option for the majority of very elderly AML patients even though a relevant clinical selection is operated at diagnosis, on the other hand they suggest that selected patients can take substantial advantage of intensive chemotherapy. Probably, the adoption of clinical tools such as PS and severe co-morbid disease as unique criteria to assign patients to intensive regimens is misleading. Therefore, any effort should be made to precisely identify additional prognostic factors useful to discriminate at diagnosis the elderly patients in whom chemotherapy may result in a true improvement of CR achievement and survival. The low number of patients treated with intensive regimen in our series does not allow to draw any conclusion as concerns association between pretreatment characteristics and response. However, in a larger cohort of AML patients aged more than 60, we have recently demonstrated that unfavorable karyotype and high serum LDH level are significantly related to CR achievement and duration.[31] Other authors have investigated additional clinical and biologic parameters resulted as having high predictive prognostic value.[32-34]

Thus, on the basis of pre-treatment characteristics at diagnosis, it seems possible to identify a specific subset of elderly AML patients with high probability of achieving CR of prolonged duration. Knowing that these patients will not withstand more than a single moderate-intensity cycle and many of them display a functional multidrug resistance, the addition of idarubicin or mitoxantrone instead of DNR could be helpful, as previously suggested.[35-37] Our current policy for these patients consists of a combination of IDA/ARA-C given intravenously to patients needing hospitalization, while a totally oral regimen including IDA, etoposide and 6-thioguanine[38,39] is reserved to subjects in whom a home-care program is feasible. Upfront experimental approaches, based on experimental drugs with a novel mechanism of action and/or offering a theoretical chance to circumvent multiple drug resistance gene product,[40] should be probably offered to patients with adverse biologic features at presentation, since conventional chemotherapy is in most cases ineffective as well as costly and is associated with high mortality and morbidity rate.

Contributions and Acknowledgments

FF and S Mirto concepted and designed the study. MA, CC and S Magrin analyzed data. FF and S Mirto drafted the paper and revised it critically. GM followed the patients clinically. FF gave the final approval.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Received on September 15, 1997; accepted on November 7, 1997.

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