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THE TREATMENT OF ACUTE MYELOID LEUKEMIA IN BRAZIL: PROGRESS AND OBSTACLES

Wolmar Pulcheri, Nelson Spector, Marcio Nucci, José Carlos Oliveira de Morais, Glicínia Pimenta, Halley Pacheco de Oliveira

Hematology and Pathology Services, University Hospital, Federal University of Rio de Janeiro, Brazil

ABSTRACT

Background. **Substantial progress has been made in the treatment of acute myeloid leukemia in the last two decades. We wanted to evaluate the outcome of intensive chemotherapy and the influence of recent therapy changes in underprivileged patients treated in a large urban public university hospital.**

Methods. **The records of all patients treated for acute myeloid leukemia from 1980 to 1993 were analyzed.**

Results. **109 patients were identified; 41 did not receive any treatment for the leukemia because of infectious and/or hemorrhagic complications of advanced disease. Median survival in this group was 4 days. The other 68 patients received one of two induction protocols: TAD from 1980 to 1985 (n=23) and ara-C plus daunorubicin from 1985 to 1993 (n=45). The complete remission rate was 56%, disease-free survival 24% and overall survival 15% at 13 years. Overall survival was better for patients treated with ara-C plus daunorubicin than with TAD (19% versus 8%, p=0.01). This is attributed to a reduction in infection mortality after ceftazidime and amikacin replaced cephalotin, carbenicillin and amikacin as the antibiotic regimen.**

Conclusions. **The most effective intervention in our population would probably be an improvement in the primary health care system, so that earlier diagnosis could allow the treatment of a larger fraction of patients.**

Keywords: acute myelocytic leukemia, acute nonlymphocytic leukemia, acute promyelocytic leukemia, developing countries

In the last two decades substantial progress has been made in the treatment of acute myeloid leukemia (AML). Advances have occurred as a result of the optimal utilization of chemotherapeutic agents, improved antimicrobial support, and specialized nursing care.[1-3]

Almost all published experiences in the treatment of AML come from referral centers in wealthy countries. It remains to be determined how the results produced in that *milieu* translate into the treatment of an unselected group of patients in a public hospital of a third world country, a setting in which the majority of the world's AML patients are likely to be treated.

In an effort to evaluate the results in this setting, we undertook an analysis of patients with a diagnosis of AML admitted to the Federal University of Rio de Janeiro Hospital over the past 13 years.

Materials and Methods

We reviewed the charts of all patients with primary AML, as defined by the French-American-British (FAB) classification system,[4] admitted between April 1, 1980 and January 15, 1993. Patients with a history of myelodysplasia, other antecedent hematologic cancers, and those previously exposed to cytotoxic chemotherapy or radiation therapy were excluded. FAB subclassification was based on a consensus slide review by four experienced hematologists (WP, NS, MN and HPO).

Until November 1985, the remission induc-

Correspondence: Nelson Spector, M.D., Rua Maria Angélica 326/501, Jardim Botânico, Rio de Janeiro, 22461-150 Brazil.
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tion regimen consisted of thioguanine 100 mg/m^2 orally every 12 hours on days 1 to 7, cytarabine 100 mg/m^2/d by continuous intravenous (IV) infusion on days 1 to 7; and doxorubicin 30 mg/m^2 on days 1, 2 and 3 (TAD). After November 20, 1985 induction was changed to ara-C 200 mg/m^2/7 days plus an anthracycline for three days, either daunorubicin 45 mg/m^2 or doxorubicin 30 mg/m^2 (7+3).[5] In this regimen, patients with residual leukemia at day 14 received a similar second induction course (5+2). Post-remission treatment evolved from 12 maintenance cycles in the early TAD era, according to the CALGB 7921 protocol, to 4 courses of infusional ara-C at a dose of 400 mg/m^2 and doxorubicin 30 mg/m^2 on days 1 to 3, and finally, in the last three years, to 2 courses of high-dose ara-C 1 g/m^2 every 12 hours on days 1 to 4 and doxorubicin 30 mg/m^2 on days 1 to 3. Patient follow-up continued through July 30, 1993.

During the entire treatment period patients with advanced age or with other complicating factors (general debility, evidence of very advanced leukemia with clinical instability due to infectious and/or hemorrhagic complications) were initially managed without chemotherapy in an attempt to prepare them for remission induction.

