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Preliminary Results of a Phase II Trial of Aclacinomycin in Acute Leukaemia and Lymphosarcoma

An Oncostatic Anthracyclin that is Rarely Cardiotoxic and Induces no Alopecia

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Summary. *A phase II trial of which preliminary results are available for 22 patients indicates that aclacinomycin applied in a continuous modality induced complete and partial remission in four of nine patients with acute lymphoid leukaemia that was resistant to all previously available drugs, and in four of eight patients with stage V lymphosarcoma (leukaemic).*

Bone-marrow toxicity was the major side-effect.

Only one patient of 20 suffered from cardiac toxicity; no one had alopoecia. This very low incidence of myocardial lesions and the absence of hair loss had been predicted, respectively, by our electron microscope study of the myocardium and the light electron microscope study of the skin of golden hamsters [7], a test that detects frequent severe myocardium and skin toxicities for adriamycin and some anthracyclin analogues such as detorubicin, which was found to be toxic in a high percentage of patients in a clinical trial conducted by the E.O.R.T.C. Clinical Screening Group [8].

Introduction

Daunorubicin (DRB) [1, 9] and adriamycin (ADM) [4] have been widely used, the first in leukaemia, the second in leukaemia, haematosarcoma, and solid tumors, with remarkable oncostatic efficiency. They have been used either singly or in combinations [5]. However, in all conditions, their use has been limited because of two major side effects: (a) alopoecia: some patients refuse to be exposed to a drug that suppresses hair growth; (b) cardiotoxicity: although a given total dose has been calculated below which the myocardial risk is low [6], this risk is not nil, and in any case, the agent is generally not used beyond this total dose, which reduces its 'operational' action.

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Hence the considerable interest in other anthracyclins that have been considered to be less cardiotoxic and to cause less hair loss than ADM: we have systematically submitted all of them to a double test, electron microscope study of the myocardium and light microscope study of the skin of golden (cardiopathic) hamsters receiving three administrations per week of the dose corresponding (for mouse-hamster equivalence) to the optimally efficient dose, as far as survival is concerned, for murine L 1210 leukaemia [7]. The French detorubicin (DTR) [8, 12, 13] appears to be as cardiotoxic and to cause as much hair loss as ADM; the Italian 4′-epiadriamycin [3] is slightly less cardiotoxic, but causes the same hair loss as ADM; the American AD 32 [2] (*N*-trifluoro-acetyl adriamycin-14-0-valerate) appears to be significantly less cardiotoxic and to induce no alopoecia; the Japanese aclacinomycin (ACM) [11, 18] appears to be the least cardiotoxic and this preparation also induces no alopoecia [7].

Hence, after the Japanese [17] phase I trial in man, we started a phase II trial in man of aclacinomycin, the very preliminary results of which will be reported in a short communication.

Materials and Methods

Aclacinomycin or 2-ethyl-1,2,3,4,6,11-hexahydro-2,5,7-trihydroxy-6,11-dioxo-4-((0-2,3,6-trideoxy-α-L-glycero-hexopyranos-4-urosyl-(1-4)-0-2,6-dideoxy-α-L-lyxohexopyranosyl-(1-4)-2,3,6-trideoxy-3-(dimethylamino)-α-L-lyxo-hexopyranosyl) oxy)-1-naphthacenecarboxilic acid methyl ester (Fig. 1) was discovered and produced by Umezawa [18], who showed its murine oncostatic activity and found it less cardiotoxic in mice than ADM.

The protocol chosen for leukaemia and haematosarcoma involved continuous daily administration of the agent at the dose of 10–20 mg/m²/day, the duration depending on the result and/or the toxicity. The total dose varied from 42–600 mg/m².

The criteria of eligibility for the trial were the same as for the E.O.R.T.C. phase II trials [10] and for our own methodological and ethical concept of phase II trials [14]. The 22 subjects who were

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entered in the present trial and in whom the effect is evaluable are mentioned in Table 1, which indicates their age, sex, and disease and its phase of evolution (all were in a perceptible phase and all had been previously treated without success; none were in remission).

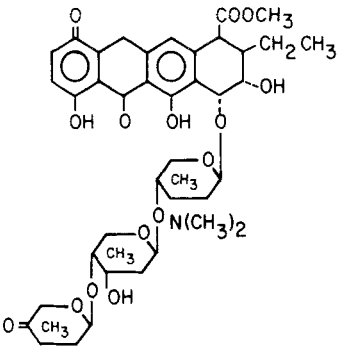

Fig. 1. Formula of aclacinomycin

Results

Table 2 shows the preliminary results: one complete and three incomplete remissions ($2 \geqslant 50\%$) were obtained in acute lymphoid leukaemia (ALL) patients resistant to all previously available drugs active in this disease; two complete and two incomplete remissions (one $\geqslant 50\%$) were obtained in patients with lymphosarcoma (stage V or leukaemic) [16].

