Therapeutic outcomes of older patients with acute myeloid leukemia

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ABSTRACT

الأهداف: تقييم النتائج العلاجية للوكيميا النخاعية الحادة (AML) في المرضى المسنين.

الطريقة: أجريت هذه الدراسة في مستشفى جامعة آغا خان – كراتشي – باكستان على مدى 11 عام الماضية خلال الفترة من يناير 1997م إلى أغسطس 2008م. وهذه دراسة سلسلة حالة وصفية. قمنا بالتحقق من أثر المرض، وطرق العلاج المختلفة على نتائج هذه الفئة من السكان.

النتائج: اشتملت الدراسة على عدد 55 مريض للتقييم 60> عام تم تشخيصهم باللوكيميا النخاعية الحادة AML بما في ذلك 34 (61.8%) من الذكور، و 21 (38.2%) من الإناث. كان متوسط العمر هو 67 عام (مدى 86-60 عام) في وقت العرض. سبق اللوكيميا النخاعية الحادة AML خلل التنسج النخاعي 15 (27.2%) مريض. لوحظ ارتفاع الوراثيات الخلوية في 3 (5.4%) مريض. تلقى 40 مريض العلاج الملطف، بينما تلقى 15 مريض فقط العلاج الكيميائي. في المجموعة الأخيرة المصابة باللوكيميا النخاعية الحادة AML الأولية n=10 أظهر مريض واحد مقاومة المرض في حين ظهرت الوفاة في 8 مريض. كان معدل العيش العام في جميع المرضى (46.7-103.5 أيام CI 95%). لم تسجل أي ميزة للعيش للمرضى الذين تلقوا العلاج الكيميائي بالمقابل الذين تلقوا العلاج الملطف.

خاتمة: تدل المراجعة الحالية على ارتفاع معدل الوفيات بين المرضى الذين يعانون من اللوكيميا النخاعية الحادة في منطقتنا. لا يتحمل المرضى الذين تم علاجهم بالعلاج الكيمائي الأدوية السامة وتوفوا بشكل مبكر مقارنة مع اللذين تلقوا العلاجات الملطفة فقط.

Objectives: To evaluate the therapeutic outcomes of acute myeloid leukemia (AML) in elderly patients.

Methods: This study was conducted at the Aga Khan University Hospital, Karachi, Pakistan over 11 years from January 1997 to August 2008. This was a descriptive case series study. We investigated the impact of disease biology and various treatment protocols on the outcome in this population.

Results: A total of 55 evaluable patients (>60 years of age) were diagnosed with AML including 34 (61.8%) males and 21 (38.2%) females. The median age was 67 years (range 60-86 years) at the time of presentation. The AML was preceded by myelodysplastic syndrome in 15 (27.2%) patients. High-risk cytogenetics were observed in 3 (5.4%) patients. Forty patients received palliative treatment while only 15 received chemotherapy. Of the last group with primary AML (n=10), there were 2 remitters, one showed resistant disease while 8 had induction death. The overall mean survival was 75.1 days (95% confidence interval: 46.7-103.5 days) in all patients. There was no survival advantage in patients treated with chemotherapy versus those conservatively treated.

Conclusion: We found high mortality among aged patients with AML in our setting. Patients receiving chemotherapy were extremely intolerant to toxic drugs and succumbed earlier than patients receiving palliative care only.

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Acute myeloid leukemia (AML) is the most frequent malignant disorder of myeloid progenitor cells, with an annual incidence of 3.8 cases per 100,000 in all age groups. Its incidence however rises sharply to 17.9 cases per 100,000 in patients aged 65 years and older,[1] with approximately 60% of all cases of AML occurring

