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Acute Promyelocytic Leukemia: Results of Treatment by Daunorubicin

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Daunorubicin induces complete remissions in about 50% of patients with acute promyelocytic leukemia. The median duration of these remission is 26 mo. Failures are mainly due to hemorrhages as a result of disseminated intravascular coagulation during the first 5 days (25%) or due to sepsis during the second and third week (25%). Long-term survivals are more frequent than in the other acute granulocytic leukemias.

FOLLOWING THE FIRST REPORT of acute promyelocytic leukemia,[1] we gave a complete description of this variety of acute leukemia in 20 patients.[2] The distinct cellular morphology, severity of hemorrhages secondary to fibrinopenia, as well as its fulminant course, were characteristic and led to a separate classification of acute promyelocytic leukemia (APL). Since 1967, we have used daunorubicin in the treatment of 44 patients with APL and in this report we compare the results of such treatment with the course of 36 patients treated up to 1967 before the drug was available. The striking sensitivity of APL to daunorubicin has completely changed its prognosis and will undoubtedly lead to renewed interest in this unique form of acute leukemia.

MATERIALS AND METHODS

This report includes 80 patients with APL; 73 in our department and 7 patients of Professor B. Dreyfus; all were seen between 1963 and 1971. The limited number of patients confirms the relative rarity of this disease; approximately 5% of all acute leukemias. The age and sex distribution are shown in Table 1. As was pointed out

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Table 1. Distribution of Cases in Promyelocytic Leukemias

	Males		Females		
	Before Daunorubicin	After Daunorubicin	Before Daunorubicin	After Daunorubicin	Total
Adults	9 (1 CR)*	18 (5 CR)	11	22 (11 CR)	60 (17 CR)
Children < 20 yr	5 (2 CR)	3 (2 CR)	11 (1 CR)	1 (1 CR)	20 (6 CR)
Total	14 (3 CR)	21 (7 CR)	22 (1 CR)	23 (12 CR)	80 (23 CR)

*CR, complete remission.

previously, extramedullary infiltration is rare in APL,[3] and the diagnosis depends in all patients on the cytologic studies of bone marrow smears.[4]

Promyelocytes are characterized by an immature, eccentric, and not very large nucleus that is often irregularly shaped and obscured by numerous cytoplasmic granules. These granules are the most important characteristics of the cell; they may be small and form a sort of red dust that hides the cytoplasmic basophilia, may be large resembling normal azurophilic granulations, or both forms can be present. Large rod-shaped Auer bodies are not uncommon. These promyelocytic cells may constitute the entire blastic proliferation, or they may be associated with undifferentiated cells. Cytochemical studies show myeloperoxidase positivity and A-SD chloronaphtol acetate esterase positivity, as well as nonspecific esterase activity; malignant promyelocytes share these features with normal promyelocytes.

Before 1967, when daunorubicin became available, we treated 36 patients with various combinations including: prednisone and 6-mercaptopurine (6-MP) in 28 cases; prednisone, 6-MP, and methotrexate (five cases); or 6-MP and methyl-glyoxal guanyl hydrazone (GAG) in three cases.[5] After 1967 all patients were treated with daunorubicin, and the following schedule can be recommended: four daily injections of 2 mg/kg or 60 mg/sq m, a rest of 3 days, and further treatment on the basis of the cytologic picture of the bone marrow. Two difficulties should be pointed out. Because of rapid coagulation, the smear may sometimes give the impression of medullary aplasia before it has actually occurred, which may lead to treatment being stopped too soon; conversely, certain innocuous nonfunctional promyelocytes can persist for some time, and the relatively high proportion of these in a poor marrow can lead to treatment being prolonged, thus producing irreversible aplasia.[6] The median dose necessary to obtain a response was 300 mg/sq m.

RESULTS

The over-all results show a striking increase in complete remissions (CR) after daunorubicin (Table 2). Eleven patients died within 5 days after diagnosis, the time necessary for bone marrow hypoplasia to occur if dauno-

Table 2. Promyelocytic Leukemias: Overall Results

	Before Daunorubicin	After Daunorubicin
Death within 5 days after diagnosis	6	11 (5 deaths before treatment)
Complete remissions	4	19
Death in aplasias without blasts	1	9
Death with persistent blastosis	25	5
Total	36	44
	30 patients assessable	39 patients treated by daunorubicin
Rate of complete remission	4/30 (13%)	33 patients assessable 19/34 (55%)

Table 3. Progression of Promyelocytic Leukemias With Time

Day	Death From Hemorrhage	Death From Septicemia	Complete Remission
0–5	11	—	—
5–10	1	3	—
10–20	1	6	2
20–30	—	3	12
30–40	—	—	5

rubicin had been given immediately. All of these deaths were due to massive cerebromeningeal hemorrhages (Table 3). Before 1967 there were only four CRs in 30 assessable patients (13%), as compared to 19 of 33 (58%) thereafter. Before daunorubicin the risk of hemorrhage remained great even after the fifth day, 23 of 26 died of bleeding diathesis, whereas after 1967 this risk became negligible. On the other hand, more daunorubicin-treated patients died with septicemia.

