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# Phase II Studies of Mitozolomide in Melanoma, Lung and Ovarian Cancer

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**Abstract**—*Seventy-seven patients were treated with oral mitozolomide to assess the activity of this drug in melanoma, lung and ovarian cancer. Partial responses were seen in five of 18 evaluable patients with small cell lung cancer (SCLC) and three of 20 with melanoma. No activity was apparent in non small cell lung or epithelial ovarian cancer.*

*The major toxicity was myelosuppression which necessitated reduction in the initial dosage from 115 to 90 mg/m². However, even at this dose level, unpredictable WHO grade 4 toxicity occurred in non-pretreated patients. Thrombocytopenia was more common than leucopenia and eight patients required platelet transfusion for spontaneous or tumour-related haemorrhage. Myelotoxicity was considered responsible for two deaths and was a significant contributory factor in a further three. Non-haematological toxicity was minor.*

*Thus, despite demonstrable activity in SCLC and melanoma, unpredictable myelosuppression is likely to preclude further assessment in combination chemotherapy regimes in these tumours.*

## INTRODUCTION

CURRENTLY available cytotoxic drugs have limited activity in non small cell lung (NSCLC) cancer [1] and melanoma [2]. The problem in small cell lung (SCLC) and ovarian cancers is that of failure to eradicate the tumour despite impressive clinical and pathological responses with combination chemotherapy [3, 4]. There is therefore a continuing need to evaluate new drugs in these tumours.

Mitozolomide was synthesized at Aston University [5]. In preclinical studies it was highly active against murine tumours [6] and human tumour xenografts of SCLC and melanoma were apparently eradicated in nude mice [7]. During Phase I studies of intravenous mitozolomide, responses were seen in two of 10 patients with ovarian cancer [8]. These data suggested that further evaluation of mitozolomide was warranted.

The Phase I data indicated that the major toxicity of intravenous mitozolomide was myelosuppression: non-haematological toxicity was minimal [8, 9]. Furthermore, oral bioavailability was approx. 100% of the same intravenous dose [8]. The current studies were to determine the activity of the oral preparation. The lung and melanoma studies were conducted in Glasgow, whereas the ovarian cancer study was organized on a national basis by the Cancer Research Campaign Phase II Subcommittee. Response data have already been reported for ovarian cancer [10] and melanoma [11], patients are included here to complete the overall assessment of toxicity and efficacy.

## PATIENTS AND METHODS

Entry into these Phase II studies required an ECOG performance status <2, together with adequate bone marrow reserve (WBC >4.0 × $10^9$/l; platelets >100 × $10^9$/l) and renal function (serum creatinine <150 mmol/l). The characteristics of the treated patients are shown in Table 1. Of the 20 patients with melanoma, 11 had visceral metastases. The majority of patients with SCLC (12 of 20) had extensive disease whereas only five of 17 patients with NSCLC had distant metastases. Seven women with ovarian cancer had disease outwith the peritoneal cavity.

Gelatin capsules of mitozolomide were swallowed after a 4–6 h fast to maximize absorption. Initial patients received 115 mg/m², based on the Phase I toxicity data [8]. However, severe myelosuppression in the first 11 patients necessitated protocol revision and subsequent patients received 90 or 100 mg/m² with discretionary dose reduction to 70 mg/m² for those with extensive prior therapy. Capsule formulation of 50, 60 and 70 mg mitozolomide permitted treatment with the selected dose ± 5%. Retreat-

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*Table 1. Characteristics of patients receiving mitozolomide*

| | Melanoma | Lung cancer | | Ovarian cancer |
|---|---|---|---|---|
| | | SCLC | NSCLC | |
| Number | 20 | 20 | 17 | 20 |
| M:F | 12:8 | 10:10 | 15:2 | 0:20 |
| Median age (range) | 57 (25–75) | 60 (37–75) | 60 (37–70) | 61 (38–72) |
| Mean ECOG performance status | 0.7 | 1.2 | 0.8 | 1.35 |
| Prior chemotherapy | 11 | 9 | None | All |
| Prior nitrosourea | 4 | — | — | — |
| Mean number per drugs (range) | 2.3 (1–4) | 4.8 (3–5) | — | 3.2 (1–6) |
| Prior irradiation | 2 | 4 | 2 | None |

SCLC = small cell lung cancer; NSCLC = non small cell lung cancer.

ment was scheduled at intervals of 6 weeks, provided that haematological recovery had occurred. Full blood counts were performed weekly in most patients and subsequent dose modification was based on nadir values. WHO Grade 4 toxicity precluded retreatment, and a 25% reduction was recommended for Grade 3 myelosuppression. A similar 25% dose reduction was instituted if retreatment was delayed by Grade 1 myelotoxicity. Patients with persistent Grade 1 toxicity at 8 weeks were withdrawn from the study and further mitozolomide doses were discretionary.

