Topotecan in the Treatment of Brain Metastases. A Phase II Study of GOIM (Gruppo Oncologico dell'Italia Meridionale)

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Abstract. *Background: Topotecan is able to cross the blood-brain barrier (BBB) and has been demonstrated to be active in brain metastases from small cell lung cancer (SCLC). Patients and Methods: The aim of this study was to evaluate the efficacy and toxicity of topotecan at a dosage of 1.5 mg/m^2 for 5 consecutive days every 3 weeks in patients with brain metastases from various neoplasms. Results: Among the 19 patients enrolled, objective responses were observed in 2 out of 3 patients affected by brain metastases from SCLC. Stable disease was observed in 8 more patients (4 breast, 3 non-SCLC and 1 colon). According to the Simon two-step design, patient accrual was stopped because of the low response rate observed in the first 19 patients treated (early stopping rule). The G 3/4 haematological toxicity was severe, with 37% neutropenia, 21% thrombocytopenia and 16% anaemia, respectively. Conclusion: Our data do not support the use of topotecan in patients with brain metastases, except for SCLC. In addition, the haematological toxicity prevents the use of this regimen in elderly and poor performance status patients.*

Brain metastases are a common complication in cancer patients and an important cause of morbidity and mortality. They develop in approximately 10 to 30% of adults with systemic cancer. Each year in the United States, an estimated 100,000 to 170,000 new cases of brain metastases are diagnosed (1-3). The number may be increasing as a result of the increased ability of magnetic resonance imaging (MRI) to detect small metastases and improvements in systemic therapy, leading to longer patient survival (1, 3-6). Metastatic tumours arise, in order of frequency, from primary lung cancer in 35 to 50% of cancer patients, either from non-small cell lung cancer (NSCLC) (7) or even with a higher frequency occurring from small cell lung cancer (SCLC); breast cancer (10 to 30%); malignant melanoma (30 to 40%); renal cell carcinoma and colorectal cancer (5%). Only 15% of all metastases to the brain are caused by other systemic neoplasms including leukaemia, lymphoma and sarcoma (3). Malignant melanoma, lung carcinoma and breast carcinoma frequently result in multiple metastases, whereas patients with colorectal and renal-cell carcinoma more commonly have single metastases (8). Clinical symptoms of cerebral metastases include headache, changes in mental status, somnolence, cranial nerve palsies, dysphasia, visual deficits, hemiparesis and focal or generalised seizures. As a consequence of metastatic spread to the CNS (central nervous system), physical, cognitive and emotional functions are slowly eroded and these functions are very rarely recovered in spite of treatment with surgery, radiotherapy or chemotherapy.

The general perception among clinicians has historically been that chemotherapy is ineffective for the successful treatment of brain metastases, largely for the following reasons: a) impaired delivery of chemotherapy into the CNS due to the impenetrability of the blood-brain barrier (BBB) and the routine use of corticosteroids, which re-establishes disrupted BBB function; b) drug resistance of solid tumour clones that are capable of metastases to the CNS; and c) CNS metastases occurring in the setting of drug failure of the primary disease. However, a number of studies have demonstrated that systemic chemotherapy is also active in brain localisation of the disease and responses up to 50% are achievable with chemotherapy in intracranial lesions from NSCLC (9), although combined treatment with radiotherapy is usually more effective (10).

Topotecan is a semi-synthetic camptothecin derivative that selectively inhibits topoisomerase I in the S-phase of the

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cell cycle, interfering with the replication and transcription processes in the tumour cell, which eventually leads to cell death. Topotecan is an established treatment in patients with recurrent SCLC, with overall tumour response rates >20% reported for extensive systemic disease in patients with good performance status (11-14). In addition to its well-established activity against primary tumours, topotecan freely penetrates the BBB and measurable levels of topotecan and its metabolites can be detected in the cerebro-spinal fluid (CSF) (15-18). The aim of this study was to evaluate the efficacy and toxicity of topotecan administered as an *i.v.* bolus infusion for 5 consecutive days in patients affected by brain metastases from various tumours.

