Eur J Cancer Clin Oncol, Vol. 24, No. 9, pp. 1481–1489, 1988.
Printed in Great Britain

0277–5379/88$3.00 + 0.00

Therapeutic Efficacy of Danazol in Myelodysplastic Syndromes

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Abstract—*Sixteen unselected untreated patients with primary myelodysplastic syndromes (MDS) and various combinations of blood cytopenia were treated with danazol, an attenuated androgen reported to be of some value in these conditions. After a 12 week trial (danazol 600 mg/day/p.o.), anaemia improved in 4/14 patients, with transfusional requirements being reduced by 50% or more in four other cases (response 57%). An enhanced reticulocyte production was documented in 6/13 cases (46%), and thrombocytopenia resolved in 5/8 (62%). Results of the granulocyte count were less satisfactory, with only one partial response obtained among five cases. A normalization of the monocyte count was seen in 3/5 patients with chronic myelomonocytic leukaemia, with one of them achieving a complete haematological and clinical remission lasting 6 months. Circulating blast cells decreased significantly (50% or more) in 4/6 cases. Although clinical symptoms from anaemia and bleeding disappeared in responsive cases, four patients developed acute non-lymphocytic leukaemia. Danazol was well tolerated and produced no acute or chronic toxicity. The drug appears useful in the management of anaemic and thrombocytopenic MDS patients.*

INTRODUCTION

THE primary myelodysplastic syndromes (MDS) constitute a heterogeneous group of clonal blood diseases characterized by a disordered marrow function, various combinations of blood cytopenia, and a propensity for the development of acute leukaemia [1]. At the present, treatment for MDS is unsatisfactory and unrewarding, only little benefit being produced by a number of approaches ranging from supportive care only to aggressive combination chemotherapy [2–4]. Most MDS patients are elderly people facing a multitude of collateral medical problems that make difficult when not contraindicated the use of some of the potentially active drugs. An effective treatment for MDS, therefore, should restore as a near normal haemopoiesis as possible, prevent the progression to acute leukaemia, and produce little or no toxicity.

Danazol, an attenuated synthetic androgen [5], recently received attention as capable of improving thrombocytopenia in a small series of multiply transfused MDS patients [6]. From this and other reports [7,8], danazol appeared able to improve to some extent also red and white cell production, thus raising interest in it as a potential new candidate for the treatment of MDS.

Accepted 28 April 1988.
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To evaluate the clinical and haematological effects of danazol on a relatively large patient population, we have conducted an open, uncontrolled study on 16 new MDS patients, who have been given oral daily danazol (600 mg) for 12 consecutive weeks. The results are reported and discussed below.

PATIENTS AND METHODS

Patients

Sixteen consecutive patients with a recent diagnosis of primary MDS formed the study group: eight were male and eight female. Median age was 72 and range 51–80 years. No patient had been given any sort of therapy during the previous 3 months. The diagnosis of MDS was formulated upon the criteria proposed by the French–American–British (FAB) Group [9]. Four patients were severely anaemic (Hb less than 8 g/dl) requiring transfusions with packed red cells (median 4 units per month) over the previous 3–6 months. Anaemia was moderate in two (Hb 8–10 g/dl), and mild in eight (Hb 10–12 g/dl). Thirteen patients were reticulocytopenic (less than 30×10^9/l), five granulocytopenic (less than 1.5×10^9/l), and eight thrombocytopenic (less than 120×10^9/l). Circulating blast cells could be detected in six cases, ranging from 0.2 to 1×10^9/l (median 0.6). There were five patients with an absolute monocytosis of greater

than 1 × 10^9/l. FAB diagnosis and clinico-laboratory details of patients are shown in Table 1.

Danazol treatment and response evaluation

The decision to start treatment was taken if any of the following were found: haemoglobin concentration below 11 g/dl or continuous transfusional requirements for at least 3 months; polymorphonuclear cell count below 1.0 × 10^9/l; platelets below100 × 10^9/l. Two patients (Nos. 7 and 9) had all three features, one (No. 10) had two, and the remaining presented with one. These data were confirmed through an observation phase of 3–20 months, during which a trend towards worse clinico-haematological conditions was demonstrated, and institution of treatment was felt appropriate. The basic outline of the study, drug scheduling, and possible adverse effects were explained to patients; written consent was not requested.

