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Phase II study of Amsacrine in Refractory Lymphomas. A Report of the EORTC Early Clinical Trials Group

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Abstract—*Forty-three patients with advanced measurable lymphoma, progressive after conventional therapy, were entered into a phase II study of* m-*AMSA* 90-120 mg/m^2 *every* 3 weeks. *Five patients were ineligible and response could not be evaluated in four patients. For HD there were two partial responses* (14%), *lasting* 6 *and* 41 weeks, *in* 14 *evaluable patients. Among* 20 *evaluable patients with NHDL three* (15%) *achieved partial remission, but duration of response could not be evaluated. One patient with diffuse histiocytic lymphoma died of infection at* 4 weeks, *a second with lymphoblastic lymphoma was given high-dose steroids commencing at* 6 weeks, *and the third patient with nodular poorly differentiated lymphocytic lymphoma refused further treatment after one course. Leucopenia was more marked in patients with NHDL (WBC nadir* × 10^9/l, *median* 2.2, *range* 0.2–4.3) *than in HD (WBC nadir* × 10^9/l, *median* 2.8, *range* 0.85–7.2), *as was thrombocytopenia. There was one toxic death and one life-threatening infection, both secondary to myelosuppression. Non-haematological toxicity was mild.* m-*AMSA has marginal activity in previously treated lymphomas and causes considerable myelosuppression.*

INTRODUCTION

AS A GROUP the malignant lymphomas are generally highly responsive to chemotherapy. A large number of agents have shown activity in these diseases [1]. In the last decade the use of chemotherapy has resulted in a significant proportion of patients presenting with generalised disease enjoying long-term relapse-free survival [2–7]. Despite this, patients continue to die of lymphoma, either because their disease is primarily resistant to chemotherapy or due to relapse following successful remission induction. Although many agents have been demonstrated to induce temporary regressions, salvage therapy is rarely successful in terms of relapse-free survival and there is a continuing need for effective new agents in lymphoma [8].

Amsacrine [*m*-AMSA, 4′-(9′acridinylamino)-methanesulfon-*m*-anisidide, NSC 249992] is one of the many aminoacridines synthesised by Cain and Atwell [9]. *m*-AMSA acts as an intercalating agent with DNA, but other mechanisms of action may account for its antitumour activity [10–12]. It is metabolised by the liver and excreted in the bile [13]; thus plasma clearance is reduced in the presence of liver impairment [14]. Its dose-limiting toxicity is myelosuppression, other toxicities such as nausea and vomiting, alopecia and phlebitis being mild at doses rcommended for solid tumours [15–17].

Tumour regressions [16–19] have been observed in phase I studies in leukaemias and lymphomas [15, 16], and there have been hints of activity in a variety of solid tumours [15, 17, 19, 20]. In phase II studies the efficacy of *m*-AMSA against refractory leukaemias has been confirmed [21–28] and responses have been observed in lymphoma, but the data are sparse [29, 30]. In a large number of broad and disease-orientated phase II trials,

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response rates in a variety of solid tumours have always been less than 10% [31–37]. This study was conceived as part of a broad phase II trial in 1979. A separate report on solid tumours has already been published [37].

MATERIALS AND METHODS

Criteria for eligibility

Patients with all histological types of lymphoma, both Hodgkin's and non-Hodgkin's, were accepted into this study, provided they had progressive disease on conventional therapy and measurable lesions. Criteria for entry into the study included age 15–75 yr, Karnofsky performance status 50 or above, no chemotherapy within 3 weeks prior to entry, no radiation therapy to an indicator lesion within 6 weeks prior to entry, adequate haematological (WBC $\geqslant 4.0 \times 10^9/l$, platelets $\geqslant 1000 \times 10^9/l$), hepatic excretory (serum bilirubin $\leqslant 50$ μmol/l) and renal function (creatinine $\leqslant 150$ μmol/l). Patients with leukaemic progression (defined as chronic lymphatic leukaemia >10,000 lymphocytes in peripheral blood, acute lymphoblastic leukaemia >30% diffuse infiltration of the marrow with blasts) were excluded, as were patients with active symptomatic disease in the central nervous system. Informed consent was required.