Management of infection was as follows. Up to 1988 antibacterial prophylaxis was not employed; starting in 1988 we began to administer quinolones routinely to all neutropenic patients over 15 years old. The use of antifungal prophylaxis (oral nystatin, ketoconazole or itraconazol) was decided by each physician on a case-by-case basis. Empiric antibiotics were given to all febrile patients (two or more axillary temperature readings above 38°C in a 24-hour period, or a single reading of 38.5°C or higher) with neutropenia (fewer than 0.5×10^9/L neutrophils) following an initial clinical and laboratory evaluation. Until October 1988 the combination of cephalothin, amikacin and carbenicillin was used; at this time the antibiotic regimen was changed to ceftazidime and amikacin. The inclusion of a third antibiotic (anti-gram-positive or anti-anaerobe) was dictated by clinical findings.

Antibiotic therapy outcome was evaluated at days 4 and 6, and at the end of treatment. Patients without gram$^+$ coverage and still febrile at day 4 were also given an anti-gram-positive antibiotic. If fever persisted at day 7, intravenous amphotericin B was introduced. Antibiotic and antifungal therapy was continued until the number of granulocytes was greater than 1×10^9/L.

Platelet support was provided in the case of bleeding, or whenever the platelet count was less than 20×10^9/L. Platelets were collected from randomly selected donors. Red cell transfusions were administered in order to mantain the hematocrit above 27% or on clinical grounds. Plasma transfusions for patients with disseminated intravascular coagulation were not routinely performed.

The chi-square test was used to compare differences in proportions. In addition, the 95% confidence interval for the difference between proportions was calculated when appropriate. The 95% confidence interval around differences between means was calculated for continuous variables. The Wilcoxon two-sample test was used to determine the p value. Survival curves are actuarial and were constructed using the product-limit method of Kaplan and Meier. The hypothesis that survival curves for patient subgroups were equal was tested with the Mantel-Cox statistic.

Results

Patient characteristics

A review of hospital records identified 109 patients admitted with a diagnosis of AML during the study period. Table 1 shows the characteristics of these patients. The mean time elapsed between onset of symptoms and diagnosis of AML was 45 days.

Patients excluded from further analysis

A total of 41 patients were admitted with a clinical condition that precluded immediate chemotherapy. The median age in this group of untreated patients was significantly higher than that of the treated group (52 years compared to

Table 1. Patient characteristics at presentation.

Characteristic	*Patients treated*	*Patients not treated*	*All patients*
No. of patients	68	41	109
Age (years), median	31	52	33*
Sex			
Male	34	23	57
Female	34	18	52
FAB classification			
M1	4	1	5
M2	19	9	28
M3	16	10	26
M4	16	10	26
M5	11	11	22
M6	1	0	1
M7	1	0	1
Hematocrit (L/L), mean	24.4	23.9	24
White cell count (x 10^9/L), mean	41.2	96.8	62.1**
Platelets (x 10^9/L), mean	106	63	90.5
Bleeding (%)	22 (32)	18 (44)	40 (37)
Infection (%)	19 (28)	15 (37)	34 (31)

* p = 0.0001; ** p = 0.002

31 years, p=0.0001), with ten of the 41 untreated patients presenting with age over 60. Their mean white cell count was also higher (96.8 $\times 10^9$/L compared to 41.2$\times 10^9$/L, p=0.002). The mean time between onset of symptoms and diagnosis was 52 days compared to 35 days in treated patients. More importantly, the median survival among untreated patients was only 4 days (range 0-61 days), attesting to the severity of their condition at admission to our hospital. All further analysis of treatment results was restricted to the 68 patients who actually received a remission induction regimen.

Treatment results

TAD was used for remission induction in the first 23 patients. Starting in November 1985 the 7+3 regimen was employed in the remaining 45. Complete remission (CR) was attained in 38 patients (56%) and was the most important factor for survival; of the 30 who did not enter CR1, none reached a CR with second-line treatment and their median overall survival was only one month. However, five of the 23 patients who received a high-dose reinduction course had a prolonged survival (5-24 months) even without attaining a complete remission.

The mean time to diagnosis was strongly correlated with response: 34 days in patients who attained CR and 76 days in those who did not (p=0.002, 95% CI for the difference, 11.1 to 72.9).

When the protocols TAD and 7+3 were compared, there was a non-significant trend towards higher CR rates with the 7+3 (62% versus 43%; p=0.14, 95% confidence interval –0.05 to 0.43). The overall survival for patients treated with 7+3, however, was significantly superior to that of those receiving TAD (19% versus 8%, p=0.01). Overall actuarial survival for the 68 treated patients was 15% at 13 years (Figure 1).