Danazol (Danatrol™, Maggioni-Winthrop SpA, Milan, Italy) was administered orally at a total daily dose of 600 mg (200 mg 8 hourly) for 12 consecutive weeks, after the original study by Cines *et al.* [6], and then discontinued in all cases. No maintenance or intermittent schedule was adopted, nor did patients receive in association drugs known to affect in any way blood count and bone marrow function. Patients were seen fortnightly, each time having a complete physical examination and a full blood count. The frequency of blood transfusions was recorded, as well as the occurrence of toxic side-effects: dyspepsia, weight gain, pruritus, skin changes. Liver function tests were performed only if clinically indicated. The effects of danazol therapy on the clinical and haematological parameters were evaluated, for the purposes of the study, after 6 and 12 weeks (bone marrow aspirates at the 12th week only), and again 6 weeks after stopping the drug (15 patients). A response to treatment was arbitrarily defined as any or more of the following [10]: >50% decrease from baseline in transfusion requirements; increase in haemoglobin level of >2 g/dl without red blood cell support; >50% increase from baseline in absolute granulocyte count; normalization (complete response) or >50% increase (partial response) from baseline in platelet count among thrombocytopenic cases; >50% decrease from baseline in bone marrow and circulating myeloblasts; and a normalization of excess monocytes in patients with CMML.

RESULTS

Peripheral blood and marrow changes observed during danazol therapy are summarized in Table

Table 1. *Clinico-haematologial features and outcome of* 16 *patients with myelodysplastic syndrome*

Case No.	Age/ sex	Physical findings and complaints	Blood count				% marrow blasts	MDS subtype*	Survival (months) and outcome
			Hb (g/dl)	Rets	PMN (x 10^9/l)	Plt			
1	80/F	Weakness	7.4	22.7	1.6	180	<5	RA	48+, lost to follow-up
2	76/F	Splenomegaly	7.8	11.2	1.2	110	<5	RA	41+, stable
3	69/M	Hepatomegaly	11.5	10.5	1.6	85	<5	RA-S	42+, stable
4	65/M	Weakness	10.7	27.7	4.1	390	<5	RA-S	16+, stable
5	60/M	Bruising	12.2	14.3	10.3	55	7	CMML	33+, stable
6	78/F	Hepato-splenomegaly	10.7	12.2	3.1	150	6	RAEB	30+, stable
7	63/M	Weakness	7.9	27.5	0.7	80	5	RAEB	7, acute leukaemia
8	66/M	Weakness	10.6	69.8	9.8	330	8	RAEB	17+, stable
9	73/M	Weakness	10.6	74.4	0.27	65	10	RAEB	18, acute leukaemia
10	63/M	Hepatomegaly	11.4	19.5	0.6	55	5	RAEB	12, acute leukaemia
11	51/F	Weakness	10.3	105	2.9	350	10	RAEB	16+, stable
12	78/F	Weakness	11.8	7.9	0.6	140	25	RAEB-T	17+, stable
13	73/F	Hepato-splenomegaly, bruising	8.8	21.6	10.8	100	10	CMML	6, acute leukaemia
14	72/F	Weakness	5.7	4	7.7	150	15	CMML	6, sepsis
15	76/F	Hepatomegaly	9.9	20.8	2.8	160	20	CMML	16, sepsis
16	74/M	Bruising	13.5	46.5	9	40	5	CMML	13+, stable
Normal range			12–16	30–100	1.5–7	120–350			

*RA = refractory anaemia; RA-S = RA with ringed sideroblasts; RAEB = RA with excess of blasts (5–20%); RAEB-T = RAEB in transformation (blasts 20–30%); CMML = chronic mylo-monocytic leukaemia.