Tumours were evaluated clinically at intervals of 4–6 weeks and chest radiology repeated if indicated for tumour measurement prior to each mitozolomide dose. More extensive radiological investigations including abdomino-pelvic ultra-sonography and computerized tomography were repeated 3 monthly. On the basis of these measurements, response was classified as: Complete response (CR): regression of all evaluable tumour, confirmed on two observations not less than 4 weeks apart. Partial response (PR): >50% reduction in the sum of the products of the maximal perpendicular tumour dimensions, persisting for a minimum of 4 weeks in the absence of new lesions. No change (NC): a change in tumour measurements insufficient to qualify for a partial response or progressive disease. Progressive disease (PD): >25% increase in the sum of the products of maximal perpendicular tumour dimensions or the appearance of any new lesion.

## RESULTS

Forty-five patients received only a single dose of mitozolomide; 23 had two doses and nine received three or more courses.

### *Toxicity*

Myelosuppression was a major problem. It was considered responsible for two deaths among the first 11 lung cancer patients who received 115 mg/m$^2$. Subsequently, all patients were treated with lower doses and median nadir blood counts were more acceptable (Table 2). However, eight patients developed Grade 4 thrombocytopenia after an initial dose of 90 or 100 mg/m$^2$; four of these eight had received no prior treatment and bone marrow infiltration was not evident from the appearance of pretreatment blood films. Despite dose reduction, mitozolomide was considered to have contributed to three further deaths, and six patients required platelet transfusions for spontaneous ($n$ = 3) or tumour related haemorrhage. Septicaemia was not seen at doses below 115 mg/m$^2$ and only one patient experienced Grade 4 leucopenia.

The degree of myelosuppression was dose related (Table 2) though dose alone failed to predict Grade 4 toxicity. There was no apparent association with age (Fig. 1a) or renal function (Fig. 1b). Limited pharmacokinetic data were available which indicated that the extent of thrombocytopenia was unrelated to peak drug levels or total drug exposure as determined by AUC (J. Slack, personal communication).

The median time to platelet nadir was 28 days (range 20–45); leucopenia tended to occur later (median day 35: range 22–50). Retreatment was delayed by myelotoxicity in five of 32 patients receiving a second course. Three patients had doses reduced for previous Grade 3 toxicity and four who initially received 115 mg/m$^2$, were retreated with 90 mg/m$^2$. Myelosuppression was notably less severe though one patient had Grade 4 thrombocytopenia. Three patients received 4 or more doses and prolonged Grade 1–2 toxicity regularly delayed treatment, despite appropriate dose reductions.

Non-haematological toxicity was minor. Antiemetic therapy was not routinely prescribed and 26 patients (34%) experienced no gastrointestinal symptoms. Nausea occurred with 19% of all courses given in a total of 17 patients and vomiting in 36% (30 patients). Emesis usually occurred 3–6 h after

*Table 2. Myelosuppression following the first dose of mitozolomide*

| Dose | No. of patients | Nadir WBC Median | Nadir WBC Range | Nadir platelet count Median | Nadir platelet count Range |
|---|---|---|---|---|---|
| 1. *Prior therapy* | | | | | |
| 115 mg/m² | 4 | 2.3 | 0.4–3.2 | 42 | 13–45 |
| 100 mg/m² | 3 | 4.5 | 0.9–15.5 | 90 | 12–243 |
| 90 mg/m² | 22 | | | | |
| 70 mg/m² | 10 | 4.8 | 1.3–9.3 | 130 | 37–226 |
| 2. *No prior therapy* | | | | | |
| 115 mg/m² | 7 | 2.8 | 1.0–5.1 | 29 | 9–141 |
| 100 mg/m² | 13 | 2.5 | 1.0–8.2 | 66 | 11–115 |
| 90 mg/m² | 14 | 2.8 | 2.1–9.4 | 114 | 20–410 |

Data recorded for 73 of 77 patients; nadir blood counts omitted in four patients due to early deaths in two and non-availability in two.

