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A Phase II Study of Idarubicin (4- Demethoxydaunorubicin) in Advanced Myeloma

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Abstract—*Idarubicin (IDA) is an anthracycline analog which differs from the parent compound by the substitution of a C4 methoxyl group with an hydrogen atom in the aglycone moiety. This drug has shown greater potency and activity in experimental and human leukemias and lymphomas by intravenous and oral routes of administration together with less cardiotoxicity than doxorubicin (DX) and daunorubicin (DNR). We have treated 15 patients with advanced multiple myeloma (MM) refractory or relapsed to standard chemotherapy regimens.*

The treatment schedule consisted of idarubicin 40 mg/m² orally on day 1 every 3 weeks for 6–8 months. We obtained 8/14 partial response, 4/14 minor response and 2 progressions. One patient was not evaluable for the response because of liver toxicity not related to IDA administration. The median duration of response was 8 months with a minimum of 2 and a maximum of 12 months. Hematologic toxicity occurred in about 20% of patients and no treatment was delayed. Cardiotoxicity, defined as impairement of left ventricular ejection fraction (LVEF), was observed in one case. The major systemic toxicity observed was nausea in 80% of patients and vomiting in 40%. Hair loss resulting was socially acceptable. These results indicate that IDA is useful as a single agent, easy to administer, not cross resistant with DX and recommended for a combination regimen.

INTRODUCTION

IDARUBICIN (4-demethoxydaunorubicin) (IDA) is a new anthracycline analog with a mechanism of action similar to DNR [1], which in experimental models has revealed a higher therapeutic index than DX and DNR [2]. In humans it has been shown to be an active agent in acute leukemia [4, 5] and malignant lymphoma [6], even if orally administered. In this Phase II study IDA was used as a single agent in patients with resistant or relapsed multiple myeloma (MM). The aim was to assess the activity of this drug when orally administered, to evaluate its toxicity and its therapeutic value as rescue for patients not responding to conventional chemotherapy and particularly those refractory or poorly responsive to DX.

PATIENTS AND METHODS

Fifteen patients with advanced multiple myeloma (MM) entered this study. Diagnosis was done according to the Myeloma Task Force [7]. All patients had been treated with conventional protocols according to the stage of disease [8]. Eight of them had received prior DX. Patients either had become resistant to standard treatment (11 patients) or relapsed (four patients); the latter had at least a 6 months interval from last therapy. At study entry the age ranged from 43 to 78 years (median 54 years) and the performance status from 50 to 90 (Karnofsky scale), median 80. Pretreatment evaluation included complete blood count and differential, one SMAC chemistry panel, serum and urine electrophoresis (ETF) and immunoelectrophoresis (IETF), immunoglobulin level, bone marrow plasma cells (BMPC) evaluation, skeletal X-ray, ECG and echocardiogram for the assessment of left ventricular ejection fraction (LVEF). Patients were staged according to Duric and Salmon [9]. IDA (4-demethoxydaunorubicin) was supplied by Farmitalia Carlo Erba R. & D. Milan (Italy) in 5, 10 and 25 mg capsules for oral administration. The drug was employed at a dose of 40 mg/m² every 3 weeks from one to nine cycles.

The patients were examined at the beginning and then every 3 weeks before starting each drug course with a complete hemogram and biochemical profile; every three courses, with bone marrow aspiration and ECG plus echocardiogram. At the end of six cycles of therapy patients were evaluated for

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Table 1. Main patient characteristics

Total	15
Median age in years	54
Range	43–78
Sex male/female	3/12
Median Karnofsky P.S.	80
Range	50–90
IgG myeloma	11
IgA myeloma	2
Light chain myeloma	2
Prior chemotherapy	15
Prior doxorubicin	8
Mean total dose mg/m²	189
Range mg/m²	40–352
Refractory myeloma (patients)	11
Relapsed myeloma (patients)	4

response with the following criteria:

Complete response (CR) was defined as complete disappearance of disease.

Partial response (PR) was defined as decrease of 50–75% in the serum and/or urine M peak; BMPC infiltration reduced to below 50% initial level.

Minimal response (MR) was a reduction of less than 50% of BMPC and improvement of clinical findings and PS.

Progression (P) was defined as refractoriness to treatment and increased serum or urine M peak and/or BMPC infiltration.

