A Randomized Trial of Amsacrine and Rubidazone in 39 Patients With Acute Promyelocytic Leukemia

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Thirty-nine patients with untreated acute promyelocytic leukemia (APL) were randomly allocated to receive rubidazone (zorubicin) 200 mg/m²/d, days 1 to 4 plus cytarabine (Ara C) 200 mg/m²/d, days 1 to 7 (arm A, 21 patients), or amsacrine (Amsa) 150 mg/m²/d, days 1 to 4 plus Ara C 200 mg/m²/d, days 1 to 7 (arm B, 18 patients). Prophylaxis of disseminated intravascular coagulation was made by platelet transfusions and heparin. In case of leukemic resistance, patients received a second course with 2 days of rubidazone (arm A) or Amsa (arm B) and 3 days of Ara C. Patients who achieved complete remission (CR) received three consolidation courses with the two drugs used for induction and maintenance therapy for 3 years. Two patients in arm A and one in arm B were allografted in first CR. Initial characteristics were similar in both arms. In arm A, 18 patients (86%) reached CR, two had hypoplastic death, and one had leukemic resistance after two courses. In arm B, 12 patients (66%) achieved CR, two had early death (CNS bleeding, one case; ventricular fibrillation, one case), and four had resistant leukemia after two courses. The difference in CR rate between the two arms was not significant. In arm A, disease-free survival (DFS) showed a plateau at 54.3% after 34 months (95% confidence interval [CI], 32.1% to 74.9%), with eight CRs longer than 34 months. In arm B, DFS was significantly shorter ($P < .03$), showing a plateau at 16.7% after 38 months (95% confidence interval, 4.7% to 44.6%), and only two prolonged CRs were seen. The difference in DFS remained significant after censoring allografted patients and patients who died in CR (one in arm A, two in arm B). Our results suggest that Amsa-Ara C combinations may be inferior to anthracycline-Ara C combinations in the treatment of APL, because they seem to provide shorter DFS and, possibly, a higher incidence of initial leukemic resistance. However, studies with larger numbers of patients are required.

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ACUTE PROMYELOCYTIC leukemia (APL) is a specific entity among acute nonlymphocytic leukemias (ANLL), characterized by predominance of abnormal promyelocytes in the bone marrow (M3 subtype in the French-American-British [FAB] classification),[1,2] a propensity to disseminated intravascular coagulation (DIC),[3] and the presence, in most cases, of a specific translocation (15;17).[4] Since the introduction of anthracyclines, and particularly daunorubicin (DNR), prophylactic platelet transfusions, and heparin during induction, the complete remission (CR) rate has greatly increased in APL.[3,5] Several investigators have also reported longer remissions in APL as compared with other types of ANLL,[4,5] although this remains disputed.[6]

In 1981, Arlin et al[7] showed that amsacrine (Amsa) in combination with cytarabine (Ara C) was effective in relapsing APL. In 1984,[8] they reported that a combination of Amsa, Ara C, and thioguanine (6TG) (AAT) gave at least as high and possibly a higher CR rate than a combination of DNR, Ara C, and 6TG (DAT) in a randomized trial, and their findings were later confirmed in a larger number of patients.[9] These results prompted us, in 1984, to start a multicenter trial (protocol APL84) randomly allocating an anthracycline (rubidazone) and Amsa in previously untreated APL.

PATIENTS AND METHODS

Patient Entry

From October 1984 to September 1988, 41 previously untreated APL patients diagnosed in 10 French hematology centers were entered in the APL84 trial. Diagnosis of APL (classical hypergranular APL or microgranular variant form) was made according to FAB criteria.[1,2] Two patients were excluded: review of the slides in one case showed an actual diagnosis of M2 ANLL, and one patient died before the

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onset of treatment. All other patients were considered assessable. Cytogenetic analysis was performed at diagnosis in 25 cases and showed a t(15;17)(q22;q11) in 23 of them, with the remaining two patients having normal karyotype. Diagnosis of DIC was considered when, in the absence of significant liver disease, at least two of the following criteria were present: fibrinogen less than 1.8 g/L, prothrombin time less than 60% or factor V less than 60%, and fibrin split products greater than 40 μg/mL. All patients had DIC at presentation (31 patients) or developed DIC after the onset of chemotherapy (eight patients).