Among the 38 patients in CR1, overall survival was 13.7 months and disease-free survival 24% at 13 years. Nine patients remain alive in CR1, with a median overall survival of 49 months. Eight patients died in CR1 due to infectious complications of aplasia. Twenty patients relapsed, eight of whom entered a second complete remission, but only 3 are alive in CR2. One patient was lost to follow-up in CR1.

Infectious complications were the main cause of death in the 68 treated patients (39%). The infectious death rate was 55% (21 deaths in 40 patients) when the antibiotic regimen used for fever and neutropenia consisted of cephalotin, amikacin and carbenicillin, but this figure decreased to 21% (6 deaths in 28 patients; p = 0.005, 95% CI 0.09 to 0.5) when the association of ceftazidime and amikacin became the standard antibiotic regimen.

Discussion

One finding that stands out in this series is that no less than 37% of the patients admitted with AML were too ill to receive any treatment and had a median survival of only 4 days. We believe this to be the consequence of a group of factors present in Brazil's deficient health care

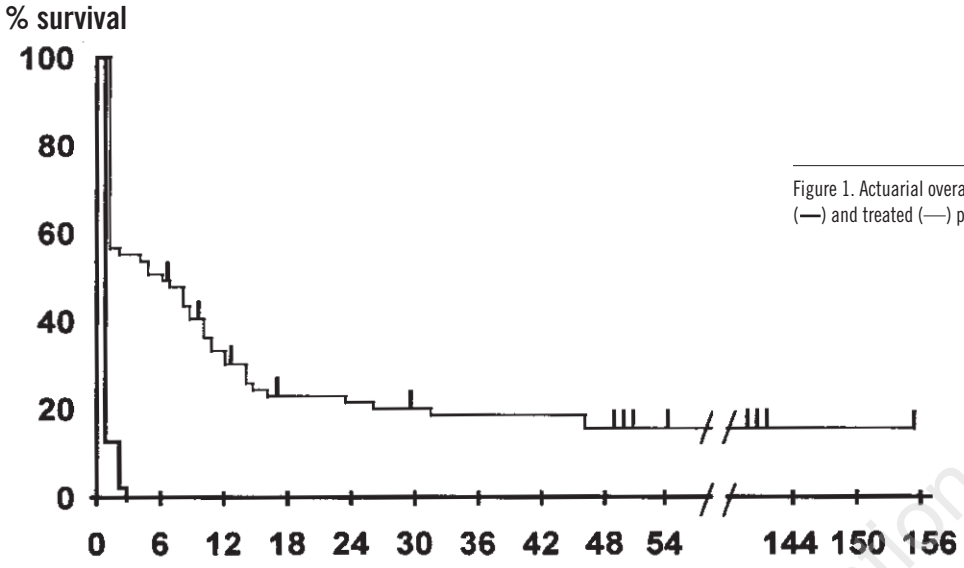

Figure 1. Actuarial overall survival in untreated (—) and treated (—) patients.

system; inadequate primary medical care results in delayed access to health professionals and in delayed recognition by health professional of the underlying severity of symptoms of fever and/or anemia. The mean time from onset of symptoms to diagnosis of AML was 52 days in untreated patients – certainly an excessive interval for this disease. This delay in diagnosis was also inversely correlated with the rate of CR. Another relevant aspect of poor primary health care is patient vulnerability to infectious complications resulting from chronic oro-dental or cutaneous pathologies.[6]

Attainment of CR at the first attempt is a well-known determinant of prolonged survival in AML.[7] In this series it was a *sine qua non*. We cannot easily explain why no patients entered CR if they failed the first induction regimen; however, typical limitations in our setting, such as a permanent shortage of anti-neoplastic drugs which makes it impossible to use high-dose ara-C at full measure, and the unavailability of second-line drugs in the country certainly hindered our efforts in this group of patients.

Patients treated with the 7+3 protocol had a better outcome than earlier ones who received TAD: overall survival increased from 8% to 19%. This improvement should be attributed mainly to the lower mortality from infections after ceftazidime replaced cephalotin and carbenicillin. When this change took place protocol 7+3 was already in use, and therefore it favored only the patients treated with this regimen. This shift to better antimicrobial coverage was certainly the most important achievement for AML patients in our hospital.