Patients and Methods

Patients with cerebral metastases from various neoplasms were eligible for this study. In particular, the eligible patients were affected by SCLC, ovarian cancer or breast cancer previously treated with systemic chemotherapy, or by NSCLC, malignant melanoma and renal cell carcinoma not previously submitted to chemotherapy. Inclusion criteria were: brain metastases from the previously-mentioned tumours not amenable to definitive locoregional treatment and not requiring immediate radiotherapy; no radiotherapy or other systemic chemotherapy in the previous 28 days; measurable lesion (>1 cm diameter) assessed with CT or MNR; age >18 years and <75 years; performance status (ECOG) ≤2; life expectancy of more than 3 months; biochemical parameters such as haematopoiesis, liver and renal functions within normal limits (ANC >1,500 mmc; Hb >10 g/dl; platelets >100,000 mmc; bilirubin <1.5 mg/dL; AST/ALT <2N or <5N if liver involved); informed consent. The patients were treated with topotecan 1.5 mg/m^2/day as a 30-min intravenous infusion for 5 consecutive days repeated every 21 days. The first evaluation was performed after 2 courses of therapy, while patients with responsive or stable disease (according to WHO criteria) continued for a maximum of 6 courses. Toxicity was assessed according to the NCI CTG common toxicity criteria. Clinical, biological and radiological evaluation (brain CT scan) were carried out during the week before the first administration of topotecan, and drug activity was evaluated every 8 weeks. Objective responses (OR) were defined as follows: complete response (CR), the disappearance of all lesions; partial response (PR), a decrease of ≥50% in the sum of the product of the longest perpendicular diameters in the target lesions; stabilisation (SD), a decrease or increase of ≤25% in the same lesion; and progressive disease (PD), an increase in ≥25% in any indicator lesion. The statistical analysis of survival curves was carried out by the Kaplan-Meier method, and comparison of survival was calculated by log-rank tests. For calculation of the sample size of the study, the two-step design described by Simon was adopted (19). According to this design, after the first 19 patients a minimum of 15% objective response (complete plus partial) was required (3 out of 19 patients responding) in order to continue enrolling up to 42 evaluable patients.

Results

From July 2002 until July 2004, 19 consecutive patients with cerebral metastases were registered from the Medical Oncology Department of the Istituto Oncologico of Bari, and from the General Hospitals of Campobasso, Manduria and Castellaneta, Italy. The main characteristics of the 19 evaluable patients entered on the study are presented in Table I. There were 8 men and 11 women, with a median age of 61 years (range 43-73 years) and a median ECOG performance status of 1. Six patients had primary breast, 11 patients lung (3 SCLC) and 2 patients colon cancer, respectively. Ten patients had a single intracranial lesion not amenable to radiotherapy and 9 patients multiple intracranial lesions. Moreover, 18 out of 19 patients at the point of study entry presented extracranial disease as primary cancer or metastatic spread. Five patients affected by NSCLC were not pre-treated with chemotherapy, whereas the remaining 14 patients had previously received at least one line of systemic therapy. Only one patient affected by SCLC had previously received radiotherapy as prophylactic whole brain irradiation (Table II). Partial response was observed in 2 out of 19 patients after the 2 induction cycles (10.5%). Both responses were observed in SCLC patients previously submitted to chemotherapy. Stable disease was observed in 8 patients (4 breast, 3 NSCLC and 1 colon). Nine patients progressed on therapy, 7 of whom were treated with palliative radiotherapy.

Table I. *Patient characteristics.*

Enrolled	19
Median age	61 (range 43 - 73)
Male / Female	8/11
PS ECOG 0/1/2	3/11/5
Primary breast	6
Lung	11 (3 SCLC)
Colon	2
Pretreated with chemotherapy	14
Pretreated with radiotherapy	1
Chemonaïve	5 (all NSCLC)
Presence of extracranial disease	18/19
No. of cycles administered	60
Median cycle/patient	3

The patients received a median of 3 cycles of topotecan, ranging from 1 to 8. The median overall survival for all patients entered on the study was 29 weeks (range 4-56) and the median survival for non-responding *vs.* responding patients was 24 and 40 weeks, respectively. The study was concluded early, because according to the two-step design described by Simon, the response observed in the first 19 patients was less than the minimum requirements to continue the study with 42 patients. Only 2 patients responded out of the 19 treated (10.5%), whereas the minimum response requested for study continuation was 3/19 (15%). With regard to toxicity, the main side-effects observed are summarized in Table III. The dose-limiting toxicity was neutropenia, which caused an early death in a

Table II. *Response rate in brain metastases treated with topotecan.*

Type of response	No. of patients	%
Complete	--	--
Partial	2	10.5
Stable	8	42
Progression	8	42
Not evaluable (early death)	1	5.5

Table III. *Toxicity.*

Toxicity	No. of patients (%) with G 1-2	No. of patients (%) with G 3-4
Neutropenia	2 (10.5)	7 (37)*
Anaemia	4 (21)	3 (16)
Thrombocytopenia	2 (10.5)	4 (21)
Diarrhoea	3 (16)	1 (5)
Vomiting	1 (5)	1 (5)
Alopecia	15 (79)	4 (21)
Peripheral neuropathy	2 (10.5)	--
Mucositis	--	1 (5)

*rescued in 6 patients with G-CSF.