Treatment

Patients were randomly allocated to receive (Table 1) either a combination of rubidazone (zorubicin or 22050RP; laboratoires Roger Bellon, Nevilly Sur Seine, France) 200 mg/m²/d (intravenous [IV] push) from day 1 to 4 and Ara C 200 mg/m²/d (continuous infusion) from day 1 to 7 (arm A) or Amsa 150 mg/m²/d (1-hour infusion) from day 1 to 4 plus Ara C 200 mg/m²/d (continuous infusion) from day 1 to 7 (arm B). In arm A, rubidazone was used instead of DNR because, in the experience of our group,[10,11] it was as efficient in ANLL as DNR (200 mg/m² of rubidazone having shown the same antileukemic effect as 80 mg/m² of DNR) and was possibly less cardiotoxic. Rubidazone has also been used extensively in ANLL by another institution.[12] In case of failure to reach CR, patients randomly allocated to arm A received rubidazone 200 mg/m²/d for 2 days plus Ara C 200 mg/m²/d for 3 days, and patients randomly allocated to arm B received Amsa 150 mg/m²/d for 2 days plus Ara C 200 mg/m²/d for 3 days. If CR was not achieved with this salvage regimen, patients were considered as having resistant leukemia and were excluded from the study. Patients who achieved CR received three consolidation courses of rubidazone/Ara C (arm A) or Amsa/Ara C (arm B), followed by maintenance chemotherapy with mercaptopurine (6MP) and methotrexate (MTX) and reinduction courses of cyclophosphamide and mitoguazone (methylgag), during 3 years (Table 1). Two patients in arm A and one patient in arm B were allografted with a histocompatibility locus antigen (HLA)-identical sibling after one consolidation course 3 months after CR achievement.

During the induction phase, all patients received prophylactic heparin at 1.0 to 2.0 mg/kg/d and random or single-donor platelet transfusions in order to maintain platelet counts permanently above 50 × 10⁹/L.

Response

CR was defined as a decrease in the marrow blasts to 5% or less, normal marrow cellularity, a hemoglobin level greater than 11 g/dL, a granulocyte count greater than 1.5 × 10⁹/L, and a platelet count greater than 100 × 10⁹/L. Failures were classified as resistant leukemia, early death (death occurring within 7 days of the onset of treatment), and hypoplastic death (death occurring during the period of aplasia, after 7 days).

Disease-free survival (DFS) was measured according to the method of Kaplan and Meier,[13] and DFS curves were compared with the log-rank test.[14] The 95% confidence limits were evaluated by the asymmetric method of Rothman.[15]

The closing date of the study was March 10, 1991, 28 months after the last patient's inclusion.

RESULTS

Of the 41 patients, 21 were randomly allocated to arm A and 20 to arm B. Two patients (both in arm B) were excluded due to diagnosis error in one case, and death within the 24 hours before the onset of treatment in the other patient. The remaining 39 patients included eight children aged less than 15 years and 31 adults. Median age was 43 years (range, 1 to 64 years), and there were 20 males and 19 females. Initial characteristics of patients randomly allocated to arms A and B (Table 2) did not show significant differences.

In arm A, 18 patients (86%) achieved CR: 17 of them after one course and one after the salvage regimen. Two patients had hypoplastic death due to sepsis, and the last patient had resistant leukemia after the salvage regimen. This patient achieved CR with bisantrene but relapsed after 6 months and died. Seven of the patients who achieved CR relapsed after 1 to 34 months, one

Table 1. APL84 Protocol

Induction*	Consolidation†	Maintenance‡
Arm A		Continuous maintenance
Rubidazone 200 mg/m²/d × 4	Rubidazone 80 mg/m²/d × 2	Mercaptopurine 90 mg/m²/d
Ara C 200 mg/m²/d × 7	Ara C 200 mg/m²/d × 5	Methotrexate 12 mg/m²/wk
Arm B		Reinduction (every 3 months)
Amsa 150 mg/m²/d × 4	Amsa 80 mg/m²/d × 2	Cyclophosphamide 400 mg/m² day 1 and day 8
Ara C 200 mg/m²/d × 7	Ara C 200 mg/m²/d × 5	Methylgag 400 mg/m² day 1 and day 8

*Patients who did not achieve CR after the first course received an additional course with rubidazone 200 mg/m²/d × 2, and Ara C 200 mg/m²/d × 3 (arm A) or Amsa 150 mg/m²/d × 2 and Ara C 200 mg/m²/d × 3 (arm B).

†Three courses at monthly intervals.

‡Three years' duration.