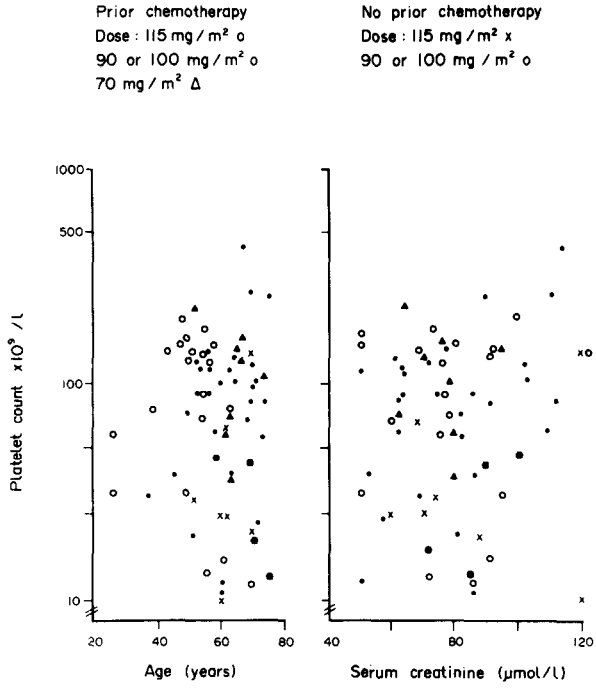


*Fig. 1. Relationship of nadir platelet count to (a) patient age, (b) renal function.*

mitozolomide ingestion, and vomitus from only one patient, within 30 min of mitozolomide ingestion, contained fragments of gelatin capsules; absorption was assumed to be incomplete in this instance only.

*Response*

Tumour response to mitozolomide is shown in Table 3. Melanoma partial responses occurred in cutaneous (1), lung (1) and liver (1) metastases; they were maintained for 3, 7 and 9 months respectively. Two of the five partial responses in SCLC were in patients relapsing after initial remission: both occurred at the primary site and were of short duration (<2 months). The three partial responses in non-pretreated SCLC occurred in both limited ($n$ = 1) and extensive (liver, $n$ = 2) stage disease and lasted 5, 4 and 9 months respectively.

Responses were seen at dose levels of 90 mg/m² or more, though an initial dose of 70 mg/m² was given to only 10 patients, nine of whom had ovarian cancer. However, there may be some association between response and myelosuppression as four of five SCLC and one of three melanoma responders had Grade 3 or 4 toxicity with the first or second dose, though this did not reach statistical significance ($P$ = 0.08).

## DISCUSSION

These data indicate that mitozolomide is an effective cytotoxic agent in some human tumours. Demonstrable activity in melanoma has been previously documented [12]. However, the responses in ovarian cancer seen during preliminary evaluation [8] could not be confirmed in this population of extensively pretreated patients. It is possible that, despite equivalent toxicity of the oral and intravenous preparations (this study, [9]), activity in ovarian cancer may be confined to the intravenous formulation. Small cell lung cancer was clearly more responsive to mitozolomide than non small cell disease. However, although remissions were seen in SCLC, the relatively delayed nadir blood counts were a problem for non-responders in that alternative therapy could not safely be administered before day 28.

It is possible that there is a significant dose/response relationship for some tumours; the two responses in ovarian cancer in the Phase I study occurred at doses of 115 and 153 mg/m² (G. Blackledge, personal communication). However, a similar proportion of melanoma responses (two of 21) occurred at 115 mg/m² [11] as were seen in this study using lower mitozolomide doses. The observed association between myelosuppression and tumour response, particularly in SCLC, suggests that biological activity may be dependent on pharmaco-dynamic parameters with appreciable interpatient variation.

*Table 3. Tumour response to mitozolomide*

| | Tumour type | | | |
|---|---|---|---|---|
| | Melanoma | Lung cancer | | Ovarian cancer |
| | | SCLC | NSCLC | |
| Number | 20 | 20 | 17 | 20 |
| Inevaluable for response | 0 | 2<br>1 early death<br>1 ?absorption | 3<br>2 early deaths<br>1 mesothelioma | 6<br>2 early deaths<br>1 ascites only<br>1 lost to follow up<br>2 NC after 1 course withdrawn for toxicity |
| Response | | | | |
| PR | 3 | 5 | 0 | 0 |
| NC | 1 | 1 | 5 | 3 |
| Progression | 16 | 12 | 9 | 11 |

The major problem with mitozolomide was unpredictable myelosuppression. The pattern of myelotoxicity is similar to that of the nitrosoureas, with the nadir occurring at 4–6 weeks and thrombocytopenia being more common than leucopenia. However, despite reducing the initial dose to levels lower than recommended on the basis of Phase I studies [8, 9], platelet transfusion requirements were unacceptably high as well as the unpredictable occurrence of Grade 4 toxicity which necessitated premature closure of accrual to the SCLC and melanoma studies. Our data further suggest that repeated doses of mitozolomide cause cumulative bone marrow toxicity with delayed blood count recovery. Thus, even if patients at risk of idiosyncratic toxicity could be identified, the use of mitozolomide in combination with other myelosuppressive drugs could be hazardous.

In conclusion, these Phase II studies indicate that promising preclinical (xenograft) studies should be interpreted with caution, since they may fail to predict the degree of normal tissue toxicity of an agent such as mitozolomide. These and similar data have led to a decision to withdraw the drug from further study.

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