Table 2. Variations of haematological parameters after danazol treatment (600 mg *daily for* 12 *weeks*) *in* 16 *patients with myelodysplastic syndrome: evaluation at the end of treatment* (12*th week*)

Parameter	No. of cases				% positive response
		Danazol therapy			
	At diagnosis	Improved	Stable	Worsened	
Anaemia (hb g/dl):					57*
absent	2	—	1	1	
mild (>10–12)	8	2	4	2	
moderate (8–<10)	2	2	—	—	
severe (<8)	4	—	4†	—	
Reticulocytopenia ($<30 \times 10^9$/l)	13	6	7	—	46
Thrombocytopenia ($<120 \times 10^9$/l)	8	5	3	—	62
Neutropenia ($<1.5 \times 10^9$/l)	5	1	4	—	20
Monocytosis ($>1 \times 10^9$/l)	5	3	2	—	60‡
Circulating blasts	6	4	2	—	66§
Marrow blasts (%):					6§
RA/RAS (<5)	4	—	4	—	
RAEB (5–<20)	6	—	3	3	
RAEB-T (20–30)	1	—	1	—	
CMML (5–<20)	5	1	3	1	

*Including four patients with reduced transfusional requirement.
†Reduced transfusional requirement (50% or more).
‡Below 0.8×10^9/l.
§More than 50% reduction.

2. Four of 14 anaemic patients achieved a normal haemoglobin concentration within 6 (case No. 11, with RAEB; and case No. 12, with RAEB-T) or 12 (cases No. 13 and 15, both with CMML) weeks of treatment (Fig. 1). Four more patients (cases Nos. 1, 2, 7 and 14), who were transfused monthly to maintain Hb above 8 g/dl, had a 50% or greater reduction of their transfusional requirements, though they remained anaemic. On the whole, concerning anaemia, a positive response to danazol was observed in 8/14 patients (57%). On the other hand, patient No. 16 became transiently anaemic during danazol, while anaemia worsened in patients Nos. 3 and 10. Reticulocytes reached normal values in 6/13 reticulocytopenic patients (Nos. 2, 5, 6, 10, 11 and 13; Fig. 2), with some of them achieving a concurrent normalization of haemoglobin (Nos. 11 and 13) or reduced transfusional requirements (No. 2).

A normal platelet count was restored in 5/8 thrombocytopenic cases (62.5%), with a partial response being observed in the remaining three. Complete responses occurred quickly, usually by the sixth week of treatment. Beyond this time platelets rose progressively, also in some non-thrombocytopenic patients (Fig. 3). The differences between initial and treatment related platelet count resulted significant when assessed by the Wilcoxon matched pairs rank test: $P < 0.005$ (basal vs. 6th week) and <0.025 (basal vs.12th week).

The neutrophil count was not greatly influenced by danazol. A temporary return to a low normal count was observed in only one out of five neutropenic cases (patient No. 13). In the remainder, whether neutropenic or not, no appreciable variation was noted. An absolute monocytosis was present at diagnosis in the five cases with chronic myelomonocytic leukaemia. Eventually, monocytosis declined below 0.8×10^9/l in three, either after 6 or 12 weeks of treatment.

Blast cells disappeared from peripheral blood smears of 4/6 patients, while persisting grossly unchanged in the marrows of all but one case. With regard to bone marrow morphological characteristics, significant improvement was seen in four cases: reduced macroblastosis and vacuolization of precursor red cells (case No. 1, experiencing reduced transfusional requirements), enhanced erythropoietic activity (case No. 6, showing a reticulocyte response), and increased erythropoiesis together with decreased dysplastic changes (case No.11, achieving normal haemoglobin and reticulocyte values). A fourth patient (No. 15), who was diagnosed as having chronic myelomonocytic leukaemia with about 20% marrow blasts, had a complete normalization of her bone marrow morphology and blood count, lasting 6 months. The striking changes observed in this case are illustrated in Fig. 4.

