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ORIGINAL ARTICLE

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Phase I study of mitoxantrone, raltitrexed, levofolinic acid and 5-fluorouracil in advanced solid tumours

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Abstract *Purpose*: We have recently evaluated the combination of raltitrexed, levofolinic acid (LFA) and 5-fluorouracil (5-FU) in advanced head and neck and colorectal cancer, and we have shown that this combination is well tolerated and has clinical activity. Clinical combination studies have shown that raltitrexed and anthracyclines can be combined at full doses without unexpected toxicities. Based on these observations, we started a phase I study of mitoxantrone plus raltitrexed administered on day 1, followed by LFA and 5-FU on day 2 in patients with advanced solid tumors. *Patients and methods*: Mitoxantrone was given at a starting dose of 6 mg/m^2, raltitrexed at a fixed dose of 3 mg/m^2, LFA at a fixed dose of 250 mg/m^2, and 5-FU at a starting dose of 750 mg/m^2. Mitoxantrone and 5-FU doses were subsequently escalated alternately up to dose-limiting toxicity. Treatment was repeated every 14 days. *Results*: Four dose levels were tested in 18 patients. All three patients treated at the fourth dose level had grade 4 neutropenia after the first cycle. Therefore, this level was defined as the maximum tolerated dose and the dose level immediately below (mitoxantrone 7 mg/m^2 and 5-FU 900 mg/m^2) was selected for further evaluation. Neutropenia was the main toxic effect. Nonhaematologic side effects were mild. One complete response and five partial responses (all but one in patients with head and neck cancer) were observed, for an overall response rate of 33% (95% confidence interval, 13% to 59%). *Conclusions*: Mitoxantrone, raltitrexed and 5-FU can be combined at doses which are close to those used in monotherapy. The observed activity is encouraging, especially in the subset of patients with head and neck cancer.

Key words Advanced solid tumours · 5-Fluorouracil · Levofolinic acid · Mitoxantrone · Raltitrexed

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Introduction

Raltitrexed is a direct and specific thymidylate synthase (TS) inhibitor, which has shown clinical activity in a broad range of solid tumours [3]. Clinical combination studies have shown that raltitrexed and anthracyclines can be combined at full doses without unexpected toxicities [7, 9]. Mitoxantrone (dihydroxyanthracenedione, DHAD) is a completely synthetic DNA intercalator based on the anthracenedione structure and may be viewed as an analogue of the anthracyclines. It has qualified as a manageable and active drug in the treatment of a number of neoplasms, with a safety profile that is much more favourable than that of anthracyclines [5].

We have recently evaluated the combination of raltitrexed, followed 24 h later by LFA and 5-FU, administered every 2 weeks, in advanced head and neck cancer (HNC) and colorectal cancer [2]. This combination is well tolerated at the doses of the two cytotoxic drugs that are given in monotherapy, and has a meaningful clinical activity. In particular, in our study, 6 of 40 patients with metastatic colorectal cancer, most of whom had been pretreated, achieved an objective response. On the other hand, 6 of 17 patients (35%) with advanced HNC achieved an objective response, which was recorded in 5 of 8 untreated patients (62.5%).

Based on the above observations, we started a phase I study of mitoxantrone plus raltitrexed administered on day 1, followed by LFA plus 5-FU on day 2, in patients with advanced solid tumours.

Patients and methods

Patient selection

Eligibility criteria for study entry included pathologically confirmed advanced solid tumours not or no longer amenable to standard therapies, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate baseline organ function defined as WBC counts ≥3000/μl, platelets ≥100,000/μl, bilirubin ≤1.5 mg/dl, serum transaminases not more than twice the upper limit of normal, creatinine clearance ≥60 ml/min, and a life expectancy of at least 3 months. Patients with more than two lines of prior chemotherapy and patients whose prior radio- or chemotherapy had been completed less than 4 weeks before were ineligible. Patients with a history of congestive heart failure or severe coronary heart disease were also ineligible. In addition, pregnancy, uncontrolled infection, cerebral metastases, concurrent or previous malignancy, and severe neurologic disease also constituted exclusion criteria. Written informed consent was obtained from each patient.

Treatment plan

Patients received mitoxantrone at a starting dose of 6 mg/m^2 diluted in 250 ml normal saline solution, followed by raltitrexed at a fixed dose of 3.0 mg/m^2 in 250 ml normal saline solution, on day 1. On day 2, LFA was given at a fixed dose of 250 mg/m^2 and was followed by bolus 5-FU at a starting dose of 750 mg/m^2. Metoclopramide was used as antiemetic coverage on both days. Mitoxantrone and 5-FU doses were subsequently escalated alternately. Doses were assigned at registration and no intrapatient dose escalation was permitted. Treatment was repeated every 14 days and withheld for 1 week (until day 21) if the neutrophil count was < 1500/μl, the platelet count was < 100,000/μl, or haemoglobin was < 9.5 mg/dl at the time of chemotherapy recycling. If treatment could not be administered on day 21 due to persistent toxicity, it was postponed to day 28, in which case a 25% dose reduction was applied to mitoxantrone, raltitrexed, and 5-FU. If full haematologic recovery did not occur within 2 weeks, treatment was discontinued.