Therapeutic regimen

m-AMSA (NSC 249992) 120 mg/m^2 was administered as i.v. infusion given over 1 hr at 3 weekly intervals. The drug was supplied by Warner Lambert Company, Morris Plains, NJ, U.S.A., and formulated as a sterile solution of *m*-AMSA 50 mg/ml in *N,N*-dimethylacetamide. Immediately before use, 1.5 ml of this solution was combined with 13.5 ml of sterile 0.0353 M aqueous solution of L(+) lactic acid and then further diluted with 500 ml of 5% dextrose per 75 mg of *m*-AMSA.

Dose modifications

The starting dose of *m*-AMSA was reduced to 90 mg/m^2 for patients who had received extensive prior chemotherapy or radiotherapy. Subsequent doses were reduced by 33% if the leucocyte nadir was $\leqslant 1.5 \times 10^9/l$ on weekly blood counts or the platelet nadir $\leqslant 50 \times 10^9/l$. There was also provision to increase the dose by 33% if there was no haematologic toxicity (leucocyte nadir $\geqslant 3.0 \times 10^9/l$, platelet nadir $\geqslant 100 \times 10^9/l$) from the previous two courses. Retreatment was delayed until haematological recovery (leucocytes $\geqslant 3.0 \times 10^9/l$, platelets $\geqslant 100 \times 10^9/l$), with a maximum of 3 weeks.

Pretreatment and follow-up investigations

Baseline studies included history and physical examination, Karnofsky performance status, tumour measurements, complete blood count, including differential white count, biochemical profile, including serum creatinine and liver function tests, chest radiograph and ECG. Other appropriate investigations for tumour measurement were performed in individual cases. Blood counts were repeated at weekly intervals, and all baseline investigations were repeated after two courses of chemotherapy and at the time of discontinuation of treatment.

Definition of response and toxicity

Criteria for response and grades of toxicity used in this study are those defined by the WHO [38].

RESULTS

A total of 43 patients were entered into this study by eight European Centres. Two patients with HD were considered ineligible because of initial low blood counts and no measurable disease respectively. Insufficient data were available to assess response in one patient. For NHDL, reasons for ineligibility in three patients were no measurable disease in two and no data in one. Three patients were not evaluable for tumour response, one of whom died the day after commencement of *m*-AMSA and two in whom high-dose steroids were commenced 2 and 14 days after the first dose of *m*-AMSA, apparently because of rapidly expanding painful nodes.

The characteristics of the 34 evaluable patients are shown in Table 1. Males predominated and patients with HD tended to be younger. All had received extensive prior chemotherapy, which had contained doxorubicin in 26 of the 34 cases. Nine patients with HD had previously received 3–7 regimes of combination chemotherapy, with major responses of varying duration. Four further patients had experienced minor response or progression through 1–3 types of combination chemotherapy. Sixteen patients with NHDL had responded to prior single-agent or combination chemotherapy, and had received a median of two regimes (range, 1–6). Disease progression through one (one patient) or two (three patients) types of chemotherapy was noted in the remaining patients. Only four patients received AMSA as second-line chemotherapy, and these were not the responders. Patients with NHDL received fewer courses of *m*-AMSA as unresponsive tumours progressed more rapidly. Two patients with HD and seven with NHDL were taken off study because of rapid disease progression after only one course. The histological types of lymphoma are shown in Table 2.

Table 1. Evaluable patient characteristics

	HD	NHDL
Age (yr)		
Median	33	62
Range	18–67	31–75
Sex		
Male	8	15
Female	6	5
Performance status		
Median	70	80
Range	50–90	50–100
Prior XRT		
None	2	4
Localised	2	10
Extensive	10	6
Prior chemotherapy		
Multiple agents	14	20
Doxorubicin	12 (86%)	14 (70%)
Sites of disease		
Lymph nodes	12	18
hilar/mediastinal	6	1
other	6	18
Pulmonary	7	2
Hepatosplenomegaly	2	2
Skin	1	3
Bone marrow	0	1
Stomach	0	1
Bones	0	1
No. of courses AMSA therapy		
Total	55	48
Median	3	2
Range	1–13	1–12

Table 2. Histology (evaluable patients)