Since hemorrhages play such a preeminent role in APL, a brief survey of their physiopathologic meaning appears in order. They were initially ascribed to fibrinolysis[7] and subsequently, Rosenthal emphasized fibrinogenopenia, abnormal clot formation, increase of factors VIII, IX, and XI, and absence of fibrinolysis.[8] Since that time, new techniques have been developed that enable recognition of fibrinogen split products (FR antigens) and of soluble complexes (SC) that result from the action of thrombin on fibrinogen.[9-11] The frequent positivity of these tests in APL makes disseminated intravascular coagulation (DIC) the most common cause of the hemorrhages. However, the problem remains complicated. Fibrinolysis and DIC cannot always be excluded, which explains the encouraging results sometimes noted with heparin as well as aminocaproic acid.[12]

We have investigated several factors that may have influenced the course of the disease in the 44 patients seen since 1967.

Environmental Factors

Age and sex are considered in Fig. 1. It appears that females are more

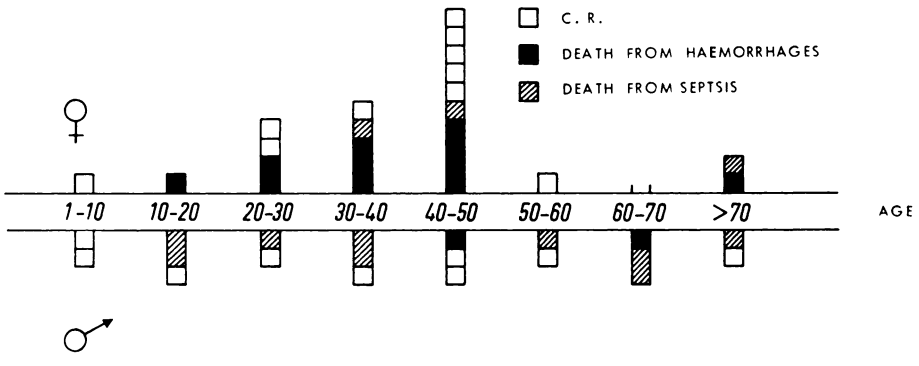

Fig. 1. Results in relation to age and sex in 44 cases promyelocytic leukemia.

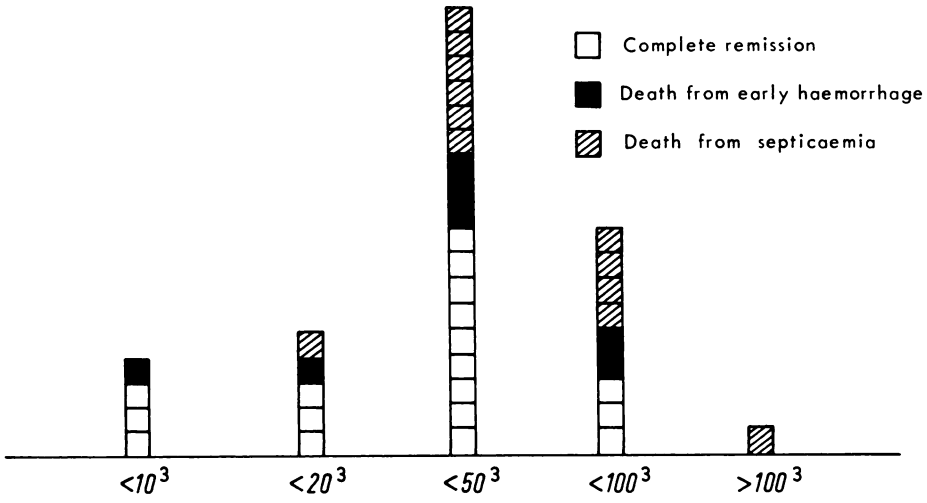

Fig. 2. Initial platelets count.

susceptible to hemorrhage than males, but that males run a higher risk of infection. Remissions were possible at all ages. The initial number of platelets had no significant influence on the prognosis (Fig. 2).

The initial leukocyte count (Fig. 3) and fibrinogen level (Fig. 4) are important. The risk of hemorrhage is low in those patients with a low leukocyte count, but as previously mentioned, there is a high incidence of patients with a low leukocyte count in promyelocytic leukemia. In those patients whose fibrinogen was less than 1 g, there was a high incidence of bleeding. There was an inverse relationship between the fibrinogen and white blood cell count, confirming the report by Quigley.[13] This was also suggested by the fact that hemorrhages occur in the first 5 days, before medullary aplasia could set in.

