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CLINICAL TRIAL REPORT

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Phase II study of Temodal in the treatment of patients with advanced nasopharyngeal carcinoma

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Abstract *Purpose*: A single-institution phase II trial of Temodal (temozolomide, SCH52365) in Chinese patients with advance nasopharyngeal carcinoma was undertaken to determine the efficacy and safety of the drug in this population. *Methods*: A total of 14 patients with metastatic or locoregionally recurrent nasopharyngeal carcinoma were entered into the study. One patient was unevaluable. Temodal was given at doses of 150 or 200 mg/m^2 daily on days 1–5 every 28 days. *Results*: In all, 30 cycles of Temodal were given with no significant toxicity. All 13 (100%) evaluable patients had progressive disease after 2 (84.6%) or 4 (15.4%) courses. *Conclusion*: Temodal given on this schedule has no activity in advanced nasopharyngeal carcinoma.

Key words Nasopharyngeal carcinoma · Temodal

Introduction

Nasopharyngeal carcinoma (NPC) is endemic in southern China, with over 95% of tumours belonging to WHO histological type III (undifferentiated carcinoma) [5, 12]. Early stages of the disease are curable by radical radiotherapy, but for patients with locoregionally advanced disease the rates of local relapse and distant metastasis are high and the resultant 5-year survival rates are poor [6]. Metastatic disease carries a poor prognosis, with the median survival being only around 9 months [10]. Both metastatic and locally recurrent NPC have been shown to be moderately chemosensitive. Cisplatin-containing regimens yield the highest response rates, although renal toxicity and neurotoxicity are not uncommon [1, 3, 4]. Non-cisplatin-based combinations have been less successful [13]. New agents are therefore needed for the treatment of advanced NPC.

Temozolomide is an orally active alkylating agent derived from imidazotetrazine. It was developed as a potential alternative to dacarbazine in view of its demonstrated antitumour activity and better toxicity profile in preclinical testing [9]. A phase I trial led to the recommendation that the starting dose for phase II studies be 150 mg/m^2 per day for 5 days every 28 days, with the dose being escalated to 200 mg/m^2 per day for 5 days in the absence of myelotoxicity [7]. Recent phase II studies have demonstrated response rates of 21% in malignant melanoma [2] and 30% in high-grade glioma [8], as opposed to only 5.5% in heavily pretreated patients with low-grade non-Hodgkin's lymphoma [11].

The present study was a phase II single-institution clinical trial of Temodal (temozolomide, SCH 52365, Schering-Plough) in Chinese patients with advanced NPC that aimed to determine the efficacy and safety of the drug in this population.

Patients and methods

Between July 1996 and July 1997, 14 patients were entered into the study. Written informed consent was obtained from every patient. All had adequate haematological, renal, and hepatic functions (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, haemoglobin ≥ 10 g/dl, urea and serum creatinine < 1.5 times the upper limit of normal, total serum bilirubin < 1.5 times the upper limit of normal, SGOT and SGPT < 2 times the upper limit of normal, and alkaline phosphatase < 2 times the upper limit of normal if arising from the liver or < 3 times the upper limit of normal if arising from bone).

Any radiation therapy was stopped more than 2 weeks before the start of treatment and any prior chemotherapy was stopped more than 4 weeks before the commencement of treatment. Pretreatment baseline investigations were performed within 14 days of study drug administration, which included visual examination of the nasopharynx; determination of the WHO performance status; haematological, renal and liver function tests; 12-lead ECG; chest X-ray; and computed tomography (CT) scan of the chest in the

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presence of lung metastases. CT scan or ultrasound of the abdomen, CT scan of the nasopharynx, and bone scan were performed only if clinically indicated. The study drug Temodal was given orally once a day for 5 consecutive days at a starting dose of either 150 mg/m^2 per day for patients previously treated with chemotherapy or 200 mg/m^2 per day for patients who had not received prior chemotherapy.

All patients had to fast for at least 4 h before and 2 h after the administration of each dose of Temodal. If no significant myelosuppression was noted on day 22 the dose was escalated to 20 mg/m^2 per day and repeated every 28 days. Common toxicity criteria (CTC) were used for all toxicity grading. Drug administration was postponed by 1 week in the absence of adequate haematological recovery (ANC $< 1.5 \times 10^9$/l, platelet count $< 100 \times 10^9$/l,). Doses were reduced to 75% for CTC grade 3 and 4 neutropenia or thrombocytopenia.