PS2 elderly patient after the first cycle. This side-effect was rescued by G-CSF in 6 more patients. Grade 3-4 anaemia and thrombocytopenia were observed in 3 (16%) and 4 (21%) patients, respectively. Alopecia was universal. Two patients, previously treated with taxanes, suffered mild to moderate peripheral neuropathy and grade 3 mucositis. Vomiting and diarrhoea were observed each in 1 patient (5%), respectively (Table III).

Discussion

The appropriate treatment of brain metastases has been a matter of debate for decades (20). The diagnosis of brain metastasis is often made in the presence of advanced systemic disease and poor performance status. However, sometimes a solitary lesion is the only sign of recurrent cancer. In most cases, surgery with radiation (or radiosurgery) is the treatment of choice. However, because of multiplicity or due to poor patient conditions, cerebral metastases are usually treated by radiotherapy alone. Unfortunately, the median survival after radiotherapy alone is only 3.6 months (21), thus new and more effective treatments are needed for these patients. Systemic chemotherapy has traditionally played a limited role in the treatment of brain metastasis due to the limited ability of most chemotherapeutic agents to cross the BBB. Although it is generally accepted that the development of brain metastases leads to some impairment of the BBB, it is unknown whether the disruption is sufficient for chemotherapeutic agents to penetrate the CNS and reach therapeutic concentrations. In addition, the intrinsic chemosensitivity of a tumour to a particular drug or regimen of agents is crucial and brain metastases arising from chemo-sensitive tumours may respond similarly to metastases elsewhere in the body (22). A prospective study, that assessed the activity of a cisplatin/etoposide regimen in patients with brain metastases, reported overall response rates of 38%, 30% and 0% for breast cancer, NSCLC and melanoma patients, respectively. These results were similar to those in patients with systemic disease who did not have brain metastases (23). Currently, only for very chemo-sensitive tumours, such as germ cell tumours, lymphomas and SCLC, is chemotherapy accepted as first-line therapy of brain metastases.

The pharmacokinetic profile and activity of topotecan in the treatment of solid tumours suggests that it may be effective in the treatment of brain metastases. Indeed, the potential antitumour activity of topotecan against brain metastases has been investigated in several studies (Table IV).

In a small, pilot study for newly-diagnosed brain metastases from breast cancer, standard-dose topotecan at 1.5 mg/m^2/day on days 1-5 of a 21-day cycle was administered instead of radiation therapy (24). Of the 16 evaluable patients, 6 (38%) achieved an OR in the CNS, including one CR and 5 PRs. An additional 5 (31%) patients achieved SD. The median overall survival time for all patients was 6.3 months. Although haematological toxicity was the major toxicity, dose reduction was limited to 3 courses. Non-haematological toxicity was rare and generally mild. The results of that study suggest that topotecan can safely be administered to patients with breast cancer previously treated with systemic chemotherapy without significant toxicity and can induce a response in brain metastases from breast cancer.

The antitumour activity of topotecan against brain metastases has also been demonstrated in patients with lung cancer (13, 24-30). Topotecan monotherapy was evaluated in 20 SCLC patients with asymptomatic brain metastases after failure of first-line chemotherapy, but without radiation therapy (25). Eighteen patients received topotecan at a dose of 1.5 mg/m^2/day on days 1-5 of a 21-day course and 2 patients received topotecan at a dose of 0.4 mg/m^2/day *via* a continuous 21-day *i.v.* infusion every 28 days. The brain metastases were monitored by CT scans on a bimonthly basis. Of the 16 evaluable patients, 4 (25%) had CRs, 6 (38%) had PRs, 5 (31%) had SDs and 1 (6%) had progressive disease in the CNS. The results of that study suggest that topotecan can induce a high OR rate in SCLC brain metastases and delay whole-brain cranial irradiation.

In a phase II study of patients with chemo-refractory and chemo-sensitive SCLC treated with topotecan at a dose of

Table IV. *Topotecan in the treatment of brain metastases.*

Study (ref)	Primary tumour	WBRT Pre/combined	Dose	No. of evaluable pts	OR	CR	PR
Depierre *et al.* (13)	SCLC	NR/1	1.5 mg/mq/day Days 1-5 q3w	9	5 (56)	1 (11)	4(44)
Oberhoff *et al.* (24)	Breast cancer	0/0	1.5 mg/day Days 1-6 q3w	16	6 (38)	1 (6)	5 (31)
Manegold *et al.* (25)	SCLC	NR/0	1.5 mg/mq/day Days 1-5 q3w	16	10 (63)	4 (25)	6 (38)
Ardizzoni *et al.* (26)	SCLC	NR/0	1.5 mg/mq/day Days 1-5 q3w	7	4 (57)	3 (43)	1 (14)
Shutte *et al.* (27)	SCLC/NSCLC	NR/1	1.3-1.5 mg/mq/day days 1-5 q3w	24	12 (50)	4 (17)	8 (33)
Korfel *et al.* (28)	SCLC	8/0	1.25-1.5 mg/mq/day days 1-5 q3w	30	10 (33)	3 (10)	7 (23)
Present study	Breast NSCLC SCLC colon	0/0	1.5 mg/mq/day Days 1-5 q3w	19	2* (10)	0 (0)	2* (10)