It is difficult to ascertain the present status AML treatment in developing countries. The obstacles that interfere with therapy in these countries make it hard for physicians to document their experiences in a way that makes them suitable for publication in international medical journals. Therefore most of these reports are published in local journals. Moreover, the critical issue of patient selection[8] is usually not discussed by the authors. The series often report the results of treated patients, failing to mention how many were excluded before treatment.

We conducted an electronic search for reports on the treatment of acute leukemia in developing countries in two medical databases: LILACS (Latin American and Caribbean countries, Panamerican Health Organization) and MEDLINE.

Few reports on the treatment of AML in Latin America were found.[9-13] Overall, the complete remission rate varied between 15% and 60%. Infection and hemorrhage were frequent during remission induction and contributed to

death in about 35% to 45% of the patients.

To our knowledge, the paper by Maia et al. is the only published series on the treatment of AML in Brazil.[13] Twenty-eight patients were treated with the TAD regimen. Eleven died during remission induction (38%) and 11 achieved complete remission. The overall actuarial survival at 48 months was 5.5%. The results of treatment in other Brazilian hospitals have been reported in national conferences. One representative abstract[14] summarizes the experience with 104 patients treated between 1987 and 1993 in a Brazilian University Hospital: the complete remission rate was 42%, with 6% of the patients dying before treatment and 46% dying during remission induction. The mortality during treatment-induced bone marrow hypoplasia in both series is much higher than the 19% recently reported by CALGB.[15] One of the reasons for this higher mortality might have been the inclusion of patients with very advanced disease who were not in adequate condition to undergo remission induction.

Results from other Latin American countries are heterogeneous, but quite comparable. Lora et al. report a complete remission rate of only 15% in the Mexican National Cancer Institute.[10] In a report from Colombia, only 22 out of 30 patients (73%) were eligible for treatment of AML-M4; complete remission was obtained in 34% of treated patients.[9] Martinez Fé et al. observed that in Cuba 82% of all deaths in adult patients with acute leukemia (myeloid and lymphoid) took place in untreated patients or during remission induction. Malnutrition was a complicating factor in 8 out of 22 patients (36%) treated for AML in another series from Mexico,[12] and the rate of complete remission achieved was very low (18%). Another group reported that malnutrition was the single most important prognostic factor in the treatment of children with acute lymphoblastic leukemia.[16] Nutritional status and other relevant aspects of patients' general health should be reported more fully by physicians from developing countries.

Very few papers from Asia and Africa could be found and most report epidemiologic data.[17-21] When treatment is mentioned, it is usually said to be inadequate due to socio-economic factors and to the lack of adequate facilities.

In the 68 patients treated in the present series, the CR rate was 56%, disease-free survival 24% and overall survival 14% at 13 years. These results are very similar to those reported from referral centers in the USA and Canada,[5,22] indicating the feasibility of standard AML treatment under substandard conditions such as lack of catheters, lack of isolation or two-patient rooms, and lack of second-line drugs. We found it mandatory to split the analysis of our patients into treated and untreated groups, lest this important finding be hidden by the inevitably poor results in the latter category.

An interesting demographic finding in this series is the proportion of patients who presented with the FAB-M3 subtype. Acute promyelocytic leukemia usually accounts for 5-10% of all cases of AML.[23] In our series, however, 24% (26 patients) presented FAB-M3. While we could not establish the presence of disseminated intravascular coagulation on the basis laboratory tests in this group of 26 patients, 19 of them died from hemorrhagic complications. This observation is in agreement with a recent study from the University of Southern California that reported Hispanic patients had a much higher incidence of FAB-M3 (40%) than other racial groups.[24] Also, in a study from Nicaragua with the support of Italian investigators, Corea et al.[25] reported that no less than 10 out of 17 children with AML presented with acute promyelocytic leukemia and had a high rate of bleeding complications.

We conclude that the main step towards better results in the management of AML in Brazil is an improvement in primary health care that will allow our patients a better chance of actually being treated for the disease. We also urge our peers in developing countries to better document and report certain essential data about leukemia treatment in this setting, including the nutritional status and other relevant aspects of the patients' general health at diagnosis, the number of patients excluded before treatment and the reasons for exclusion, and the time elapsed between onset of symptoms and diagnosis of AML. By doing this, we will be better

able to identify and compare the obstacles we face in this hard enterprise. The association of poverty and malignancy is an all-too-frequent human tragedy.

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