Every patient was studied by physical cardiac examination, electrocardiogram and echocardiography. Cardiac function was evaluated by M mode echocardiography performed by selection of left ventricular appropriate segment by cursor superimposed on the bidimensional echocardiography image. The following values were calculated: septum and left ventricular wall thickness, left ventricular diastolic and systolic diameters, left atrial dimension and the estimated ejection fraction by Quinones method.

RESULTS

The main patient characteristics are illustrated in Table 1. A total of 15 patients were treated with IDA by the oral route. Fourteen of them were completely evaluable for response. Only one patient experienced liver function abnormalities, already present before starting therapy and after one course of IDA; she was excuded from response evaluation. In 4/15 the treatment started more than 6 months from the end of prior therapy, and then the disease was considered as a true relapse. The remaining 11 patients were refractory to conventional chemotherapy and IDA followed the previous treatment within a median of 2 months. Table 2 shows the results obtained in our series: PR was achieved in 8/14; MR in 4/14; no CR was documented even after 6 or 8 months therapy. Progression occurred in two patients under treatment and the drug was stopped after four and one course, respectively. The total dose of IDA ranged between 40 and 352 mg/m² and was unrelated to the previous DX total dose administered. Six out of 11 patients considered as refractory had had previous DX. Two of them achieved PR (case 1 and case 8). In six cases the clinical response occurred before the end of 6 months therapy while in three patients the treatment was prolonged for two or three more additional cycles to obtain a better outcome of therapy.

Table 3 shows the characteristics of responding patients. A significant reduction (> 50%) of M component and BMPC has been observed after a minimum of four and a maximum of nine cycles. As indicated, the BMPC were assessed at the beginning of therapy and every 3 months. Patients 1, 3 and 5 achieved a satisfactory response within the fourth and fifth course of IDA; in cases 2 and 8 the therapy had been continued because of good response and fair tolerance. By the oral route nearly all patients had nausea; vomiting occurred in 40% of them. Only one patient had transient diarrhea at each cycle. Hair loss resulting was moderate in 26% of patients and no patients developed alopecia.

No fever or stomatitis were encountered. Mild myelosuppression, anemia (26%), and leukopenia (20%) and thrombopenia (13%) were documented. At the doses used, the WBC nadir was observed between the 2nd and 3rd course, the lowest value being 2.0×10^3 mm³ (range $4.3–2.0 \times 10^3$/mm³) without occurence of infection. Similarly, thrombopenia was recorded at the 2nd cycle without bleeding episodes. Hematological toxicity was transient and did not appear in the following courses of therapy. There was no delay or dose reduction and almost all patients recovered within 21 days.

A mild increase of liver enzymes has been detected before starting therapy in one patient (COM). After the first course of IDA the AST and ALT increased to five times the initial value. Because of that, the treatment was stopped; the enzymes were still abnormal 2 months later at the end of therapy. No later toxicity was registered in the remaining patients during or after treatment. No patient developed clinical signs of congestive heart failure. Electrocardiography changes were detected in one patient characterized by an increase of R voltage in the left precordial leads; M mode echocardiography disclosed an increase of the left ventricular diastolic and systolic diameters and a reduced ejection fraction of 60% and 42% respectively, at the total dose of 225 mg/m² IDA.

In one patient the echo-examination was not

Table 2. Therapeutic response to idarubicin according to previous treatment

Patient	Age	MM class	Prior therapy Mono	Poly	Duration (months)	DX/m² total dose	Time from last therapy (months)	Courses	Total dose (mg/m²)	Response	Duration of response (months)
1 G.C.	57	IgG(K)III A	—	VMCP × 7 BAP × 6	13	176	1	8	329	PR	11
2 R.L.	50	IgG(K)III A	—	VMCP × 12 BAP × 5	17	147	6	4	167	PR	12
3 R.E.	65	IgG(K)II A	PTC × 3	BAP × 6 VAP × 6 VMCP × 6	22	271	1	8	352	MR	3
4 M.A.	65	Ig III A	PTC × 3	VMCP × 12 BAP × 12	27	352	4	4	102	MR	2†
5 C.S.	70	Ig II A	M 860 mg	VMCP × 7	19	—	2	5	200	MR	4
6 D.M.G.	59	IgG(K)II A	—	VMCP × 6 VAP × 6	12	183	2	5	208	MR	2
7 R.A.	71	Ig II A	M 975 mg	VMCP × 12 BAP × 6	30	176	14	9	329	PR	12†
8 L.E.	58	Ig III A	—	VMCP × 18 VAP × 1	19	30	3	5	200	PR	8
9 R.G.	43	IgG(K)III A	—	VMCP × 8	14	192	2	4	160	P	
10 C.O.M.	57	IgG(K)II A	—	VMCP × 6 VAP × 6	12	180	1	1	40	Not evaluable	
11 P.M.	44	IgG(K)I A	M 456 mg	—	6	—	2	6	243	PR	9+
12 C.P.	70	IgG(K)II A	M 456 mg	—	6	—	1	5	250	PR	9+
13 Z.I.	50	IgG( )I A	—	VMCP × 6	6	—	2	6	240	PR	6
14 P.O.	78	IgG(K)II A	M 900 mg	—	12	—	32	6	240	PR	9+
15 S.L.	55	IgG(K)I A	M 900 mg	BMCP × 7	19	—	10	1	40	P	