HD	Nodular sclerosis	9
	Mixed cellularity	4
	Lymphocyte depleted	1
NHDL	Nodular mixed	1
	Nodular poorly differentiated lymphocytic	4
	Diffuse well differentiated lymphocytic	1
	Diffuse poorly differentiated lymphocytic	5
	Diffuse mixed	1
	Diffuse histiocytic	7
	Lymphoblastic	1

Table 3. Response

	HD	NHDL
Entered	17	26
Evaluable	14	20
CR	0	0
PR	2 (14%)	3 (15%)
MR/NC	5	1
PD	7	16
Overall response	5/34 (15%)	

Response to chemotherapy is summarized in Table 3. There were two PR (14%) in HD (both nodular sclerosis), lasting 6 and 41 weeks. Both patients had responded to prior combination chemotherapy regimes and both had received prior doxorubicin. Although there were three PR (15%) in patients with NHDL, one patient who had diffuse histiocytic lymphoma died of infection, secondary to myelosuppression, at 4 weeks. This patient had not responded to two types of prior combination chemotherapy, one of which had included doxorubicin. The second patient, who had lymphoblastic lymphoma, was given high-dose steroids, starting at 6 weeks, for a vasculitis (histologically proven) and duration of response cannot therefore be evaluated. This patient had responded to two types of prior chemotherapy but had not received any doxorubicin. The third patient, who had nodular poorly differentiated lymphocytic lymphoma and had received prior doxorubicin, refused further treatment after one course and was lost to follow-up.

Haematological toxicity is illustrated in Tables 4 and 5. Unfortunately, nadir WBC and platelet counts were only available for 47% of courses in patients with HD and 58% of courses in patients with NHDL, with granulocyte nadirs recorded in 27 and 31% respectively. Haemoglobin values were reported in 17 patients, nearly half of whom required transfusion at some time during the course of treatment. Myelosuppression was more marked in patients with NHDL than in those with HD, and leucopaenia was commoner than thrombocytopaenia. There was one toxic death and one life-threatening infection, both secondary to myelosuppression. Most patients were treated at a dose of 90 mg/m^2. In HD, three patients received a total of 7 courses of chemotherapy at 120 mg/m^2, and haematological toxicity seemed greater at this dose. In NHDL five patients received six courses of chemotherapy at 120 mg/m^2, but the WBC nadir did not differ significantly from that at 90 mg/m^2, although there was slightly greater depression of platelets.

Non-haematological toxicity was mild, nausea and vomiting, anorexia and stomatitis being the main side-effects. Eighteen patients, receiving 47 courses of chemotherapy, did not experience any non-haematological toxicity.

DISCUSSION

The results of this phase II study of *m*-AMSA in lymphomas—overall 15% response, 14% for HD and 15% for NHDL with no complete remissions—are disappointing. Cabanillas and co-workers [29], administering 40 mg/m^2 daily × 3 every 3 weeks, observed no responses in four

Table 4. Toxicity—leucopaenia

	HD	NHDL
No. of patients evaluable	13/14	16/20
No. of courses evaluable	26/55 (47%)	28/48 (58%)
No. of patients toxic	10/13	14/16
No. of courses toxic	17/26 (65%)	23/28 (82%)
All patients:		
WBC × 10^9/l		
Median nadir	2.8	2.2
Range nadir	0.85–7.2	0.2–4.3
Granulocytes × 10^9/l		
Median nadir	1.8*	1.3†
Range nadir	0.08–3.7	0.01–3.5
WHO grade		
1	2	1
2	5	8
3	0	3
4	2	3
Dose 120 mg/m^2:		
No. of courses evaluable	7	6
WBC × 10^9/l		
Median nadir	2.4	2.6
Range nadir	0.85–5.2	0.6–3.9
Dose 90 mg/m^2:		
No. of courses evaluable	19	22
WBC × 10^9/l		
Median nadir	3.7	2.5
Range nadir	0.9–8.2	0.2–5.9

*Based on 27% of courses.
†Based on 31% of courses.