in patients over the age of 60.[2,3] Many of these elderly patients have complex cytogenetic abnormalities that are associated with poor prognosis.[4,5] Also, risk of secondary AML preceded by myelodysplastic syndrome (MDS) or chronic myeloid leukemia (CML) is high in this population.[6] Additionally, associated co-morbid conditions, poor performance status, and reduced tolerance to chemotherapy complicate the disease process. Therefore, chemotherapy is often not successful in these patients.[6] Many physicians therefore opt for supportive care only with standard or aggressive chemotherapy protocols being reserved for a limited number of patients with relatively better prognostic factors. Treatment induction protocols for this population include: daunorubicin and cytosine arabinoside (3+7 regime) or attenuated dose chemotherapy with mitoxantrone and Cytosar or Cytosar alone.[7] Advancing age and poor performance negate their option of receiving bone marrow transplantation. The choice of therapy is largely determined by performance status of the patient and physician's preference. There is paucity of national data regarding incidence or prevalence of elderly AML. Most of the published series are based on experiences of individual centers focusing on AML in general.[8-10] As a developing country, Pakistan utilizes less than 2% of its budget on health, while per capita income is approximately $1000.[11] As can be expected, the treatment cost for cancers is borne largely by the patients or their families due to the lack of infrastructure for health support. Although our institute does offer a welfare program for supporting the treatment costs of deserving patients, it has its limitations for elderly patients owing to their poor prognosis. The cost of induction therapy alone may range from $5000-6000 in our setting. This is expected to swell further depending on the complications and length of hospital stay. Hence, many patients and their families opt for no treatment at all or supportive care only. Financial restrain is a very important deciding factor for any kind of treatment choice in Pakistan. Generally, palliative care includes red cell and platelet transfusions for anemia and bleeding episodes, and broad-spectrum antibiotic coverage for systemic infections. This treatment might assist in sustaining good quality of life in dying patients. In contrast to chemotherapy, this kind of supportive care costs $150-300 per month, which is still out of the financial reach of most patients. There is a lack of research, at a national level, addressing the important issue of management of elderly AML. It is desirable that the best therapeutic and cost-effective options be developed and practiced for resource-constrained countries. To achieve this end, we conducted this retrospective study to evaluate the therapeutic outcomes of AML in elderly patients, and to determine the most viable therapeutic option(s) by analyzing and comparing outcome of patients with and without standard treatment.

Methods. This retrospective analysis was carried out over 11 years from January 1997 to August 2008, at the section of Hematology and Bone Marrow Transplantation, Aga Khan University Hospital, Karachi, Pakistan. A computerized database search (using the International Classification of Disease Version 9.0) for obtaining anonymous information was conducted under the guidelines set by the institutional ethical review committee. Privacy and confidentiality of patients' diagnosis and management were ensured by non-inclusion of subjects' identification in computer files and patients' information being accessible to the principle investigator only. Patients aged 60 years or more with the established diagnosis of AML were included in the study. The cut off for age was selected based on previously accepted criteria for elderly AML.[6,12-14] Patients with AML less than 60 years of age and with leukemias other than AML were excluded from the study. The demographic and relevant data were retrieved using an in-house questionnaire maintaining full confidentiality for the patients. The data included clinicopathologic features, laboratory parameters, treatment protocols, complications of chemotherapy, remission status, and treatment outcomes. The cytogenetics were stratified based on a previously described classification system.[3] Patients were divided into 2 groups: those receiving chemotherapy and those who received palliative care only. Red cell and platelet transfusions were given to patients when their hemoglobin and platelets dropped below 8 gm/dl and 10 x 10^9/l. Complete remission (CR) was defined as normal peripheral blood counts with normocellular marrow with less than 5% blasts following induction chemotherapy. For remitters, disease free survival (DFS) was measured from CR to first event. Remission failures were described as either induction death (ID) secondary to treatment/marrow aplasia or resistant disease (RD) with failure to respond to induction regimes. Overall survival (OS) was measured from the time of presentation to death.

The data were analyzed utilizing version 16 the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA). The continuous data were expressed as mean ± SD. Kaplan and Meier studies were computed for survival analysis of 2 groups of patients, namely, those receiving chemotherapy versus palliative care only. Effect of variables such as age, gender, type of AML, cytogenetics, and white cell count on OS were evaluated by Cox regression analysis.

Results. A total of 276 patients were diagnosed and treated for AML during the study period. Two hundred

and twenty-one patients (80%) were below 60, while the remaining 55 (20%) were above 60. These 55 patients with elderly AML including 34 (61.8%) males and 21 (38.2%) females were eligible for the study. Thirty-four (61.8%) study participants had de novo AML, while 21 (38.2%) had secondary AML preceded either by MDS (n=15), or CML (n=6). Clinical presentation, baseline hematological, and biochemical parameters are summarized in **Table 1**, which shows that higher white cell counts and lower platelets were found in the oldest age group. The same group also showed the most deranged creatinine, lactate dehydrogenase, and uric acid levels. Results of cytogenetics were available for 25 patients (45.4%) only. Favorable (t15;17 [n=1], t8;21 [n=1]) cytogenetics were found in 2 patients, intermediate (no abnormality [n=12] t16;21 [n=1]) cytogenetics in 13 patients, and adverse (-5 [n=1], complex Del [5q], t7;17, -9, -14 [n=1], 48 XX del 4q21+10+Mar [n=1]) cytogenetics in 3 patients. Hyperploidy (n=2) and hypotriploidy (n=1) were also observed and were placed in the unknown group, as their predictive value was not known. Six patients who presented with AML secondary to CML had the t9:22/bcr-ABl genes.