Therapeutic Factors

The necessity of destroying promyelocytic cells as soon as possible in order to escape the fatal hemorrhages explains why daunorubicin, the one drug that

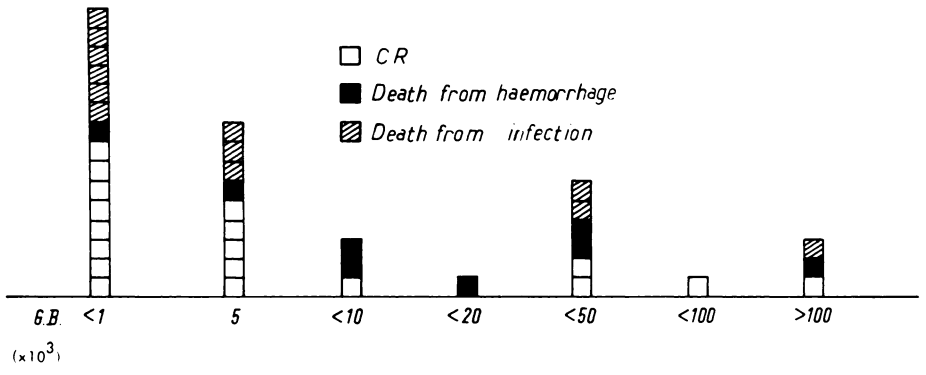

Fig. 3. Initial leukocyte count.

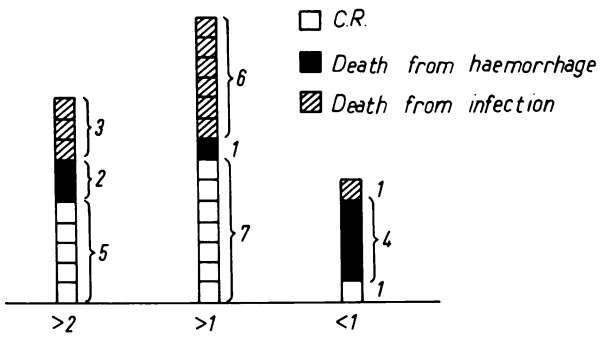

Fig. 4. Initial fibrinogen level.

causes rapid aplasia, is the emergency treatment in every case of APL. Treatment must follow the diagnosis without delay. There is simply no time to wait for usual measures, such as hyperdiuresis and allopurinol, to take effect. Since APL does not cause major infiltrations, the risk of uratic nephropathy is low compared to that of bleeding.

Figure 5 shows the total dose of daunorubicin in relation to the results. The important and most disturbing lesson to be learned from this is that the first two doses do not give much protection against the risk of hemorrhage. The possibility that initial cell lysis led to increased circulating thromboplastin cannot be ruled out. In two patients, soluble complexes, which had not been found before, appeared after the first injection of daunorubicin.

In a disease with frequent consumption coagulopathy, heparin administration would appear logical.[14,15] Biological evidence of DIC was found in 18 patients (Table 4). It could have been present in others, but the study could not be done. Heparin was used in 9 of 18 patients, and four of the nine died from hemorrhage, despite the correction of hypofibrinogenopenia and the disappearance of FR antigen and SC. On the other hand, five patients, who received no heparin, had a rapid return to normal fibrinogen levels in spite of persistent FR antigen and SC, and they achieved a complete remission.

Study of Complete Remission and Survival

Before 1967, only four patients had a complete remission after at least 1 mo of treatment. In one child the remission lasted 4 mo, but in the others relapse and death occurred within 2 mo.

With daunorubicin the complete remission starts most often after the third week, following a medullary aplasia of about 15-days duration. Three patients

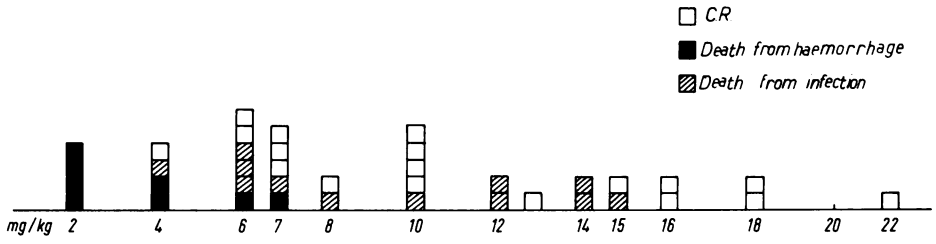

Fig. 5. Total dose of daunorubicin in relation to results.