patients with HD, three CR and three PR (23%) in 26 patients with NHDL. These promising early results were not confirmed, however, as there was only one additional response in the next 20 patients entered into the study, an overall response rate of 14% in 50 patients [39]. It is interesting to note that in the M.D. Anderson study [29] CR was only observed in patients who had previously achieved CR on first-line chemotherapy and who had received AMSA at their first relapse. No patients of this type were entered into our study. Occasional patients with lymphoma have been included in phase I or broad phase II studies of *m*-AMSA [16, 17, 40] and some partial or minor responses have been observed. A larger study at Memorial Hospital [30] showed no major responses in 15 evaluable patients treated at 120 mg/m^2 every 3 weeks, although minor temporary regressions were observed in two patients. Administering the drug by continuous infusion does not seem to be more effective, as Micetich and colleagues [41] only noted one brief remission in seven patients with lymphoma. Hutter and Meyskens [42], reporting on nine children with ALL or lymphoblastic lymphoma, found one CR in each and five minor responses, and Tan observed a PR in one of four cases of NHDL in children.

There is abundant evidence for the activity of *m*-AMSA in refractory acute leukaemia [21–28], with 22% CR and 8% PR being reported. In most cases doses of 90–120 mg/m^2 daily × 5 have been administered and in responding cases a period of marrow aplasia inevitably results. In solid tumours and lymphomas lower doses have been used, despite which some degree of myelosuppression has been common, and the lack of activity may be dose-related. Phase II studies with a myelosuppressive agent in patients with lymphoma are particularly difficult as the majority of patients have had intensive prior chemotherapy and/or radiotherapy and may well have compromised marrow reserve. In addition, many may have marrow involvement by

Table 5. Toxicity—thrombocytopaenia

	HD	NHDL
No. of patients evaluable	13/14	16/20
No. of courses evaluable	26/55 (47%)	27/48 (56%)
No. of patients toxic	4/13	7/15
No. of courses toxic	5/26 (19%)	12/27 (44%)
All patients:		
Platelets × 10^9/l		
Median nadir	103	118
Range nadir	25–340	18–303
WHO grade		
1	0	2
2	2	0
3	1	3
4	0	2
Dose 120 mg/m^2		
No. of courses evaluable	7	6
Platelets × 10^9/l		
Median nadir	117	82
Range nadir	66–215	18–136
Dose 90 mg/m^2		
No. of courses evaluable	19	21
Platelets × 10^9/l		
Median nadir	169	142
Range nadir	25–383	24–303

lymphoma, further reducing the pool of normal haemopoietic stem cells. Haematological toxicity in this study was considerable, and dose escalation would only have been possible with intensive supportive care facilities. Myelosuppression was more severe in NHDL than HD, probably due to the higher frequency of bone marrow involvement in the former disease.

This study was conceived in 1979 as part of a broad phase II study in solid tumours. A specific protocol had not been written for lymphomas and certain special problems in the management of these tumours quickly became evident. Although it was intended that only those patients receiving two courses of chemotherapy should be evaluable for response, it was clear that in NHDL particularly, massive progression, including leukaemic conversion, precluding a second course, could occur within 3 weeks, and this was clearly a failure of therapy. Many patients were on steroids or started these during *m*-AMSA treatment. Steroids may cause significant regressions of lymphomatous masses, although their activity in late-stage heavily pretreated patients is more debatable. In this study patients receiving high-dose steroids commencing after the first dose of AMSA have been excluded from analysis, although a constant low dose of steroids has been permitted. A uniform histological classification used in all participating European centres and central pathology review were also lacking. Our experience with this study has prompted the drafting of a standard phase II protocol, specifically for use in lymphomas, which addresses and attempts to define such important issues as: a uniform histological classification; measurability of disease, particularly the more difficult sites such as spleen, paratracheal, hilar and para-aortic lymph nodes; concomitant administration of steroids; aggressiveness of therapy in the presence of bone marrow involvement; leukaemic transformation; and rapid progression of disease. Since agents with low potential for myelosuppression may be more easily evaluated in late-stage lymphomas, and if active would be useful in first-line combination therapy, these compounds should have high priority for phase II evaluation in lymphomas.

Conclusion

AMSA is an agent with activity in HD and NHDL but its efficacy is low and attended by considerable myelosuppression—even used in a schedule which may well be suboptimal.

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