Only 15 patients received various chemotherapy regimens. Induction with daunorubicin (45 mg/m^2) and Cytosar (100 mg/m^2 as continuous infusion for 7 days) was administered to 6 patients, one patient was induced with oral idarubicin (12 mg/m^2) and Cytosar (100 mg/m^2 as continuous infusion for 7 days), 2 patients received induction with mitoxantrone (12 mg/m^2) with Cytosar (100 mg/m^2 as continuous infusion for 7 days), and high dose Cytosar (1.5 g/m^2 twice daily for 3 days) was administered to 2 patients. Four patients with AML secondary to CML received imatinib mesylate (600-800 mg/day). The average number of blood products in the treated group was 89 units including packed red cells and platelets.

Following induction treatment, 8 patients had ID (70%), 2 had CR (20%), and one showed RD (10%), the other 4 patients were continued on imatinib mesylate (**Figure 1**). The patient with RD had prolonged neutropenia and finally succumbed to invasive fungal infection. The DFS in 2 remitters was 45 days in one patient who then received palliative care only, and 4 days in the other who unfortunately died of intracranial bleeding. The OS was 75.1 days (95% CI: 46.7-103.5) in all patients. The overall median survival was 23 days in males and 38 days in females. The patients receiving palliative treatment only, had a median OS of 58 days versus 23 days in the cytotoxic treatment group.

Forty patients (72%) including 26 primary and 14 secondary AML cases received non-curative treatment only, including transfusion support and antibiotic administration. The decision to receive such care was based on financial reasons, clinical judgment, and patient/family's desires. None of these patients received conservative or low dose chemotherapy. Median OS was 58 days (2-423) with 6/40 (15%) patients surviving >6 months. The patients with intermediate cytogenetics showed a median OS of 64 days, and those with adverse cytogenetics, 13 days (irrespective of treatment). However, the same could not be computed for the favorable cytogenetics group owing to missing data. At the end of the study period, 43 (78%) patients had expired. Eleven patients were lost to follow up, and were

Table 1 - Demographic and laboratory parameters at presentation in 55 elderly patients with AML.

Characteristics	60-69 years	70-79 years	>80 years	All patients
Patients	35	17	3	55
Hemoglobin g/dl	7.9	9.1	9.7	8.6 (3.6-14.2)
White blood count x 10^9/l	31.4	50.9	143	13.5 (1.0 - 257)
Platelets x 10^9/l	107	89	40	52.0 (6-1337)
LDH IU/l	1875	1399	3029	1413 (365-6613)
Creatinine mg/dl	1.1	1.4	2.5	1.2 (0.4-3.6)
Bilirubin mg/dl	2.4	0.88	0.6	0.9 (0.3-13)
ALT IU/l	40	43	30	27 (12-165)
Uric acid mg/dl	4.8	6.9	10.1	5.4 (2-20)
De novo AMLFAB				
M0	1	0	0	1
M1	1	1	0	2
M2	8	1	1	10
M3	1	0	0	1
M4	6	4	0	10
M5	2	2	0	4
M6	0	0	0	0
M7	0	1	0	1
Total	**19**	**9**	**1**	**29***

AML - acute myeloid leukemia, FAB - French American Classification, LDH - lactate dehydrogenase, ALT - Alanine transaminase, *5 cases were diagnosed as AML but not FAB classified

