

## **Phase II trial of docetaxel in patients with recurrent malignant glioma: a study of the National Cancer Institute of Canada Clinical Trials Group**

Peter Forsyth<sup>1</sup>, Greg Cairncross<sup>2</sup>, David Stewart<sup>3</sup>, Michael Goodyear<sup>4</sup>, Nancy Wainman<sup>5</sup> and Elisabeth Eisenhauer<sup>5</sup>

<sup>1</sup>Department of Medicine, Tom Baker Cancer Centre and Clinical Neurosciences, Foothills Hospital, Calgary, Alberta; <sup>2</sup>Department of Clinical Neurological Sciences and Oncology, University of Western Ontario and London Regional Cancer Centre, London, Ontario; <sup>3</sup>Department of Medicine, University of Ottawa and Ottawa Regional Cancer Centre, Ottawa, Ontario; <sup>4</sup>Hamilton Regional Cancer Centre, Hamilton, Ontario; <sup>5</sup>National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada

*Key words:* docetaxel, malignant glioma, phase II

### **Summary**

*Background.* We conducted a phase II study to determine the response to, and toxicity of, docetaxel (Taxotere; Rhône Poulenc Rorer Pharmaceuticals, Inc) in patients with recurrent malignant glioma.

*Patients and methods.* Eighteen patients with recurrent malignant glioma were treated with 100 mg/m<sup>2</sup> (no prior chemotherapy) or 75 mg/m<sup>2</sup> (prior adjuvant chemotherapy) of docetaxel intravenously over 1 hour, every 3 weeks. Premedication with dexamethasone, diphenhydramine and ranitidine or cimetidine was given to all patients. Five (28%) had glioblastoma multiforme (GBM) and the rest other malignant gliomas. Eleven (61%) had an ECOG performance status of 0 or 1, and 13 (72%) were on corticosteroids at the start of treatment. Rigorous response criteria were used. All were eligible and evaluable for response.

*Results.* No complete or partial responses were observed; the objective response rate was 0% (95% confidence interval: 0–15.3%). Patients received a median of 2 cycles (range, 1–6). Grade 3 or 4 neutropenia occurred in 17 (94%) patients and was associated with fever that required intravenous antibiotics in 4 (22%) patients. An additional patient received intravenous antibiotics for an infection not associated with neutropenia. Six (33%) patients had mild hypersensitivity reactions. Onychodystrophy, peripheral edema and peripheral neuropathy were uncommon and mild.

*Conclusions.* Docetaxel has no significant activity in patients with recurrent malignant glioma.

### **Introduction**

Other than in anaplastic oligodendroglioma [1], there is no clearly effective conventional chemotherapy for patients with recurrent malignant gliomas. Many agents have been studied, but none have produced a significant number of complete or durable responses. Other approaches, including high dose chemotherapy with marrow rescue and local application of chemotherapy by polymer implants are being evaluated. Docetaxel (Taxotere; Rhône Poulenc Rorer Pharmaceutical Inc) is a

semisynthetic taxane derived from the needles of the European Yew, *Taxus baccata*. It has shown major activity in several solid tumors. Phase I trials defined the dose-limiting toxicity to be neutropenia and recommended a dose of 100 mg/m<sup>2</sup> intravenously every 3 weeks. The purpose of this phase II study was to determine the efficacy and safety of docetaxel in the treatment of patients with recurrent malignant gliomas.

## Methods

Eligibility criteria included: histologic proof of malignant glioma (Kernohan grade 3 or 4), life expectancy of  $\geq 12$  weeks, ECOG performance status of  $\leq 3$ , stable corticosteroid dose for  $\geq 2$  weeks, bidimensionally measurable enhancing tumor ( $\geq 2 \times 2$  cm), a minimum of 2 months following adjuvant radiation treatment, and 6 weeks following surgery or adjuvant chemotherapy. Recurrent glioma was defined as a worsening CT/MR scan with or without clinical changes; histologic diagnosis at recurrence was not required. Laboratory requirements included adequate hematologic (granulocytes  $\geq 2.0 \times 10^9/L$ , platelets  $\geq 100 \times 10^9/L$ ), and biochemical parameters (serum creatinine and bilirubin  $\leq 1.5$  times the upper normal limit, and aspartate aminotransferase  $\leq 2$  times the upper normal limit). Patients were ineligible if they had received any chemotherapy or radiotherapy for recurrent disease or had symptomatic peripheral neuropathy. This study was approved by the Research Ethics Boards at each institution and all patients gave written informed consent.