Toxicity was graded according to standard WHO criteria. In the case of grade 4 bone marrow toxicity or febrile neutropenia occurring at nadir, even after full recovery, drugs were administered with a reduction to 75% of the planned dose over subsequent courses. If grade 4 neutropenia occurred even with this dose reduction, a further 25% dose reduction was applied. In case of extrahaematologic toxicity of grade 2 or more (except alopecia, nausea, vomiting) occurring on day 15, drug administration was delayed until grade 1 or less had been achieved up to day 28. Granulocyte colony-stimulating factor (G-CSF) was permitted in patients with grade 4 neutropenia or febrile neutropenia.

Cohorts of at least three patients were treated at each dose level. Dose escalation proceeded if no patients had dose-limiting toxicity (DLT) after the first cycle. If one of three patients had DLT, three more patients were enrolled at that level. Dose escalation was stopped if more than one-third of patients of a given cohort had DLT, which was defined as grade 4 neutropenia or thrombocytopenia, grade 3 febrile neutropenia, grade 3 thrombocytopenia with bleeding, grade 3 nonhaematologic toxicity (except nausea and alopecia), or a delay of more than 2 weeks in chemotherapy recycling. The maximum tolerated dose (MTD) was defined as the dose level causing DLT in more than one-third of patients and the dose level immediately below was recommended for further evaluation.

Patient evaluation

At enrolment, patients were evaluated by a complete history and physical examination, performance status recording, complete blood cell (CBC) count with differential, serum chemistries, urinalysis, ECG, chest radiography, total body computed tomography (CT) scan, abdomen ultrasonography. Other examinations were performed as required in individual patients. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, CBC count and a complete biochemistry profile. ECG was repeated at the beginning of each cycle. Evaluation for tumour response was performed every four cycles of chemotherapy, with repetition of all the tests which were abnormal at baseline.

Complete response (CR) was defined as the disappearance of all symptoms and signs of all measurable disease, lasting for at least 4 weeks, during which no new lesions appeared. Partial response (PR) was defined as a reduction of > 50% in the sum of the products of the perpendicular diameters of all measurable lesions, lasting for at least 4 weeks, during which no new lesions appeared and no existing lesions enlarged. Stable disease (SD) was defined as a reduction of < 50% and an increase of < 25% in the sum of the products of two perpendicular diameters of all measured lesions, and the appearance of no new lesions. Progressive disease (PD) was defined as an increase in the product of two perpendicular diameters of any measured lesion by > 25% over the size present at entry, or the appearance of new lesions. Patients with SD or responsive disease after four courses of chemotherapy received additional treatment up to a maximum of eight courses; patients with PD were withdrawn from the study. Duration of response was measured from the date of initial documentation to the date of PD.

Results

Patient characteristics

From November 1998 to November 1999, 18 patients were entered into the study, of whom 12 had received prior chemotherapy. Among the six patients who had never been pretreated with chemotherapy, two patients with HNC had received prior radiotherapy. Squamous cell carcinoma of the head and neck represented the most frequent tumour type. Patient characteristics are detailed in Table 1. A total of 75 courses of treatment were given, for a median of four courses per patient (range, one to eight).

Dose escalation results

A total of four dose levels were tested. All three patients treated at the fourth dose level had grade 4 neutropenia after the first cycle. Therefore, this level was defined as the MTD, accrual was stopped and the third dose level was considered as recommendable for further evaluation. Dose escalation results are detailed in Table 2.

Toxicity

Neutropenia occurred in 16 of 18 patients, reaching grade 4 in ten patients, considering all delivered cycles. G-CSF was given subcutaneously in these patients at a dose of

Table 1 Patient characteristics (total 18)

Age (years)	
Median	54
Range	29–75
Sex	
Male	11
Female	7
Performance status	
0	1
1	10
2	7
Primary site	
Head and neck	7
Breast	4
Unknown	2
Nasopharynx (undifferentiated)	2
Cervix	1
Endometrium	1
Salivary gland	1
Previous chemotherapy	12
One line	8
Two lines	4
None	6

300 μg/day for three consecutive days and full haematologic recovery always occurred. Thrombocytopenia and anemia never exceeded grade 2. Stomatitis was the most frequent among nonhaematologic side effects, since it occurred in ten patients across all dose levels, and reached grade 3 in only one patient treated at the third dose level. This patient had completed radiation therapy for HNC 2 months before. Other side effects never exceeded grade 1. In particular, ECG changes were never recorded, nor did any renal toxicity or diarrhoea occur. Treatment was delayed by 1 week in 30 courses (40%) because of failure of recovery from toxicity at the date of the planned recycle. Dose reduction (25%) of the three cytotoxic drugs was performed in ten courses (13%). The mean dose intensities of mitoxantrone, raltitrexed and 5-FU actually delivered at the step selected for further evaluation were 2.8, 1.2, 360 mg/m^2 per week, respectively. No patient was withdrawn from the study because of failure of recovery from toxicity.