Assessment of response was performed after every two courses. Criteria of response were defined according to WHO criteria. A complete response (CR) was defined as the complete disappearance of all detectable tumour as determined by two observations made no less than 4 weeks apart. A partial response (PR) was defined as a reduction of at least 50% in the sum of the products of the two largest diameters of all measured lesions. Stable disease (SD) was defined as a $< 50\%$ decrease or a $< 25\%$ increase in the sum of the products of the largest diameters of all measurable lesions. Progressive disease (PD) was defined as an increase of $> 25\%$ in the size of at least one measurable lesion or the appearance of a new lesion.

Results

A total of 14 patients were entered into the study and their characteristics are listed in Table 1. One patient was ineligible for inclusion in the assessment after experiencing a serious adverse event on day 8 of cycle 1 associated with spinal cord compression due to bone metastases. The patient was withdrawn from the study. Of the 13 evaluable patients, 8 (61.5%) were chemotherapy-naive, 1 (7.7%) had received prior cisplatin as a radio-sensitizer during primary radiotherapy (RT), 1 (7.7%) had received prior carboplatin/5-fluorouracil (5FU) neoadjuvant to primary RT and carboplatin/paclitaxel as salvage therapy, and 3 (23.1%) had received prior carboplatin/5FU or carboplatin/paclitaxel as salvage therapy. The metastatic sites were the lung (61.5%), liver (38.5%), bone (38.5% and lymph glands (23.1%). In 23.1% of cases there was locoregional disease. There were multiple sites of involvement in 8 (61.5%) patients.

Table 1 Patients characteristics

Total number of patients entered	14
Number of evaluable patients	13
M/F	12/1
Median Age (years)	45
Range	38–65
WHO performance score 0/1/2	10/3/0
Sites of disease involvement:	
Lung	8 (61.5%)
Liver	5 (38.5%)
Bone	5 (38.5%)
Lymph node	3 (23.1%)
Locoregional	3 (23.1%)
Median number of courses (range)	2 (2–4)

Table 2 Toxicities encountered during Temodal treatment for 30 treatment cycles in 13 patients, shown as worst CTC grade

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	10	16	4	0	0
Leucocyte	27	3	0	0	0
Neutrophils	28	2	0	0	0
Platelets	29	1	0	0	0
Haemoglobin	25	2	3	0	0

In all, 30 cycles of Temodal were given, and the most frequently encountered toxicities are listed in Table 2. There was no major haematological or non-hematological toxicity (grade 3 or 4 CTC), and no treatment delay was necessary. In all, 11 (84.6%) patients had PD documented after 2 courses of Temodal, and 2 (15.4%) had PD documented after 4 courses of Temodal. No objective response was observed in the 13 patients. On the basis of these results, the accrual to this trial was closed; 4 patients (38.5%) were given further palliative systemic treatment. At the time of reporting, 4 patients (30.8%) had died of their disease and 9 (69.2%) were alive with disease.

Discussion

Advanced NPC has a poor prognosis after the diagnosis of distant metastasis. This reflects the aggressive nature of this disease and highlights the importance of identifying active chemotherapeutic agents. To date, the most promising results have come from cisplatin-based chemotherapy, which has been reported to yield response rates of 40–91% and has occasionally been reported to result in long-term disease-free survival in patients achieving a CR [1, 3, 4]. It has therefore been suggested that metastatic NPC may nonetheless be curable in a small subset of patients [3]. However, new active agents are needed against this aggressive disease.

Oral temozolomide has been shown to be active in malignant melanoma and primary brain tumours but inactive in heavily pretreated patients with low-grade non-Hodgkin's lymphoma [3, 8, 11]. In this phase II study, Temodal was demonstrated to be inactive when given at 200 mg/m^2 per day on days 1–5 every 28 days to patients with advanced NPC. The patient population was not heavily pretreated, with 61.5% of patients being chemotherapy-naive and 23.1% having been exposed to only one prior salvage chemotherapy regimen. The toxicities were minimal, which may suggest that the dose schedule could be suboptimal. However, the inactivity in NPC of Temodal given on a dose schedule similar to those used in other phase II trials in melanoma and primary brain tumours, has led us to conclude that Temodal has no role in the management of advanced NPC patients.

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