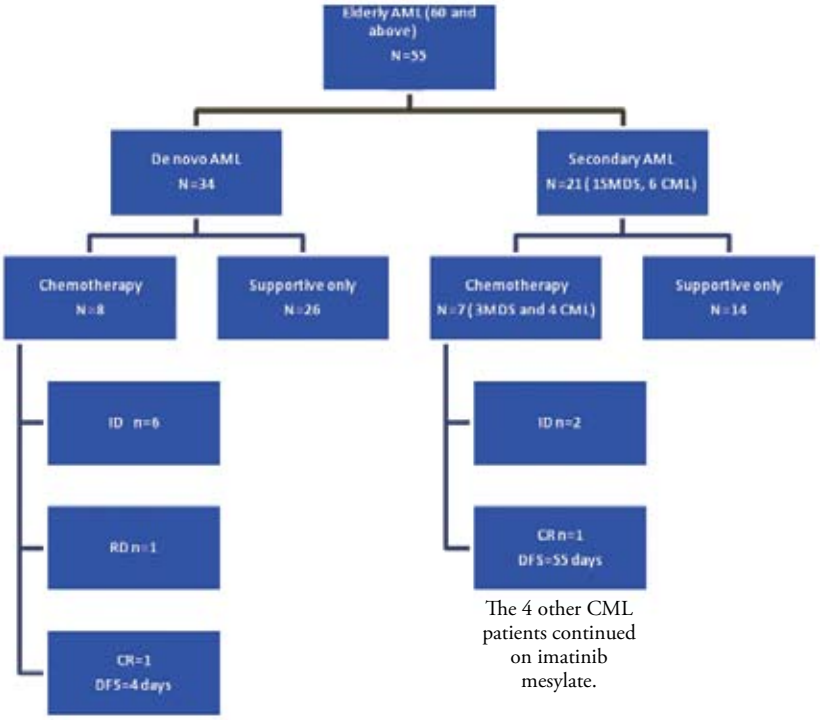

Figure 1 - Treatment modalities with their outcome in 55 acute myeloid leukemia cases. MDS - myelodysplastic syndrome, CML - chronic myeloid leukemia, ID - induction death, CR - complete remission, RD - resistant disease, DFS - disease free survival.

assumed dead. Only one patient who initially showed CR was alive with relapsed disease on last review. Causes of death for all treatment modalities combined included sepsis 18 (41.8%), cardiac arrest 6 (14%), pneumonia 5 (11.6%), intracranial bleed in one patient, and invasive fungal infection in one patient. The rest of the patients expired secondary to primary disease. Various parameters were compared for their influence on treatment response. On Cox regression analysis, age, gender (p=0.996 [95% CI: 0.485-2.069]), bone marrow cytogenetics, and type of therapy instituted were not statistically significant for any survival advantage. For FAB subtype the Cox regression analysis showed p=0.91 (95% CI: 0.79-1.05). There was also no survival difference in de novo or secondary AML (p=0.89 [95% CI: 0.31-2.77] for de novo, and p=0.74 [95% CI: 0.35-4.33] for secondary leukemias). There was no significant survival benefit in response to gender (**Figure 2**) and

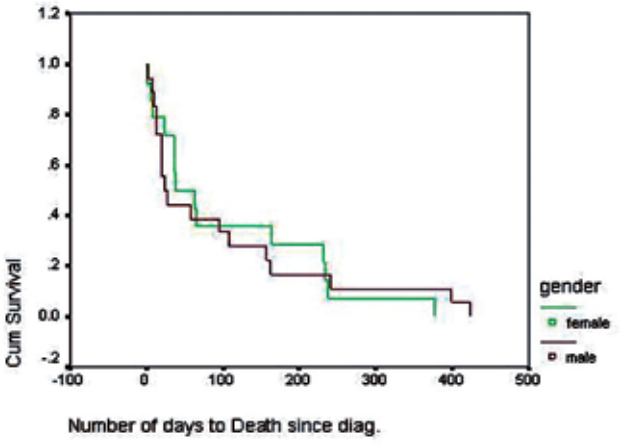

Figure 2 - Kaplan Meier survival function curve for gender.

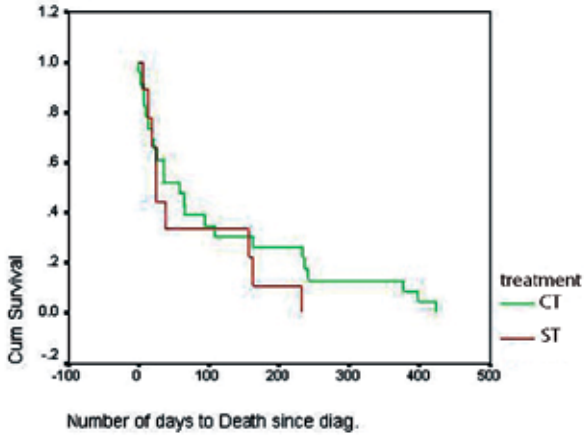

Figure 3 - Kaplan Meier survival function curve for patients who were treated with chemotherapy (CT) versus those who received only supportive treatment (ST).

those who were treated with chemotherapy versus those who received only palliative care (**Figure 3**).