Docetaxel was administered at a dose of 100 mg/m<sup>2</sup> (no prior chemotherapy) or 75 mg/m<sup>2</sup> (prior adjuvant chemotherapy) as a 1 hour intravenous (IV) infusion every 3 weeks; toxicity was graded using NCIC Clinical Trials Group Expanded Common Toxicity Criteria. In order to decrease the risk of hypersensitivity reactions and reduce the severity of cumulative edema, patients were given oral dexamethasone 20 mg 12 and 6 hours before docetaxel and 8 mg twice daily for 3 days beginning immediately after docetaxel infusion. Pre-medication also included diphenhydramine 50 mg IV and either ranitidine 50 mg IV or cimetidine 300 mg IV 30 minutes before docetaxel. Therapy continued until there was progressive disease or unacceptable toxicity. Hematology was assessed weekly and docetaxel dose reduced by 25% for nadir granulocyte counts  $< 0.5 \times 10^9/L$  for  $\geq 7$  days, platelet counts of  $< 25 \times 10^9/L$ , febrile neutropenia treated with intravenous antibiotics,  $\geq$  grade 3 infection, or bleeding requiring transfusion. For other toxic effects of  $\geq$  grade 3 severity, treatment was held until resolution and, if appropriate, docetaxel was restarted at a dose reduction of 25%. Neurologic assessment was repeated after each cy-

cle and CT or MRI scans repeated every 3 weeks whenever possible. A maximum of two cycles (6 weeks) between scans was permitted. Tumor size was determined at the maximum cross-sectional area of the enhancing mass of CT/MR scans and was calculated by multiplying the largest cross sectional diameter measured in centimeters by the largest diameter perpendicular to the first measurement. Response criteria were based on clinical neurologic findings, changes in corticosteroid dose and objective tumor size and are described in detail elsewhere [2]. Briefly, a minimum of 50% reduction in tumor size was required for a patient to be classified as having had a response. Response duration was calculated from the time the measurement criteria were first met until progression. Patients having a less than a 50% decrease and less than 25% increase in tumor size documented at least once after treatment began were classified as stable disease; duration of stable disease was measured from the time of initiating docetaxel therapy. Those with a 25% increase in tumor size were designated as having disease progression. A two stage design was used to detect a response rate of  $\geq 20\%$ : 15 patients were initially enrolled and 15 more accrued if  $\geq 1$  response was observed.

## Results

Eighteen patients (median age 42 years; range 28–68) were entered on this study (Table 1); all were eligible and evaluable for response and toxicity. A total of 49 cycles of docetaxel were administered with a median of 2 (range: 1–6). Neutropenia was the most common grade 4 toxicity and was seen in 15 of 18 patients. Febrile neutropenia occurred in one patient and four (three of whom were neutropenic) had systemic infection which required parenteral treatment. Significant thrombocytopenia was not seen. Non-significant hypersensitivity symptoms were seen in 6 patients. Mild-moderate alopecia related to docetaxel was seen in 10 and stomatitis in 8 patients. Peripheral edema was mild and present in 7 (39%) patients. Mild onychodystrophy and peripheral neuropathy were present in 2 (11%) patients each. Serial nerve conduction studies in 3 patients (before, during and after treatment) showed no electrophysiologic evi-

Table 1. Patient characteristics and non-hematologic toxicities (any grade, worst ever by patient; related or unrelated to docetaxel), n = 18 patients

	# Patients	%
Gender		
Female	9	50
Male	9	50
Performance status (ECOG)		
0	1	6
1	10	56
2	2	11
3	5	28
Histology at diagnosis		
Glioblastoma	5	28
Malignant astrocytoma	12	67
Other <sup>a</sup>	1	6
Prior therapy		
Radiotherapy	18	100
Adjuvant chemotherapy	11	61
Starting dose docetaxel		
100 mg/m <sup>2</sup>	7	39
75 mg/m <sup>2</sup>	11	61
Other medications		
Corticosteroids	13	72
Anticonvulsants	15	83
Surgery at recurrence		
Biopsy only	2	11
Resection	3 <sup>b</sup>	17
None	13	72
Toxicity: worst by patient	Total	Gr 3 or 4
Neutropenia	17	17 (15 grade 4)
Lethargy	12	6
Alopecia	14	
Febrile neutropenia	1	1
Infection	9	4 <sup>c</sup>
Hypersensitivity	6	
Diarrhea	7	
Stomatitis	8	
Vomiting	8	
Peripheral edema	7	1
Rash	5	
Onychodystrophy	2	
Peripheral neuropathy	2	

Percentage may not add up to 100 because of rounding.

<sup>a</sup>Primitive neuroectodermal tumor with predominant astrocytic differentiation.

<sup>b</sup>One had histologic confirmation after experiencing PD on docetaxel.

<sup>c</sup>Required parenteral antibiotics.

dence of peripheral neuropathy. One patient died from progressive disease while on study. No complete or partial responses were seen (95% confidence interval = 0–15.3%). Thirteen (72%) had stable disease which had a median duration of 6 weeks (range: 4–32) and the other 5 (28%) had progressive disease.