*2 out of 3 pts with SCLC responded;
WBRT=whole brain radiotherapy;
SCLC=small cell lung cancer;
NSCLC=non-small cell lung cancer;
OR=overall response;
CR=complete response;
PR=partial response.

1.5 mg/m^2/day on days 1-5 of a 21-day cycle, 7 out of 92 evaluable patients had documented brain metastases (26). Of those 7 patients, 3 with chemo-sensitive disease achieved CRs and 1 patient with chemo-refractory disease achieved a PR within the CNS. An additional patient had a mixed response, with a 42% reduction in the target lesion and the complete disappearance of another non-measurable lesion. The most common toxicities were grade 3 or 4 leukopenia and neutropenia. In a similar phase II study, 9 patients with chemo-sensitive SCLC brain metastases were treated with topotecan at a dose of 1.5 mg/m^2/day on days 1-5 of a 21-day cycle (13). Brain tumour responses to topotecan were observed in 5 out of 9 (56%) patients, including 4 PRs and 1 CR in a patient receiving concurrent radiotherapy. Three patients had SD. Haematological toxicity included non-cumulative neutropenia; non-haematological toxicity was uncommon and generally mild. The results from these 2 studies support the use of topotecan as a first-line treatment for newly-diagnosed brain metastases in SCLC, particularly in platinum-sensitive patients. For patients who achieve only PRs, consolidative radiation may be necessary.

To more closely evaluate the potential of topotecan in the treatment of brain metastases, Schutte *et al.* (27) conducted a comprehensive retrospective analysis of the antitumoral responses to topotecan from various studies that had enrolled mostly patients with SCLC brain metastases. A total of 255 patients were enrolled in the studies, including 247 with SCLC and 8 with NSCLC. Of the 42 patients with documented brain metastases, 24 (22 SCLC and 2 NSCLC) had follow-ups and were evaluable. The patients received topotecan at doses of either 1.3-1.5 mg/m^2/day *via* 30-minute *i.v.* infusions on days 1-5 of a 21-day cycle or 0.4 mg/m^2/day as a continuous *i.v.* infusion over 21 days every 4 weeks. All patients were followed-up every 2 months with CT and MRI. Of the 24 patients, 12 (50%) experienced ORs in their brain metastases (4 CRs and 8 PRs) and an additional 8 patients had SD in the brain. The median duration of survival of the 22 evaluable patients with SCLC was 6.1 months.

In a more recent multicentre study, Korfel *et al.* (28) enrolled 30 heavily-pretreated SCLC patients with symptomatic brain metastases to evaluate the activity of topotecan in the treatment of brain metastases. More than half the enrolled patients had received platinum-containing regimens, and 8 patients had been treated with prior whole-brain radiotherapy (8 in the prophylactic setting and one in the palliative setting). The first 22 patients were treated with topotecan at a dose of 1.5 mg/m^2/day on days 1-5 of a 21-day cycle, whereas the last 8 patients were treated with topotecan at a dose of 1.25 mg/m^2/day because of dose-limiting thrombocytopenia. The results of that study are summarized in Table IV (28). The OR rate in CNS lesions was 33%, including 3 CRs and 7 PRs. An additional 8 (27%) patients had SD. The OR rate in systemic lesions was 29%. These data suggest that topotecan is effective in treating brain metastases from SCLC, even in patients previously treated with platinum-containing regimens.

The results of the present study compared well with those reported in the literature, with the exception of the response in neoplasms other than SCLC. In fact, out of the 19 patients with brain metastases from various tumours (colon, breast, NSCLC and SCLC), only 2 responses were observed (out of 3 patients treated) in SCLC, whereas only SD or PD were observed in colon, breast or NSCLC. These data confirm the good efficacy of topotecan in SCLC but, in contrast with other studies, do not support the use of topotecan in brain metastases arising from other tumours. In addition, the ability of topotecan to cross the BBB suggests that it may also have a prophylactic role against brain metastases from SCLC. In conclusion, on the basis of the results from this and previous studies, the combination of topotecan with radiotherapy or with other chemotherapeutic drugs able to pass through the BBB should be recommended only for SCLC patients.

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