Discussion. Our study reconfirms the poor outcome of elderly patients with AML. We reviewed 55 such patients presenting with de novo disease in 34, and secondary leukemia in 21 cases. Overall, this aged population represented 20% of all AML cases that were diagnosed during the evaluation period. This is in sharp contrast to reports from elsewhere, where elderly patients constitute 60% or more of all AML cases.[6] It is interesting that Kakepoto et al[8] in 2002 reported 74 cases of adult AML in the age range of 14-70 years from Southern Pakistan. However, the study did not explicitly reveal the total number of 60+ patients. Similarly, a report from Northern Pakistan indicated treatment responses of AML patients, but did not mention elderly AML.[10] It appears that in our setting, AML is more of a disease of the younger population than the elderly.

The overall median survival in all patients was 2.5 months, with almost two-thirds of our patients on palliative care only. It is noticeable, though not statistically significant, that patients on supportive therapy had longer survival (1.9 months) compared to those who received chemotherapy (0.7 months). This shows that irrespective of type of AML, karyotyping, and treatment regimen used, older patients were intolerant to cytotoxics drugs. We did not randomize the 15 patients for cytotoxic therapy, and because of the multiple drug regimens used, it is difficult to evaluate the outcomes in the treated group with any degree of confidence. Eight of 34 de novo cases received induction treatment, and nearly two-thirds suffered death during induction (including 4 who were given Cytosar and daunorubicin). This confirms that older patients cannot tolerate therapy induced hematological toxicity. Only one patient who achieved CR had received Cytosar + mitoxantrone, however, the DFS was 5 days only. Hence, none of the patients with primary AML in the treated group were alive and in remission at the time of review.

The diagnosis of primary versus secondary AML did not confer any appreciable survival benefit. Three patients who had AML preceded by MDS were treated with high dose Cytosar (one patient), and daunorubicin and Cytosar (2 patients). Only high dose Cytosar was effective in achieving CR with DFS of 55 days; the other 2 patients died during the induction phase. Contrary to our experience, Kahn in 1984[15] presented 40 cases of aged AML/MDS patients treated with full and reduced daunorubicin, cytosine arabinoside, and 6-thioguanine with resultant 28% CR, and a median OS of 4 weeks. This noticeable difference emphasized that elderly AML patients in our setting had poor tolerance to cytotoxic drugs. Latagliata et al[16] in 2006 presented 67 patients with elderly AML who received supportive care only with a median survival of 201 days. In contrast, the OS in the supportive treatment group was only 58 days in the present study, with the poor performance of patients being responsible for underlying differences. **Table 2** is a comparative analysis of this study with similar studies reported from around the world. This table shows that survival is poorer in our patient population compared with other published studies.

Parameters such as presenting white cell count, age, cytogenetic group, and secondary leukemia have been associated with better outcome in the treated group.[17] In this study, we did not observe any of these factors demonstrating a beneficial outcome on survival. The small sample size and use of different drug protocols in the current work could be responsible for the lack of association between prognostic variables and outcomes.

Study limitations. This was a retrospective review and was limited in terms of sample size and absence of data such as performance score for the patients. Results of cytogenetics were not available for more than half of the patients due to varied reasons. The treatment group included 15 patients only, and they too received different drugs protocols, which made the evaluation not only difficult, but also imperfect.

Table 2 - Comparison of various studies in elderly AML patients with their outcomes.

Study	Median age	No. of patients	IC group	Supportive group	Median survival weeks in IC group	Median survival weeks in supportive group
Sebban[18]	69	70	35	12	30	4
Lowenberg[19]	71	65	31	29	21	11
Orlandi[20]	103	67	52	23	14	NG
Bassan[21]	118	60	78	0	NG	NG
Baudard[22]	235	71	108	NG	NG	3
Ferrara[23]	70	79	22	41	16	20
Spataro[24]	74	74	51	0	36	Na
Present	55	67	15	40	11	16

AML - acute myeloid leukemia, IC - Intensive chemotherapy, NG - not given, Na - not available

We conclude that further large scale studies are needed for determining survival benefit in chemotherapy versus supportive care in elderly patients with AML.

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