M = melphalan; VMCP = vincristine–cyclophosphamide–melphalan–prednisone; BMCP = BCNU–melphalan–cyclophosphamide–prednisone; VAP = vincristine–adriblastin–prednisone; PTC = peptichemio; BAP = BCNU–adriblastin–prednisone.

Table 3. Characteristics of responding patients

Patient	Age	Serum	M component (g/dl) Before	After	Bone marrow plasma cell Before	3 months	End treatment	IMI courses
R.L.	50	IgGK	7.9	4.8	60	—	25	4
R.A.	71	IgGλ	3.8	1.6	70	50	30	9
L.E.	58	λ*	8.6	4.2	70	40	40	5
P.M.	44	IgGK	3.5	1.8	50	25	10	6
C.P.	70	IgGK	4.1	1.8	30	10	5	5
P.O.	78	IgGK	4.7	1.9	70	60	30	6
Z.I.	50	IgGλ	3.7	1.8	60	50	30	6
G.C.	57	IgGK	3.2	1.7	80	60	15	8

*Proteinuria: g/24 h.

reliable because of the poor echocardiographic window and in two patients it was performed only at the the beginning of therapy, because of the interruption of IDA in one and progression of disease in a second.

DISCUSSION

The combination of melphalan and prednisone was considered for many years the most useful treatment for MM patients. In the attempt to improve the results of therapy, sequential administration of drugs not cross-resistant and with synergic effects have been used [11]. The published results of three different drug combinations, including or not doxorubicin and vincristine showed a significant difference in response rate between regimen with or without DX [12]. A troublesome problem is therapy in non-responding patients, particularly in those already treated with DX. Moreover, the use of anthracyclines is limited by their cardiotoxicity.

In our experience IDA orally administered at a dose of 40 mg/m², every 3 weeks has shown a satisfying effectiveness in MM. Our patients were all heavily pretreated and in most cases refractory to prior conventional chemotherapy including DX. The achievement of about a 50% response rate is encouraging. Moreover two patients who were not responding to previous DX regimen achieved PR with idarubicin.

This evidence would suggest a lack of cross-resistance to prior DX even in patients who received a quite high total dose but a greater number of cases

are needed to confirm this clinical observation. The transient hematologic toxicity has been overcome by 3-weeks dose-scheduling. In contrast, nausea represented the major adverse effect of IDA: it resulted in moderate degree in about one half of the cases. Compared to DX, hair loss was definitely less frequent and socially acceptable. As far as cardiotoxicity is concerned, no evidence of echocardiographic alterations was found with the exception of one patient who had increased left ventricular dimension already at the beginning of therapy. After three cycles a further increase of left ventricular distolic and systolic dimension occurred, with worsening of ejection fraction.

These alterations were still present 6 months later. On the other hand improvement of ejection fraction has been observed in three cases, probably related to amelioration of the hemoglobin level.

In conclusion, these preliminary results suggest that IDA has a significant activity against MM. Large scale trials are necessary to confirm this evidence and in particular in untreated patients either as a single agent or in a polychemotherapy regimen. Moreover, the suggestion of a lack of cross-resistance with other anthracyclines will require further confirmation in a larger series of patients; in fact the possibility of improving the response in refractory or relapsed MM patients, known to have a low response rate and prognosis, is until now one of the major questions affecting the management of this disease.

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