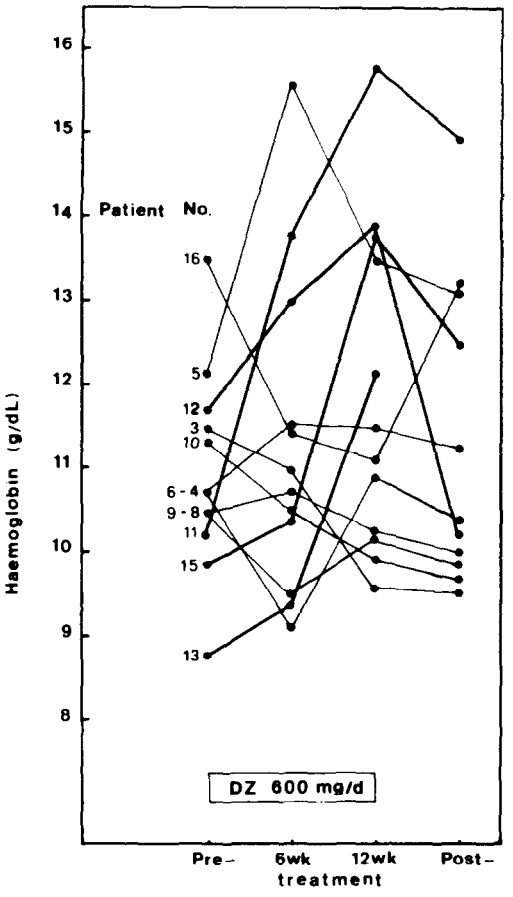

Fig. 1. Effects of danazol therapy (600 mg/day/p.o. for 12 weeks) on haemoglobin concentration from 12 non-transfused MDS patients. Post-treatment evaluation 6 weeks after stopping danazol.

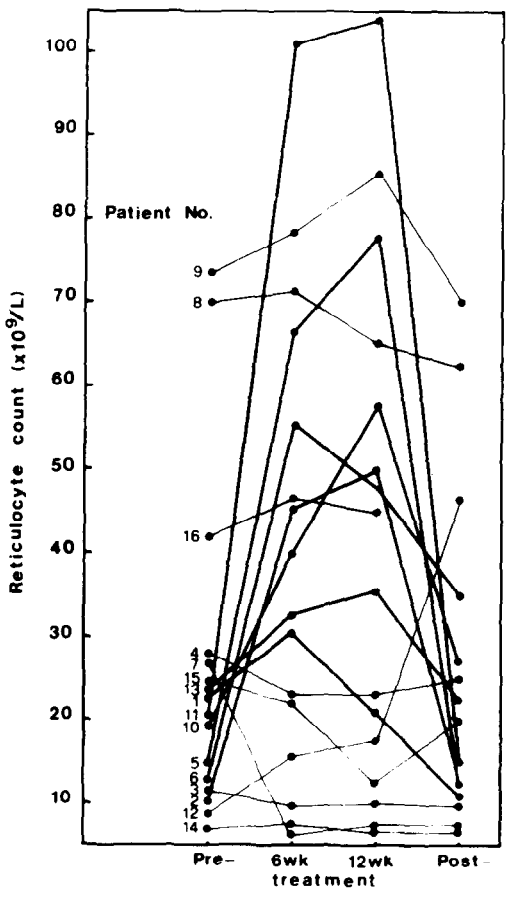

Fig. 2. Effects of danazol therapy on absolute reticulocyte count from 16 MDS patients (normal range 30–100 × 10^9/l).

