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Short communication

Positive phase II study in the treatment of advanced malignant melanoma with fotemustine

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Summary. To date, dacarbazine (DTIC) has been the most effective drug in the treatment of advanced metastatic melanoma, achieving response rates of up to 28% (mean, 21%). Multidrug responses were generally no better than those obtained using monotherapy. A quite promising clinical trial was conducted using the new nitrosourea fotemustine. A total of 19 patients presenting with advanced malignant melanoma (clinical stage IV according to the 1987 UICC classification system) underwent treatment involving a more rapid infusion of the drug and a reduction in the rest period from 5 to 3 weeks. This monotherapy with fotemustine yielded two complete responses and seven partial responses; in addition, four patients showed no change and six cases progressed after the induction cycle (median duration of response to date, 7.6 months, including four cases that have not relapsed). Fotemustine was well tolerated by the patients, with the only mild side effects being thrombocytopenia, leukocytopenia and easily controlled nausea/vomiting. Preclinical studies performed previously indicated that fotemustine inhibits enzymes involved in the ribonucleotide reduction pathway (i.e. DNA synthesis), whereby responding patients ($n = 3$) appeared to favor the thioredoxin reductase/thioredoxin electron transfer to ribonucleotide reductase, whereas non-responders ($n = 4$) expressed the alternate glutathione reductase/glutaredoxin mechanism. The 47% response rate obtained in these studies vs the 24% reported previously for fotemustine may reflect variations in enzymes in the ribonucleotide reduction pathway in different patients. However, the efficacy of fotemustine against advanced melanoma warrants more extensive trials of this drug, especially since the quality of life of the patients during and after chemotherapy was not severely affected.

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Introduction

Fotemustine (diethyl-1-[3-2 chloroethyl]-3-nitroso-ureido ethyl phosphonate) is a novel chloroethylnitrosourea that was developed by Servier/France and is currently undergoing phase II clinical trials in advanced malignant melanoma. Recently, this drug has been shown to undergo rapid metabolism through a general mechanism involving chloroethyl-group transfer to important thioenzymes in DNA synthesis (i.e. thioredoxin reductase, glutathione reductase and ribonucleotide reductase) [10, 11]. Since these enzymes are induced in the S phase of the growth cycle [3], fotemustine has been shown to inhibit effectively DNA synthesis in human melanoma cells by preventing deoxyribonucleotide biosynthesis [8]. The sensitivity and resistance of melanoma metastases and melanoma cell clones were found to depend on the respective levels of thioredoxin reductase and glutathione reductase as alternative electron donors for ribonucleotide reductase, whereby glutathione reductase was 500 times less sensitive than thioredoxin reductase to inhibition by fotemustine [10, 11]. In vivo studies in fotemustine-resistant tumors demonstrated high levels of glutathione reductase, whereas fotemustine-sensitive tumors contained high amounts of thioredoxin reductase and low levels of glutathione reductase [11].

The drug is highly reactive, affording rapid transport across the blood-brain barrier [5]. In a study using fotemustine labeled with [^{14}C]-chloroethyl in two patients presenting with ovarian carcinoma and prostate cancer, respectively, >90% of the drug degraded within 3 h [5]. Due to its rapid degradation rate and its relatively weak interaction with glutathione reductase [2, 10], fotemustine produces few side effects and is well tolerated by patients receiving this chemotherapy. Major toxicity has been limited to reversible thrombocytopenia (day 35), reversible leukopenia (day 42) and rarely mild elevation of liver enzymes (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl-transpeptidase). Nausea and vomiting have been limited and easily con-

Table 1. Results of monotherapy with fotemustine in 19 patients presenting with cutaneous metastasized melanoma of clinical stage IV

Patient number	Sex	Age	LD/ED	Site of metastasis	Measurable disease at 6 weeks	Time of relapse after induction (months)	Overall survival after induction (months)	Site of tumor progress
1	M	47	ED	Brain, skin, lymph	CR	11	18 L	Soft tissue
2	M	51	LD	Skin, soft tissue	CR	–	12 L	–
3	M	73	ED	Lung, bone	PR	–	28 L	–
4	M	62	ED	Liver, brain	PR	2.5	5.5 D	Liver
5	F	70	ED	Brain	PR	3	8 D	Brain/lung
6	F	67	LD	Skin, soft tissue, lymph node	PR	3	5 D	Brain
7	F	67	ED	Lung, spleen	PR	2	12 L	Lung
8	M	49	LD	Skin, soft tissue	PR	3	11 L	Soft tissue
9	M	31	ED	Brain	NC	14	15 L	Liver
10	M	65	LD	Soft tissue, lymph node	NC	–	15 L	–
11	F	54	ED	Lung, soft tissue, skin	PR	6	8 D	Ovary
12	M	38	ED	Brain, lymph node	NC	2	7 D	Brain, adrenal bone
13	F	40	ED	Ovary, lymph node, skin	PD	–	2.5 D	Bone, lymph nodes
14	F	70	ED	Stomach	NC	(Treatment Discontinued)	2 D	–
15	M	51	ED	Liver, lung, skin, soft tissue	PD	–	2.5 D	Liver, lung, skin
16	M	60	ED	Lung, soft tissue, skin	PD	–	1.5 D	Brain
17	M	59	ED	Lung, soft tissue, skin	PD	–	10 D	Brain
18	M	73	ED	Lung, colon	PD	–	6 D	Intestine
19	F	55	ED	Lung, liver, skin, soft tissue	PD	–	9 D	

ED, Extensive disease; LD, limited disease; L, living; D, died

Table 2. Toxic effects of fotemustine monotherapy[a] in 19 patients with advanced metastatic melanoma

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Platelets	8	4	4	2	1
Leukocytes	5	6	5	3	0
Transaminases	16	3	0	0	0
Nausea/Vomiting	9	8	2	0	0

[a] Based on WHO criteria

trolled. The major advantages of monotherapy with fotemustine reside in its low toxicity, which enables the treatment of patients on an outpatient basis and produces no significant change in the quality of life during the treatment cycles.