Table 2. Initial Findings in the Two Treatment Arms

	Arm A (n = 21)	Arm B (n = 18)	P
Sex ratio	0.82	1.37	NS
Mean age, years (range)	43 (4-64)	44 (1-63)	NS
Mean no. leukocytes × 10⁹/L (range)	10 (0.3-63)	14.4 (0.9-57)	NS
Mean no. platelets × 10⁹/L (range)	25 (9-198)	40 (3-207)	NS
Mean fibrinogen level, g/L (range)	1.4 (0.2-2.7)	1.3 (0.2-3)	NS
Leukocytes > 10 × 10⁹/L	5	6	NS
Microgranular APL variant	1	2	NS
DIC	20	19	NS

Abbreviation: NS, not significant.

patient died in CR from liver cirrhosis (attributed to alcohol abuse that existed before treatment) after 18 months, and 10 patients remained in CR after 31+ to 74+ months, including the two patients allografted in first CR. DFS showed a plateau at 54.3% after 34 months (95% CI by the asymmetric method of Rothman, 32.1% to 74.9%), with eight CRs longer than 34 months (Fig 1). No major acute or chronic drug toxicity (especially cardiac) was seen, apart from the possible exacerbation of liver failure in the patient with liver cirrhosis.

In arm B, 12 patients (66%) achieved CR: 11 of them after one course and the remaining patients after the salvage regimen. Two patients had early death: due to CNS hemorrhage on the third day of treatment in one case and ventricular fibrillation after the fourth infusion of Amsa in the other (kalemia at the time of Amsa infusion was 3.7 mEq/L). Four patients had resistant leukemia after the salvage regimen: three of them were treated with bisantrene, and two achieved CR, of 15 and 41+ months' duration, respectively. The remaining patient was crossed over to arm A, and reached CR, of 10 months' duration. Among the patients who achieved CR after Amsa-Ara C, eight relapsed after 1 to 38 months, two died of sepsis in CR after 1 and 9 months, respectively, and two patients (including the patient allografted in first CR) remained in CR after 55+ and 60+ months. Therefore, DFS showed a plateau at 16.7% after 38 months (95% CI, 4.7% to 44.6%). Apart from the case of ventricular fibrillation, no major drug toxicity was seen in arm B.

The CR rates did not significantly differ between arms A and B ($\chi^2 = 1.14, P > .2$). However, DFS was significantly longer in arm A as compared with arm B ($P < .03$; Fig 1). Because two patients were allografted in arm A versus only one in arm B, and because two patients died in CR in arm B versus only one in arm A, CR duration was also analyzed after censoring patients who died in CR at the time of death and after censoring allografted patients at the time of their transplant. This resulted in a plateau at 53.4% in arm A (95% CI, 29.6% to 75.8%) and 11.8% in arm B (95% CI, 2.1% to 45%) (Fig 2). The difference between the two arms remained significant ($P < .05$).

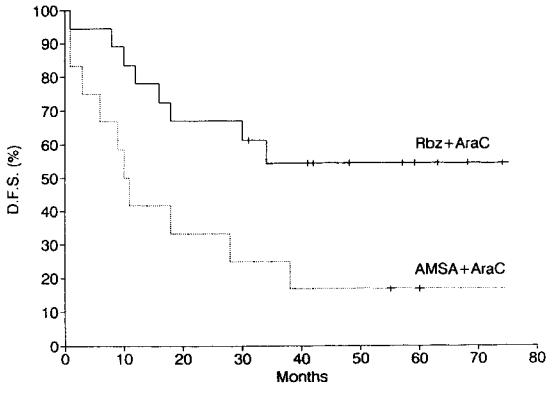

Fig 1. DFS by treatment arm. Tick marks represent patients alive in CR (two patients had the same DFS of 31 months, giving only one mark); Rbz, rubidazone.

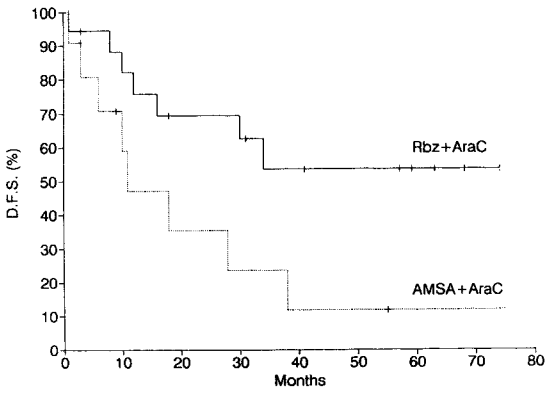

Fig 2. DFS after censoring allografted patients and patients who died in CR.