This makes about 40% responses in this preliminary trial on haemopoietic malignancies and 48% in the group composed of ALL and lymphosarcomas.

Concerning previous treatment with ADM, in none of the responders can a resistance to that drug be proven (resistance means failure at induction of remission): in the two patients of the 22 who had first been submitted to a combination of vincristine (VCR) prednisone (PDN), L-asparaginase (ASP), and ADM (at least three

Table 1. Eligibility of evaluable patients

Diagnosis	No. of patients	No. of perceptible phase (PP)	Ages (years)	Sex	
				M	F
Acute lymphoid leukaemia	9	2nd PP 5 3rd PP 4	11, 3, 3, 5, 22 10, 12, 12, 12	7	2
Acute myeloid leukaemia	3	1st PP 3	33, 32, 51	1	2
Blastic crisis of chronic myeloid leukaemia	1	3rd PP 1	29	0	1
Hodgkin's disease	1	3rd PP 1	44	1	0
Lymphosarcoma (leukaemic)	8	1st PP 3 2nd PP 2 3rd PP 3	56, 16, 54 7, 12 12, 32, 31	6	2
Total	22			15	7

Table 2. Results in terms of induction of remission

Diagnosis	No. of patients evaluated	Complete regression	Partial regression		Failure
			$\geqslant 50\%$	$< 50\%$	
Acute lymphoid leukaemia	9	1	2	1	5
Acute myeloid leukaemia	3	–	–	1	2
Blastic crisis of chronic myeloid leukaemia	1	–	–	–	1
Hodgkin's disease	1	–	–	–	1
Leucaemic lymphosarcoma	8	2	1	1	4
Total	22	3	3	3	13
		13,3%	13,3%	13,3%	
		27%			
		40%			

cycles, ADM 20 mg/m²/week) without success, no response could be achieved with aclacinomycin.

The three complete regressions were obtained with a total dose of 52–225 mg/m²; the three partial regressions were obtained with doses varying between 200 and 285 mg/m²; thus in this small series, the response to the drug could not be related to the dose used. However, all the patients but one were submitted to a total dose of over 200 mg/m² in total; in one case toxicity precluded such a high dose.

Toxicity

Table 3 shows the toxic manifestations recorded during and after the trial: ACM was myelotoxic in 15 of 20 patients in whom the haemopoietic effect was evaluable; two patients were not evaluable because of previous hypoplastic bone marrow. Three patients of the eight who had leukopaenia had infections and five of the 13 who had thrombocytopaenia had haemorrhage, but infection and haemorrhage were easily controlled by symptomatic care and no lethal toxicity was observed. The details concerning the haematological tolerance can be seen in Table 4. It should be noted that all the patients who presented a regression had major toxicity with severe peripheral aplasia.

The digestive side effects were seen in rare vomiting (5%); diarrhoea was common at the end of the treatment (days 15–20): however, it could not be attributed to the drug alone, because of the patients' aplastic status.

What should be underlined is that only one patient of the 20 in whom the effect of ACM on the heart was evaluable presented a cardiac intolerance with negative T waves in V_3–V_4 derivations after a total dose of 42 mg; the drug was discontinued and the ECG normalized after 2 days. This patient was a 6-year-old male child with ALL, and he entered complete remission under this very low dose of ACM.

No patients in the 12 in whom alopoecia was not present before ACM application suffered from this side effect.

Table 3. Toxicity

Type	Rate	
Haematologic	15/20	(75%)
Anaemia	5/20	(25%)
Leukoneutropaenia	8/20	(40%)
Thrombocytopaenia	13/20	(65%)
Digestive (vomiting)	1/20	(5%)
Cardiac	1/20	(5%)
Alopoecia	0/12	

No lethal toxicity

Discussion

This preliminary result: (a) indicates the oncostatic efficiency of ACM in acute lymphoid leukaemia and in lymphosarcoma, two very similar if not identical lymphoid neoplasias [16]; (b) is in agreement with that of our experimental study of myocardial and alopoecic side-effects, which were exceptional or absent in our trial as they were in our experiment in golden hamsters [7].

This correlation of the experimental tests for these toxicities is confirmed by our experience with adriamycin [15] and with detorubicin [8], which are toxic to heart and skin in both studies. Bone-marrow toxicity appears to be the most important side-effect of aclacinomycin; in this trial it may be related to the continuous modality of administration.

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Table 4. Details of haematological toxicity[a]

Haemoglobin	15%	1	Platelets	100	4	Neutrophils	500–1000	1
(% of fall)	15%–30%	1	(10^3/mm³)	50–100	4	(mm³)	100– 500	2
	30%	3		20	5[b]		100	5[c]
		5			13			8

[a] To be evaluable, patients had to have in blood count: HGB > 10 g/l; Platelets > 40,000/mm³; Neutrophils > 500/mm³

[b] Three infections (no death)

[c] Haemorrhage (no death)

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