An understanding of the biochemical and pharmacokinetic properties of fotemustine convinced us to change the phase II C protocol [2] by giving a more rapid infusion of the drug and shortening the interval between the induction and the maintenance cycles from 5 to 3 weeks.

Patients and methods

A total of 19 patients (12 men, 7 women) mean age of 54 years (range, 31–73 years) received fotemustine monotherapy. All subjects exhibited cutaneous metastasized melanoma of clinical stage IV (according to the 1987 UICC classification system). Based on WHO criteria, 15 subjects were found to have extensive disease (ED) and 4 limited disease (LD). The locations of metastases in each patient are presented in Table 1. A performance status (Karnofsky index) of >90% was a prerequisite for selection of the patients. Because fotemustine is photolabile and decomposes in solution (4% decomposition/h in distilled water), an infusion containing 100 mg/m^2 was prepared from the crystalline form of the drug immediately before intravenous administration over a total period of $\leq$60 min. The new treatment protocol involves one administration/week over 3 weeks (induction cycle) followed by a 3-week rest period, with weekly assessments of the laboratory values being carried out mainly to control the blood cell count and the hepatic and renal parameters. Tumor staging [including an X-ray of the thorax, computed tomography (CT) of the abdomen, a cerebral CT, a bone scan and ultrasound of the liver] was done prior to the first treatment and to each maintenance cycle in the same center. The treatment was repeated every 3 weeks in all responding patients.

Results

Table 1 shows the results of monotherapy with fotemustine. Responses were scored according to WHO criteria as measured from the 1st day of treatment of the induction cycle. Altogether, 9/19 (47%) patients responded to the drug. Two subjects achieved a complete response (CR); one lasted 11 months, and the second patient remains disease-free at 11 months posttreatment. Seven individuals showed a partial response (PR). Four subjects showed no change in tumor size (NC), with two cases remaining stable for 14 months and the others, for 2 and 1 month, respectively. The confidence interval was determined for the overall response rate; the confidence limits in this analysis were 24%–71%. Patients exhibiting progressive disease (PD) after induction had a poor prognosis, with the mortality being 83% and the mean survival being 4.3 months (one patient remains alive after 10 months). At the present time, the overall mean survival for all 19 patients, including 8 survivors, is 9.1 months; for the latter 8 subjects, the mean survival to date is 14.3 months.

Toxicity was assessed according to WHO criteria; the data are summarized in Table 2. The eight surviving patients continue to undergo maintenance therapy every 3 weeks; all are doing well and have thus far developed no major side effects.

Discussion

For 15 years, the chloroethylnitrosoureas have been in limited use for the treatment of glioma, Hodgkin's lymphoma, lung cancer, colorectal cancer and melanoma [7, 12]. The homologous drugs carmustine (BCNU), lomustine (CCNU), methyl-CCNU and nimustine (ACNU) often produce cumulative renal, bone marrow and pulmonary toxicity [7, 12]. It has been suggested that this severe toxicity is attributable to the inhibition of glutathione reductase, which leads to a decrease in the level of the important anti-oxidant reduced glutathione [1]. Fotemustine differs from the other chloroethylnitrosoureas only in the presence of a diethylphosphonate group attached to an alanine residue. The presence of this non-polar group enables rapid transport of the drug into all organs and tissues [5]. As compared with BCNU, fotemustine has been shown to be a poor inhibitor of glutathione reductase [1, 9], and this property could explain its failure to produce the toxicity usually associated with the chloroethylnitrosoureas.

Unfortunately, the resistance of glutathione reductase to the drug appears to determine the response of individual patients to fotemustine therapy. Recently, seven metastases were obtained from four patients exhibiting malignant melanoma who were treated with fotemustine [10]. Two subjects showed a PR after the induction cycle and two failed to respond. Four tumors from the two responding patients showed high amounts of thioredoxin reductase and low levels of glutathione reductase activity. However, three tumors from the non-responding patients exhibited high levels of glutathione reductase and low amounts of thioredoxin reductase [10, 11]. Therefore, the development of acquired resistance to fotemustine after an initial response appears to be due to a switch from the thioredoxin reductase/thioredoxin pathway to the glutathione reductase/glutathione pathway for electron donation to ribonucleotide reductase [4]. Since glutathione reductase is 500 times less sensitive than thioredoxin reductase to inhibition by fotemustine, a switch in metabolic pathways might be expected to overcome the cytostatic action of the drug as an inhibitor of DNA synthesis in the S phase of the growth cycle [3, 8].

Like the other chloroethylnitrosoureas, fotemustine is rapidly degraded, showing a half-life of 90 min in serum [5]. Careful handling of the drug together with a more rapid infusion time appeared to facilitate the delivery of higher concentrations to the tumor. Shortening the rest period from 5 to 3 weeks also seemed to contribute to an increase in the response rate from the previous 24% to the 47% obtained in the present study in stage IV patients [2, 6, 9]. Considering the observed maintenance of a good quality of life during chemotherapy and the minimal side effects encountered, we believe that fotemustine monotherapy is a good choice for the palliative treatment of advanced malignant melanoma. Perhaps greater success could be achieved in patients exhibiting limited disease.

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