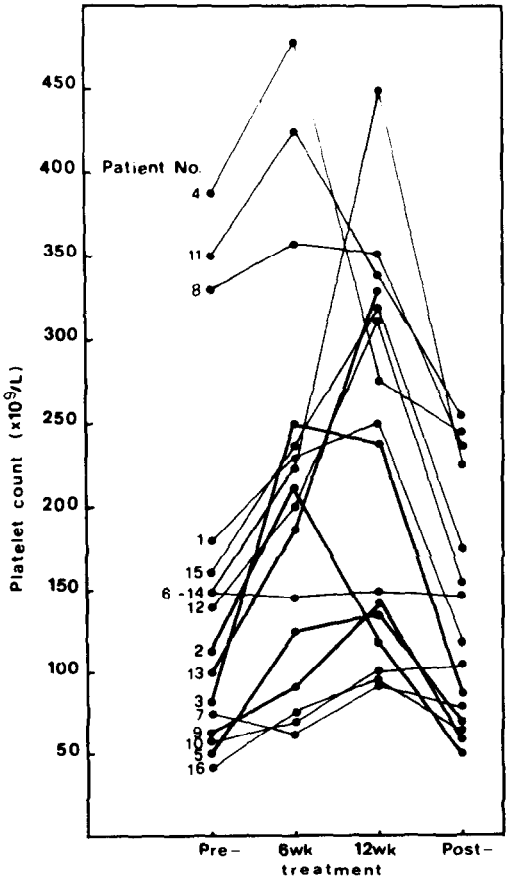

Fig. 3. Effects of danazol therapy on platelet count from 16 MDS patients (normal range 120–350 × 10^9/l).