Table 4. Heparin Therapy

	Total No. of Patients	No Serial Coagulation Study	Biological Evidence of DIC*	Heparin Therapy
Complete remission	19	11	8	3
Death from hemorrhage	13	9	4	4
Death from infection	12	6	6	2

*In most cases, disseminated intravascular coagulation (DIC) was proved by FR antigens and by soluble complexes. In some cases, however, soluble complexes were not studied or were not found because of technical problems.

benefited from white cell transfusions during their aplasia. A word of caution: myeloid regeneration can involve temporary excess of promyelocytes, but these appear cytologically different from the pathologic promyelocytes. Hemostatis is normal throughout the remission.

Remission reinforcement with daunorubicin and methyl-GAG was given to 17 of the 19 patients, but it is not possible to assess the importance of this reinforcement. All patients received remission maintenance therapy with 6-MP and methotrexate at starting doses of 90 mg/sq m/day and 15 mg/sq m/wk, respectively. In practice, these doses had to be adjusted for hematologic tolerance in most patients. In three patients, whose hematologic balance was kept normal with low maintenance doses, benign viral infections produced transitory hypoplasia affecting all three cell lines.

The duration of the complete remissions is remarkably long (Fig. 6), a median of 26 mo as compared to the 7 mo median in the acute myeloblastic leukemias. There was no relapse before the fifth mo. Four patients have been in remission for more than 4 yr and are leading normal professional and family lives.

In cases of relapse, the cytologic picture was identical to that of the first episode, and death was due to cerebral hemorrhage in three patients and to sepsis in five.

DISCUSSION

The striking activity of daunorubicin in APL illustrates important relationships between a given drug and a given cytologic variety of acute leukemia. The dramatic difference in survival of patients who achieved or failed to achieve a complete remission emphasizes the need of avoiding the risks of the remission induction period. The most dangerous one is that of hemorrhage, and massive platelet transfusions are imperative in APL.

In spite of the frequent finding of FR antigen and SC, suggesting the presence of DIC, the indication for heparin therapy remains controversial and should perhaps be restricted to the high-risk patients, those with an initial fibrinogen level of less than 1 g/100 ml.

In contrast to the risk of hemorrhage as a result of DIC, so specific for the promyelocytic form of acute leukemia, the risk of infection is common to all granulocytic forms. To prevent infection, oral administration of nonabsorbable antibiotics and aseptic environment (not available in our department) can be

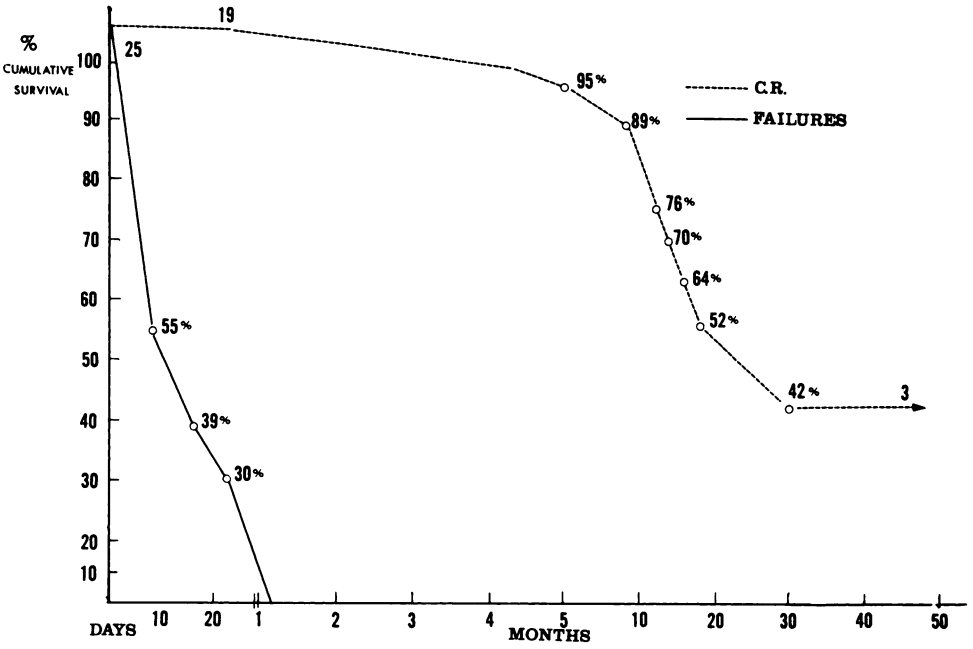

Fig. 6. Survival times of patients with complete remissions and of therapeutic failures in promyelocytic leukemia.

considered; to reduce it, the precise chemotherapeutic dose adjustment must be found; to combat it, white cell transfusions and bacteriologic studies as a guide for antibiotic therapy must be carried out.

Acute promyelocytic leukemia, while sharing the problems of all granulocytic leukemias, has also some very specific aspects. While until a few years ago, its fulminant course was the main characteristic, the expectancy of an unusual number of long-term survivals is now probably the most interesting and recent feature.

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