## Discussion

We conclude that docetaxel given as in this study lacks significant activity in recurrent malignant glioma; no responses were seen and although 72% of patients were classified as having stable disease, it was of extremely short duration in the majority. The toxicities observed were similar to those seen in other phase II studies. Neutropenia was common and febrile neutropenia or severe infection was seen in 5 (28%) patients. Patients who had received prior adjuvant therapy and were given a lower dose of docetaxel (75 mg/m<sup>2</sup>) experienced similar degrees of myelosuppression (9/11 grade 4) to previously untreated patients given 100 mg/m<sup>2</sup> (6/7 grade 4). All patients received premedication and hypersensitivity reactions were mild. Fluid retention and nail toxicities were both mild and uncommon but the interpretation of this observation must be tempered by the fact that few patients received more than two treatment cycles and both of these toxicities are related to cumulative docetaxel dose.

The failure to observe any responses in this study was disappointing. Although *in vitro* studies of docetaxel have not been published, the other taxoid undergoing clinical evaluation, paclitaxel, has activity in glioma cell lines [3]. Furthermore, paclitaxel has been shown to penetrate gliomas in patients at therapeutic concentrations [4]. Thus it was reasonable to hope the same would be true of docetaxel, although this has not been shown as yet. It is also possible that the lack of response was due to altered taxane metabolism because most patients were taking anticonvulsants. Lower than expected plasma levels [5] and toxicity [6] when paclitaxel has been administered to glioma patients on anticonvulsants have been observed. We did not measure docetaxel levels but the frequency of grade 4 neutropenia and severe infection/febrile neutropenia we observed is compatible with other

docetaxel trials suggesting the serum levels were adequate and do not explain the lack of objective responses.

There is no other published phase II study of docetaxel in glioma. However, there are two trials of paclitaxel in recurrent gliomas [6, 7]. The first of these documented "response rate" of 35% but included stable disease patients as responders. The significance of stable disease is unclear given the routine use of steroids in these patients. The results with paclitaxel are being pursued in other studies, specifically in combination with radiation [8], but we do not feel, on the basis of our results, that further investigation of docetaxel is warranted in this disease.

### Acknowledgements

This study was coordinated by the Clinical Trials Group of the National Cancer Institute of Canada. The authors thank Frank Lu for statistical advice and Robin Cooper and Michelle Hynes for typing the manuscript. We would also like to thank the following investigators for entering patients on this study: Karl Belanger, Hopital Notre Dame, Montreal; Stan Gertler, Ottawa Regional Cancer Centre – Civic Hospital Division; Anthony Whitton, Hamilton Regional Cancer Centre; Carol Sawka, Toronto-Sunnybrook Regional Cancer Centre; David Macdonald, London Regional Cancer Centre; Dorcas Fulton, Cross Cancer Institute, Edmonton.

This trial was supported by grants from the National Cancer Institute of Canada and Rhône-Poulenc Rorer Pharmaceuticals Inc.

### References

1. Cairncross G, Macdonald D, Ludwin S, Lee D, Cascino T, Buckner J, Fulton D, Dropcho E, Stewart D, Schold C Jr, Eisenhauer E, Wainman N: Chemotherapy for anaplastic oligodendroglioma. *J Clin Oncol* 12:2013–2021, 1994
2. Macdonald DR, Cascino TL, Schold SC, Cairncross JG: Response criteria for phase II studies of malignant glioma. *J Clin Oncol* 8:1277–1280, 1990
3. Cahan MA, Walter KA, Colvin OM, Brem H: Cytotoxicity of taxol *in vitro* against human and rat malignant brain tumors. *Cancer Chemother Pharmacol* 33:441–444, 1994
4. Heimans JJ, Vermorcken JB, Wolbers JG, Eeltink CM, Meijer OWM, Taphoorn MJB, Beijnen JH: Paclitaxel (TAXOL) concentrations in brain tumor tissue. *Ann Oncol* 5:951–953, 1994
5. Fetell M, Grossman SA, Balmaceda C, Leu JG, Erlanger BF, Rowinsky E, Khandji AG, Yue N, Zeltman M: Clinical and pharmacologic study of pre-irradiation Taxol administered as a 96 hour infusion in adults with newly diagnosed glioblastoma multiforme (GBM). *Proc Am Soc Clin Oncol* 13:179, 1994 (abstr 504)
6. Prados M, Schold C, Spence A, Berger M, McAllister L, Mehta M, Gilbert M, Fulton D, Chang S: Phase II study of taxol in patients with recurrent malignant gliomas: North American Brain Tumor Consortium. *Proc Am Soc Clin Oncol* 14:146, 1995 (abstr 281)
7. Chamberlain MC, Kormanik P: Salvage chemotherapy with paclitaxel for recurrent primary brain tumors. *J Clin Oncol* 13:2066–2071, 1995
8. Glantz MJ, Choy H, Kearns CM, Cole BF, Mills P, Zuhowski EG, Saris S, Rhodes CH, Stopa E, Egorin MJ: Phase I study of weekly out-patient paclitaxel and concurrent cranial radiation in adults with astrocytomas. *J Clin Oncol* 14:600–609, 1996

*Address for offprints:* Peter Forsyth, MD, Department of Medicine, Tom Baker Cancer Centre, 1331 29th Street N.W., Calgary, Alberta, T2N 4N2, Canada. Phone: 613-545-6430; fax: 613-545-2944