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Treatment of Acute Myeloid Leukemia and Myelodysplastic Syndrome by Low Dose Cytosine Arabinoside *

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A. Introduction

Recent reports by Baccarani and Tura [2], Moloney and Rosenthal [9], and Housset et al. [6] prompted us to treat 12 acute myeloid leukemia (AML) and 4 myelodysplastic syndrome (MDS) patients with low dose cytosine arabinoside (Ara-C). In all patients, conventional chemotherapy was contraindicated because of previous inefficacy, advanced age, or heavy comorbidity. Ara-C was given in a dose of 10 mg/m² s.c. every 12 h for 14–28 days. All patients received one or two courses. If bone marrow revealed more than 5% blasts 1 week after the end of therapy, another course was started. Patients who obtained a complete or partial remission received maintenance chemotherapy with low dose Ara-C (10 mg/m² s.c. every 12 h) for 8 days every 3 or 4 weeks.

B. Results

Nine patients obtained a complete remission (CR), three a partial remission (PR), and four did not respond. Clinical data of the nine patients with complete remission are summarized in Table 1. The three patients who obtained a partial remission were: a 70-year-old woman in first relapse of M_1 leukemia after TAD chemotherapy; a 31-year-old woman in first relapse of M_4 leukemia after TAD chemotherapy; and a 51-year-old man with RAEB who did not respond to TAD chemotherapy. Karyotype was normal in the two women and abnormal in the man (43,X0,del 2 (p14), −8, −9, +del 12 (p11), 17p+, −20). Duration of PR in the three patients was 1 month (death from unrelated disease), 4+, and 12 months.

Four patients did not respond. The first was a 37-year-old man in first relapse of M_4 leukemia with cutaneous, renal, and myocardial leukemic involvement. Chromosome analysis revealed a near hypotetraploid pattern. The second patient was a 43-year-old woman with M_2 leukemia following RAEB resistant to TAD chemotherapy. She had a normal karyotype. The third patient, a 73-year-old man, had AML following polycythemia vera. His karyotype was abnormal (46, XY, +3p+, −9, 20q−). The fourth patient was a 62-year-old woman with RAEB and the pathologic karyotype 46,XX,5q−.

In all patients, treatment was well tolerated without nausea, vomiting, hair loss, or hepatic toxicity, but in all of them peripheral pancytopenia developed or worsened under therapy, necessitating multiple red cell and platelet transfusions. In spite of pronounced neutropenia and thrombocytopenia, no serious infectious or hemorrhagic problems were encountered. Bone marrow cytology revealed hypoplasia or aplasia in most patients, but in some patients it remained normocellular with signs of differentiation. The first sign of bone marrow recovery was a rapid rise in platelets about 10 days after the end of therapy.

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Table 1. Clinical data of the nine patients who obtained a complete remission

Case	Sex, age	FAB classification	Blood leukocytes ($\times 10^9$/l)/ % blasts	Bone marrow % blasts	Karyotype	Pretreatment	Number of courses/ duration (days)	Duration of CR (months)
1	M,66	M_1 post-RAEB?	2.5/0	62	46,XY	None	2/21	2
2	M,70	M_2 post-RAEB	2.3/6	30	46,XY	None	2/28 and 14	4
3	M,81	Acute, megakaryoblastic leukemia	5.4/31	58	46,XY	None	1/21	7
4	F,74	M_2	1.1/37	45	46,XX	None	1/23	1+
5	M,61	M_1	3.5/0	65	46,XY	NR after Pred-Dauno-Onc-Aspar	1/15	9
6	F,69	M_1	11.3/46	73	46,XX	First relapse after TAD	2/21	15+
7	F,50	M_4 Eo	2.4/0	35	46,XX	Second relapse after TAD	1/27	7
8	M,75	RAEB	10.1/9	6	47,XY, +8	None	2/21	12+
9	F,75	RAEB in transformation	1.3/0	22	46,XX	none	1/21	3+

C. Discussion

Stimulated by the in vitro studies of Lotem and Sachs [7] and Sachs [11], who showed the capacity of low dose Ara-C to induce differentiation in certain leukemic cells, Baccarani and Tura [2], Moloney and Rosenthal [9], and Housset et al. [6] were the first to obtain complete and partial remissions with low dose Ara-C in patients with AML and MDS. Later, these results were confirmed by Andrey et al. [1], Baccarani et al. [3], Castaigne et al. [4], Manoharan [8], Mufti et al. [10], Wisch et al. [13], and Solal-Celigny [12], whereas Haagenbeek et al. [5] did not find any favorable effect of this type of treatment.

Our results in 16 patients with 9 CR and 3 PR argue strongly in favor of a convincing effect of low dose Ara-C in certain types of AML and MDS. In addition, compared with conventional chemotherapy, this type of treatment was well tolerated without major complications, in spite of considerable pancytopenia. Further studies must find out which patients are candidates for low dose Ara-C and how results, especially duration of CR, can be improved. Based on our experience during the last few months, we think that patients with rapidly progressive disease are not candidates for this type of treatment whereas patients with slowly progressive disease may benefit from low dose Ara-C. It seems noteworthy that 10/11 patients with a normal karyotype had a response and only 2/5 patients with a pathologic karyotype.

So far, the mechanism of this type of treatment is unclear. Pancytopenia and bone marrow hypoplasia argue in favor of a cytostatic effect. On the other hand, our series included some patients without pronounced bone marrow hypoplasia and with cytologic signs of maturation of blasts. This phenomenon was also observed by Castaigne et al. [4]. The mechanism of low dose Ara-C could be approached by diffusion chamber studies, immunologic markers of differentiation, and cytogenetic studies. Unfortunately, there was only one patient with a chromosomal anomaly (47,XY,+8) who achieved CR. In remission, he had a

normal karyotype. In this patient, bone marrow aplasia was severe, suggesting a cytostatic effect of therapy.

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