Response evaluation

Of the 18 patients entered, 14 completed at least four courses of chemotherapy and were formally assessable for response. Four patients (two patients with nasopharyngeal cancer, one patient with unknown primary tumour, and one with HNC) died before completion of four courses because of overt disease progression. These patients were considered as treatment failures, according to intention to treat analysis. One CR and five PRs were observed among all treated patients, for an overall response rate of 33% (95% confidence interval, 13% to 59%). Apart from a patient with cancer of the cervix treated at the second dose level, who had a PR, all of the other five responses were observed among the seven patients with HNC, all of whom had recurrent disease after chemoradiotherapy (five patients) or radiotherapy alone (two patients). Median duration of response for the subset of patients with HNC was 5 months (range, 2 to 8+ months). Previous chemotherapy for HNC patients consisted of a combination of docetaxel and cisplatin, which was administered for three cycles before radiation therapy. The median interval from previous chemotherapy was 13 months (range, 6 to 22 months).

Discussion

This study was started following our previous phase I trial with raltitrexed plus LFA plus 5-FU [2], in which a very encouraging activity in advanced HNC and colorectal cancer was observed. The above study, the first in which raltitrexed was given in a biweekly schedule, clearly demonstrated that it is possible to combine raltitrexed and 5-FU at the doses used in monotherapy, with a raltitrexed dose intensity which is substantially higher than that achievable with the standard every-3-week schedule. The encouraging results might point to a potential synergism between the three drugs.

In the present study we tested the combination of mitoxantrone with raltitrexed, folinic acid and 5-FU. As in the previous study, the schedule of drug administration was chosen in keeping with experimental and clinical data, which suggested that an adequate interval should elapse between raltitrexed and 5-FU administration for a synergistic effect to occur [6], while a relatively high dose of folate is indicated immediately before the administration of 5-FU. Our previous preclinical experience in three colon cancer cell lines (LoVo, GEO and SW620), and in three HNC cell lines (KB, ZA, HOC313) suggested that if LFA and 5-FU are administered 24 h after raltitrexed, not only does LFA not interfere with raltitrexed uptake and polyglutamation, but there is a clear schedule-dependent synergism between the three drugs [1]. We preferred to use a regimen

Table 2 Dose escalation results

Level	Mitoxantrone/ raltitrexed/ 5-FU (mg/m^2)	Number of patients	DLT			Response
			Number	Type	Grade	
1	6/3/750	3	0	–	–	0
2	6/3/900	6	2	Neutropenia	4	2 PR
3	7/3/900	6	2	Neutropenia	4	1 CR; 2 PR
4	7/3/1050	3	3	Neutropenia	4	1 PR

which included intravenous bolus 5-FU administration since it could be administered entirely on an outpatient basis, thus substantially lowering costs and improving patient compliance. Previous data confirming the activity of the drug when administered as intravenous bolus in this setting [4] encouraged us in the choice of this treatment schedule.

We are now in the process of testing other compounds in combination with our original raltitrexed-LFA-5-FU regimen. The partially nonoverlapping toxicity profile of mitoxantrone with respect to the other drugs used, along with the clinical feasibility of full-dose combinations of raltitrexed and anthracyclines in other ongoing clinical studies [7, 9] lend support to our choice of including mitoxantrone in the treatment schedule. The results of our dose-escalation clearly demonstrate that it is possible to combine mitoxantrone, raltitrexed, and 5-FU at doses which are close to those used in monotherapy. In particular, mean dose intensity of raltitrexed actually delivered at the level which was selected for phase II is considerably higher than that achieved with the standard every 3-week schedule. Such a high dose intensity could be achieved since toxicity was moderate.

As expected, neutropenia represented the main toxic effect and was the DLT. Although neutropenia was observed in nearly all patients, even at the lowest dosages, it was never febrile and was easily reversible. G-CSF was utilized in grade 4 neutropenia and induced complete haematologic recovery within a median of 3 days. Thrombocytopenia and anemia were never troublesome side effects, since they never exceeded grade 2. Only one case of grade 3 stomatitis in a patient with recently irradiated HNC was observed. Other extrahaematologic side effects never exceeded grade 1. In particular, ECG changes were never recorded, while renal toxicity, which has occasionally been a concern in other clinical trials with raltitrexed alone or in combination [8], was never observed with our schedule. The observed activity in our study is encouraging. In particular, five out of seven patients with recurrent HNC (all but one previously treated with chemo- plus radiotherapy) achieved an objective response. A phase II study in this subset of patients is ongoing in order to better estimate the activity of the regimen.

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