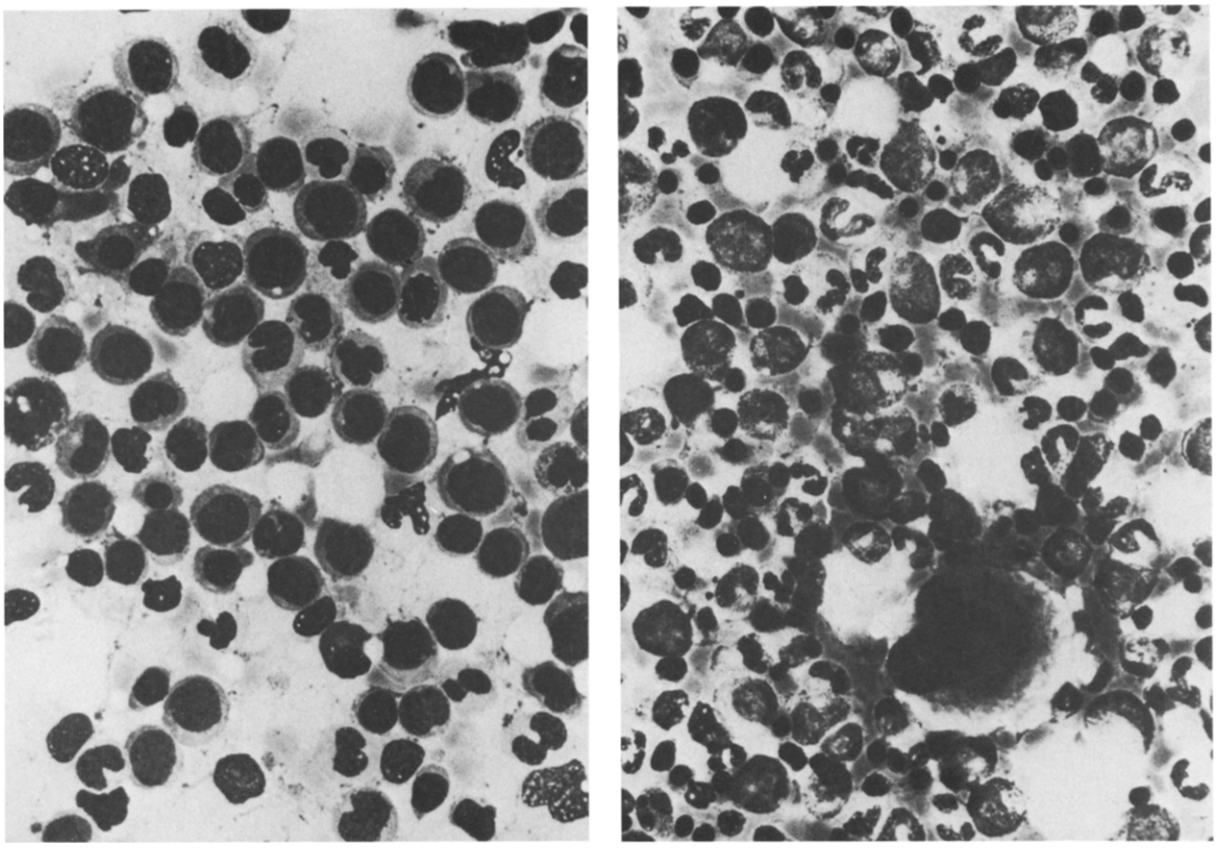

Fig. 4. The picture illustrates bone marrow changes occurring in patient No. 15 upon danazol therapy (May–Grunwald–Giemsa stain, × 320). Bone marrow at diagnosis (left) showed focal accumulation of blast cells and atypical monocytes, reduced erythropoiesis and megakaryopoiesis, abnormally hypogranulated and hyposegmented neutrophils. Remission marrow (right) showed normal cellularity and myelopoiesis with abnormal mononuclears below 5%.

Fifteen patients were evaluable 6 weeks after stopping danazol. Data analysis at this time showed a trend towards lower haemoglobin, reticulocyte and platelet values, with the exception of patient No. 16, who reached a normal haemoglobin concentration. In particular, reticulocytes fell rapidly below the normal range in 5/7 patients, as did the platelet count in another 4/5 patients who had had a complete response (Figs. 2 and 3, column 4). A progression to acute leukaemia has occurred, so far, in four cases (Nos. 7, 9, 10, and 13), in one during danazol therapy. Danazol was restarted or continued at this time, but no positive effect observed.

Some patients (see Table 1) were symptomatic before starting treatment, either because of bleeding or anaemia. These symptoms were relieved by the improvement of blood cytopenia obtained with danazol. Danazol was well tolerated, and no toxicity attributable to the drug was noticed throughout the study.

DISCUSSION

It appears from this study that danazol, under certain circumstances, may be a useful agent for the management of primary myelodysplastic syndromes. Ease of administration, tolerability, absence of toxicity and rate of positive responses make a therapeutic attempt worthwhile in MDS patients for whom other treatment modalities are unsuitable or contraindicated. In this category fall a number of cases with serious collateral illnesses or too advanced age. By using the schedule we have adopted, 600 mg daily for 12 weeks, positive effects on haemoglobin concentration and platelet count are to be expected in one third to one half of cases, thereby contributing to reduce morbidity from anaemia and bleeding in these patients.

Cines *et al.* [6] reported for the first time on anaemia improved by danazol in MDS, followed by Adler *et al.* [7]. Furthermore, Keyhani *et al.* [11] observed a significant improvement not only of anaemia, but also of leukopenia and thrombocytopenia in 11 patients with paroxysmal nocturnal haemoglobinuria, a marrow disorder closely related to MDS [12]. On the other hand, Lippman *et al.* [13], Doll *et al.* [14], and Buzaid *et al.* [15] were unable to confirm any benefit from danazol in 11 anaemic MDS patients, six cases of acquired idiopathic sideroblastic anaemia, and 20 variously cytopenic MDS patients, respectively. In the studies from Lippman *et al.* [13] and Buzaid *et al.* [15], however, danazol was likely administered for an insufficient time (4–6 weeks) to allow detection of recovery from anaemia in potentially responsive cases. In fact, in the four cases of our series showing a response, the haemoglobin concentration rose relatively late, between the sixth and twelfth week of treatment. Interestingly, a rise in reticulocytes did not closely parallel or predict a concurrent haemoglobin increase. We think that anaemic MDS patients should be given danazol for no less than 12 weeks before concluding for the inefficacy of treatment, and that an early rise in reticulocytes should not be taken as the unequivocal evidence of a positive response. Our data are in partial agreement with Doll *et al.*'s [14] and Buzaid *et al.*'s [15], as danazol induced no haemoglobin increase in the two patients with sideroblastic anaemia. Danazol could be unsuitable for this particular subset of myelodysplastic syndrome, as far as anaemia is concerned. Variations of transfusional requirements provided another means of evaluating response. Blood transfusions were diminished by approx. 50% or more in four patients of our series, an obvious clinical benefit for the lessened risk of contracting blood transmitted diseases and iron overload.