DISCUSSION

In this multicenter trial of treatment of APL, a very low incidence of fatal bleeding during induction therapy (one in 39 patients) was seen. This is lower than the incidences of 9% to 25% reported in recent large series of APL.[4,6,9,16-20] However, Arlin and Feldman,[21] also recently reported only one fatal hemorrhage in 55 induction attempts and attributed this low incidence to the vigorous platelet policy they applied, which was also applied in our study. The beneficial role of heparin, although probable,[3,4,16,17] remains more controversial.[22,23]

Using AAT, Arlin et al[8] obtained CRs in seven of seven patients with previously untreated APL, whereas only five of nine patients treated with DAT reached CR. Results of this randomized trial between Amsa and DNR were subsequently updated by Cunningham et al,[9] showing 11 CRs in 12 patients (92%) with AAT and seven CRs in 13 patients (54%) with DAT. Although the difference was not significant, a benefit of Amsa over DNR was suggested by these two studies. In the report by Cunningham et al, however, the seven CRs with DAT were all obtained after one course. Patients who failed to achieve CR after one course were crossed over to AAT. In contrast, three of the 11 CRs with AAT were only obtained after a second course of AAT, with those three patients not having been crossed over to DAT after failure of the first course of AAT. Therefore, adequate comparison between the two treatment arms could only be made by comparing results after one induction course: seven CRs in 13 patients (54%) with DAT and eight CRs in 12 patients (66%) with AAT.

In our patients, no significant difference in CR rate was found after induction with rubidazone-Ara C or Amsa-Ara C. However, four patients in the Amsa arm (21%) had resistant leukemia, as compared with only one in the rubidazone arm. APL is very sensitive to DNR,[5] which, when administered alone at sufficiently high doses, gives CR rates of 65% to 85%.[16,19,20,24,25] In most reported series of APL treated with DNR (with or without Ara C), fewer than 5% of the patients had resistant leukemia, with failure to reach CR being generally due to bleeding complications.[4-6,16-20,24-26] In the present report, the anthracycline antibiotic we used was 22050 RP (rubidazone) instead of DNR, because rubidazone, in the experience of our group, is as effective as DNR in ANLL and may have less toxicity, especially cardiac toxicity.[10,11] Results obtained in the rubidazone arm confirm that this drug, in combination with Ara C, is highly effective in APL and, like DNR, is rarely associated with leukemic resistance. Idarubicin, another anthracycline, has also shown high antileukemic activity in APL when used alone in 27 APL patients, with a CR rate of 81% and resistant leukemia in only one patient.[27] The relatively high incidence of resistant leukemia we observed with Amsa raises the possibility that this drug may be less effective than anthracyclines in inducing CR in APL, but demonstration of this point would require larger numbers of patients.

A major finding in our patients was the significantly shorter DFS in the Amsa arm as compared with the rubidazone arm. In the rubidazone arm, the DFS curve reached a plateau at 54.3% after 34 months, with no subsequent relapse. Prolonged DFS has been reported in many series of APL treated with anthracyclines,[4,16,19,26,28] and, although this has not been demonstrated in a randomized trial, the use of prolonged maintenance chemotherapy (as in the present trial) may prolong DFS in APL.[16,25,29] In the Amsa arm of our trial, however, DFS was significantly shorter than in the rubidazone arm. Because of a slight imbalance in the number of allografted patients and patients who died in CR between the two treatment arms, CR duration was also assessed after censoring those patients (at the time of transplant and of death, respectively), but the difference remained significant. In the experience of Cunningham et al,[9] remission duration with AAT was difficult to assess, because four of 11 complete responders underwent allogeneic bone marrow transplantation. Of the seven remaining patients, three relapsed and four remained in CR after 42+ to 84+ months. On the other hand, of the seven patients who achieved CR with the DAT regimen, only one was allografted, and the other six relapsed. Although the difference was not significant, these results suggest that AAT might produce longer CR than DAT. However, Cunningham et al had obtained more prolonged DFS in their earlier DAT protocols, and suggested that the poor DFS obtained in their last DAT protocol could have been due to less intensive and shorter consolidation and maintenance therapy.

The good results (three CRs obtained in four treated patients) of bisantrene as salvage chemo-

therapy in patients who failed to achieve CR after two courses of rubidazone-Ara C or Amsa-Ara C are noteworthy. Toxicity was limited in our study, with the exception of ventricular fibrillation due to Amsa in one patient, whose kalemia was in the lower range of normality. At least 31 cases of serious ventricular arrhythmias leading to cardiopulmonary arrest have been reported with Amsa, and 37% of those patients had hypokalemia.[30]

In conclusion, results of this multicenter randomized trial confirm that a very low incidence of deaths due to bleeding can now be obtained at the initial phase of APL by using intensive platelet support and, possibly, heparin. Prolonged DFS can be obtained with anthracycline-Ara C combinations, adequate consolidation therapy, and, possibly, prolonged maintenance therapy. Our results, contrary to those reported by Arlin et al[8] and Cunningham et al,[9] do not support a similar effectiveness of Amsa-containing regimens in APL. Although significant differences in DFS were seen in our series between Amsa and rubidazone, the number of patients remains limited, and a larger series of patients would be required to settle this issue.

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