Eur J Cancer Clin Oncol, Vol. 24, No. 12, pp. 1905–1906, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00

Letter to the Editor

Brain Metastases of Lung Cancer: Excessive Toxicity of High Dose VP 16 213

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ADMINISTERED at high doses, etoposide (VP 16 213) diffuses in the cerebrospinal fluid (CSF) and crosses the hematomeningeal barrier [1, 2]. Kleisbauer *et al.* recently reported a 30% response rate in the treatment of cerebral metastases of lung cancer using high dose VP 16 213 [3]. Utilization of this treatment at our institution had to be stopped, however, owing to a high incidence of severe toxicity.

From September 1984 to September 1987, nine patients with CT-diagnosed brain metastases were entered in our study (Table 1). Mean patient age was 60 years (range 52–70). All patients had histologically confirmed lung tumors: two squamous cell tumors, four adenocarcinomas, three anaplastic small cell tumors. Brain lesions were the first metastatic site in eight patients; six patients had multiple brain metastases, and four patients had metastases both in the brain and in the other organs. One patient had previously received chemotherapy. None of the patients had received irradiation to the brain. Our protocol consisted of six doses of 250 mg/m^2 VP 16 213 spaced 12 h apart (Table 1). Courses were repeated every 28 days if the platelet count was >100,000/mm^3 and the leukocyte count >3000/mm^3. Toxicity and responses were evaluated using WHO criteria [4] and CT.

Accepted 8 July 1988.
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Toxicity was severe and consisted primarily of hematologic manifestations (Table 1). Five patients died in deep aplasia with a major infectious syndrome; three patients developed myelotoxicity and mucitis (grade 4) after the first cycle. Patient No. 6, who had no history of cardiovascular disease, died of heart failure 19 days after the second cycle.

Three of the nine patients were evaluable for response: one partial remission, one stabilization, and one progression (Table 1). Only those patients who responded to the treatment had prolonged survival: 26 and 30 weeks (an anaplastic small cell tumor and an adenocarcinoma).

This series was characterized by both severe toxicity (especially hematologic) and only a 22% response rate (2/9). Boguikouma *et al.* [5] reported a 30% response rate in a series of 28 patients but also had a high incidence of toxicity (12 deaths). Kleisbauer *et al.* [3] obtained similar results with identical toxicity (seven deaths in a series of 19 patients). In these last two studies, the median survival was respectively 26 and 24 weeks for responders. However, the overall survival was only 10 weeks for Kleisbauer *et al.* [3]. In our series, only the two responders benefited from prolonged survival. Eight of our nine patients had not received any chemotherapy or radiotherapy before administration of the VP 16 213; five of them died of hematologic toxicity and three developed grade 4 myelotoxicity.

Utilization of high doses of VM 26 for the treatment of brain metastases of anaplastic small cell

Table 1. Patient characteristics and outcome

Patient No. and sex	Age (years)	PS	Pathology	Previous chemotherapy with VP16/ without VP16	No. cycles with VP16	Response	Toxicity	Survival (weeks)
1 M	63	2	Small cell	9/9	1	NE	Lethal	1
2 M	70	3	Squamous	0/0	1	NE	Lethal	1
3 M	60	2	Small cell	0/0	2	NE	Lethal	7
4 M	55	2	Adenocarcinoma	0/0	1	NE	Lethal	1
5 M	52	2	Adenocarcinoma	0/0	1	NE	Lethal	1
6 M	63	2	Squamous	0/0	2	NE	Cardiac grade 4	8
7 M	55	2	Small cell	0/0	4	PR	Myelo. grade 4, mucositis grade 4	26
8 F	61	2	Adenocarcinoma	0/0	6	SD	Myelo. grade 4, mucositis grade 4	30
9 M	54	2	Adenocarcinoma	0/0	1	PD	Myelo. grade 4, mucositis grade 4	4

M: male; F: female; PS: performance status; NE: not evaluable; PR: partial response; SD: stable disease; PD: progressive disease.

cancers gives similar results but with a more acceptable level of toxicity [6]. Compared to the median survival obtained by irradiation of brain metastases (2–10 months) [7], and in view of its hematologic and mucosal toxicity, high dose therapy with VP 16 213 gave an unacceptably high incidence of adverse effects. Search for other therapeutic combinations must thus be continued.

Acknowledgement—The authors wish to thank Nancy Rameau for translating the manuscript.

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