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Short communication

Phase I study of mitozolomide on a once daily for 5 days schedule

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Summary. In a phase I study mitozolomide was given on a once daily for 5 days schedule to 18 patients with a variety of malignancies. Non-hematological toxicity was negligible. Significant myelosuppression occurred at a total dose as low as 62.5 mg/m^2 per course. In particular, thrombocytopenia, which was unpredictable, precluded dose increments beyond 15 mg/m^2 per day (or a total of 75 mg/m^2). Antitumor effects were not observed. The 5-day schedule of mitozolomide appears to have no advantage over administration once every 3–4 weeks, and may even be more dangerous than the latter schedule.

Introduction

Mitozolomide is an imidazotetrazine antitumor agent, which was synthesized at Aston University in Birmingham [7]. The drug has shown pronounced activity against a broad spectrum of murine test tumors [3] as well as against human tumor xenografts (SCLC and melanoma) in nude mice [1]. In clinical phase I studies in which the drug was given in a single dose every 3–5 weeks, mitozolomide was found to have minimal non-hematological toxicity up to a dose of 115 mg/m^2, the major toxicity being thrombocytopenia and some degree of nausea [4, 6]. From preclinical studies it is known that the administration of mitozolomide once daily for 5 days is as active as the single-dose administration [3].

The aim of this study was to determine the maximum tolerated dose of mitozolomide using a daily $\times 5$ i.v. schedule, to identify the toxicity profile of this schedule, and to define a safe mode of administration for subsequent phase II studies.

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Patients and methods

All patients included in this study had histologically confirmed cancer for which no conventional treatment was available; an ECOG performance score of 0–3; an age of between 14 and 75 years; adequate liver and renal function; a WBC count of >3,000/mm^3; and a platelet count of >100,000/mm^3. Patients had had no anticancer therapy in the preceding 3 weeks (6 weeks for nitrosourea and mitomycin C) and had recovered from the toxic effects of prior treatment. All patients gave their witnessed oral informed consent. The starting dose was 12.5 mg/m^2 daily $\times 5$, based on data from the first phase I studies [4, 6], and the drug was given by brief i.v. infusion over 1 h. Courses were repeated every 4 weeks or after full recovery from toxicity. In cases of delayed toxicity, intervals between treatments were appropriately lengthened in subsequent courses.

Dose increments were planned to follow a modified Fibonacci scheme, and at least three evaluable patients were entered at each dose level. An interval of at least 1 week was required before the entry of patients at any given dose level. A 3-week interval was required for the entry of patients into the next dose level so as to take delayed toxicity into account. At non-toxic doses, one increment in dose was permitted within each individual patient, but further increments required new patients. Patients were scheduled to receive at least two courses of therapy. Responding patients were allowed to continue on mitozolomide, with doses being adjusted according to individual tolerance.

Table 1. Patient characteristics

Patients (n)	18
Men/women	12/6
Median age (range)	46 (21–7) years
Median ECOG performance status (range)	1 (0–3)
Median number of prior cytostatic agent (range)	2 (0–7)
Number of patients without prior chemotherapy	2
Tumor types:	
Colorectal	3
Melanoma	3
Head and neck	2
Ovarian	2
Renal	2
Unknown primary	2
Others	4

Table 2. Hematological toxicity

Dose (mg/m² daily)	Patients (n)	Courses (n)	Nadir WBC Median (range) (× 10⁹/l)	Nadir platelet count median (range) (× 10⁹/l)
10	3	9	5.5 (2.3–5.6)	115 (90–130)
12.5	7	14	4.5 (1.1–7.3)	50 (33–180)
15	9	17	4.3 (2.1–9.4)	90 (25–254)

One patient was treated at two dose levels

Results and discussion

The characteristics of the 18 patients entered in this study are shown in Table 1. There were 12 men and 6 women with a median age of 46 (range, 21–71) years and a median performance score of 1 (range, 0–3). Two patients had not undergone prior chemotherapy. Tumor types included melanoma and colorectal, head and neck, ovarian, unknown primary, renal, testicular and breast cancers, as well as Ewing's and soft-tissue sarcomas. A total of 40 courses (median number/patient, 2; range, 1–5) were given at only 3 dose levels. Toxicity was scored according to standard WHO criteria [5].

The first patient was treated at 12.5 mg/m² daily × 5, developed grade 3 thrombocytopenia (nadir, 40,000 platelets/mm³), and died of hemorrhage from necrotic tumor. Three subsequent patients received 10 mg/m² daily × 5 (nine courses), and only one course was associated with grade 1 thrombocytopenia. Grade 3 thrombocytopenia was observed in 3 of 14 courses (7 patients) at 12.5 mg/m² daily and in 2 of 17 courses (9 patients) at 15 mg/m² daily. Thrombocytopenia typically occurred around day 28 and recovered after a median of 13 days (range, 7–23 days). Only one course was associated with grade 3 leukocytopenia (at 12.5 mg/m² daily). The data on hematological toxicity are summarized in Table 2.

Non-hematological toxicity was negligible. Only one patient experienced grade 2 nausea and vomiting during one course. No other non-hematological toxicity was observed. No objective tumor responses were recorded, although three patients experienced stabilization of their disease for >3 months.

This study was undertaken to find a safer mode of administration of mitozolomide, since previous phase I studies had shown that the drug caused unpredictable myelosuppression when given once every 3–4 weeks. The data from this phase I trial indicate that the 5-day schedule has no advantage over administration once every 3–4 weeks and that, in fact, significant thrombocytopenia occurs at a total dose as low as 62.5 mg/m² per course. The trial was stopped since it was felt to be unsafe to increase the dose beyond 15 mg/m² per day (or a total of 75 mg/m²). Although mitozolomide has been documented to show activity against human cancer, including melanoma [2], the drug has been withdrawn from further studies because of unpredictable and life-threatening myelosuppression.

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