Our results confirm the original observation from Cines *et al.* [6] and Kornberg *et al.* [8] that danazol may significantly increase the platelet count in thrombocytopenic MDS patients. Platelets rose quickly and stood at normal or even higher levels in the majority (62.5%) of the patients treated, until they were taking the drug. Notably, some non-thrombocytopenic patients developed a mild thrombocytosis, a finding to be further discussed. Contrary to this, we could not demonstrate a positive effect of danazol on the neutrophil count of granulocytopenic patients, having observed only one partial response out of five neutropenic cases. This result is similar to what Cines *et al.* [6] and Buzaid *et al.* [15] have reported, while it differs from the largely positive experience of Keyhani *et al.* [10] in paroxysmal noctural haemoglobinuria. Although the small number of cases and the different subsets of disease considered might account for this discrepancy, our study does not support a promising role for danazol in granulocytopenic MDS cases.

A basic issue to address is whether danazol may prevent or delay the progression to acute leukaemia in MDS, thus contributing to prolong the patient survival. At the time of this writing, four of 16 patients (25%) in our study developed acute non-lymphocytic leukaemia. Since the estimated risk of acute leukaemia transformation for MDS patients is 12–38% [16], danazol should have no or very little capacity in reducing the spontaneous pace of the disease towards an acute transformation. The data on blast cell content of marrows, remaining grossly unchanged in all but one case, would also support this view. The single patient with chronic myelomonocytic leukaemia showing a complete response represents a remarkable exception. That danazol can suppress a neoplastic cell growth has been recently documented in human endometrial

carcinoma [17]. Since danazol can bind to multiple classes of steroid receptors [5], a suppression of the growth of leukaemic cell clones is theoretically possible, provided leukaemic cells bear on their surface the appropriate receptor.

The mode of action of danazol in MDS remains complex and not fully understood. A reduced platelet clearing by the macrophage system and reduced erythrocyte destruction through suppression of immune phenomena are the mechanisms thought to operate in MDS [6, 8]. A recent report, in addition, indicated that danazol might increase the marrow erythropoietic activity [18]. Our study shows that factors other than inhibition of immune phenomena are likely to be involved, for three reasons. One is that an increased platelet count was obtained also in some non-thrombocytopenic cases, as mentioned above; the second that reticulocytes rose rather than diminished during danazol administration in the majority of responsive cases, a finding not explainable by inhibition of immune haemolysis; and the third that an enhanced erythropoietic activity of bone marrow was morphologically ascertained in some cases.

Patients Nos. 7 and 12, however, in whom reduction of transfusional requirements and improvement of haemoglobin, respectively, were associated with a persisting low reticulocyte count, might represent examples of reduced immune-mediated red cell destruction or macrophage clearing. On the contrary, one patient (No. 10) developed anaemia associated with reticulocytosis while on treatment; because of the subsequent rapid evolution to acute non-lymphocytic leukaemia, these changes could simply result from a worsening of marrow ineffective haematopoiesis, independent of danazol. Other findings, such as the decrease in circulating blasts and monocytes in some patients, could perhaps be the consequence of a moderately improved haemopoiesis, redistribution of cells, a bias caused by the small number of cases, or a combination of any of these factors.

In conclusion, danazol produced some clinical and laboratory improvements in anaemic and thrombocytopenic patients with myelodysplastic syndrome. Following withdrawal of the drug, a rather quick return to pre-treatment values occurred in most of the responsive cases, an observation which lends further support on the effectiveness of therapy, and also suggests that maintenance treatment should be considered in responding cases. A warning seems necessary, however: since the degree of peripheral cytopenia was not as severe in our patients as in those from another comparable study that gave mainly negative results [15], we think that some haematological characteristics predicting a likely positive response could be identified. We can suppose that only those cases showing relatively mild cytopenia could benefit from danazol treatment, whereas those presenting with more advanced disease or nearer the end point of acute leukaemia transformation could not. The apparent inability of danazol in preventing this latter event in four cases is in keeping with this interpretation. Danazol was safe and well tolerated, even in long-term management. Issues to be clarified by controlled trials include the role of a maintenance or intermittent schedule, the use of higher doses, and association with other drugs.

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