Our results seem to suggest that 4-MPR is the major determinant of plasma IGF-1 decline (negative Δ). This is in keeping with our previous observations of a dominant role of 4-MPR in determining another principal effect of fenretinide administration, namely, the decline of plasma retinol levels [5]. We may also speculate that the reversal of effect induced by 4-HPR and 4-MPR concentrations on ΔIGF-1 as a function of age, is due to age-related differences in the metabolism and in tissue distribution of the two compounds, which are partially different in both mice [6] and in human mammary gland [7]. 4-MPR appears to be less extensively metabolised than 4-HPR and selectively concentrated in adipose tissue from which it may be slowly released [7]. In humans, 4-MPR has a longer half-life than 4-HPR [4], potentially exerting a prolonged effect in circulation, while having the same potency as 4-HPR in in vitro differentiation assays [8]. In addition, the metabolism to 4-MPR has recently been shown to be critical to the antiproliferative effect of 4-HPR on the growth of breast cancer cell lines [9]. Thus, the preferential effect of 4-MPR on IGF-1 may have a pharmacological explanation or, alternatively, be the result of a selective biological action elicited by 4-MPR itself, supporting a leading role for 4-MPR in determining some of the main biological effects induced in vitro by treatment with fenretinide.


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Fotemustine and Tamoxifen Combination Therapy in Metastatic Malignant Melanoma. A Phase II Study

C.J.A. Punt, J.H. Tytgat, P.A. van Liessum and B. Gerard

Several studies have shown that the addition of tamoxifen to chemotherapy may enhance the response rate in patients with metastatic malignant melanoma [1-4]. Fotemustine, a nitrosurea, has activity against melanoma as a single agent [5-7], with a response rate of 24.2% in the largest study with 153 patients [5]. Tamoxifen enhances in vitro the cytotoxic effect of fotemustine on melanoma cell lines expressing oestrogen receptors [8]. In patients with metastatic melanoma, high-dose tamoxifen may result in a higher complete response rate compared with low-dose tamoxifen [9]. We, therefore, initiated a phase II study of high-dose tamoxifen and fotemustine in patients with metastatic melanoma.

Eligibility criteria included histologically confirmed metastatic melanoma, measurable progressive disease, age 18-75 years, WHO performance status ≤ 2, life expectancy ≥ 3 years.

Table 1. Patients' characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Median age (range)</td>
</tr>
<tr>
<td>Median WHO performance (range)</td>
</tr>
<tr>
<td>Previous therapy</td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>≥ 3</td>
</tr>
<tr>
<td>Metastatic sites</td>
</tr>
<tr>
<td>Cerebral</td>
</tr>
<tr>
<td>Visceral</td>
</tr>
<tr>
<td>Non-visceral</td>
</tr>
</tbody>
</table>

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months, WBC $\geq 4 \times 10^9/\text{l}$, platelets $\geq 100 \times 9/\text{l}$ and no prior treatment with nitrosoureas. Treatment consisted of one induction cycle of tamoxifen 160 mg orally daily from days 1 to 14 and fotemustine 100 mg/m² intravenously (i.v.) on days 8 and 15. Patients were evaluated weekly for toxicity and after 6 weeks for response. In the absence of tumour progression, as defined by WHO criteria, patients received maintenance cycles of tamoxifen 160 mg daily for 7 days and fotemustine 100 mg/m² on day 8, to be repeated every 3–4 weeks depending on haematological recovery. Patients were then evaluated every three cycles for response. 14 patients were entered into the study, 1 was ineligible and not included in the evaluation. Patient characteristics are shown in Table 1. All 13 patients received the induction cycle, and 6 patients received a total of 23 maintenance cycles. Toxicity was mainly haematological (anaemia/leucopenia/thrombocytopenia), and generally grades 2–3. However, 2 patients had grade 4 thrombocytopenia. Thromboembolic complications, as have been described during tamoxifen therapy, did not occur [2]. 3 patients had grade 2–3 nausea/vomiting.

2 female patients achieved a complete response. One previously untreated patient had an extensive pleural mass which gradually became smaller and completely disappeared after the sixth maintenance cycle (Figure 1). After 13 months, a painful bone metastasis was visible at a site not previously documented, for which she received radiotherapy. She is presently alive at 24 months without evidence of disease. The other complete response occurred in a patient previously treated with chemotherapy and radiotherapy who had two subcutaneous lesions of 13 $\times$ 2 and 10 $\times$ 2 cm, respectively, which disappeared after the induction cycle. She received a total of six maintenance cycles. This response is ongoing at 19 months. 3 patients with brain metastasis at the start of treatment all progressed at this site. The overall response rate was 15% (95% confidence interval 2–45%). Median overall survival was 6 months (range 1–24+). In contrast to others [6], we did not find activity in patients with brain metastases, but the number of these patients was too small for a definite conclusion. Of note, both responders in our study were females, which is in agreement with an earlier observation that mainly women appear to benefit from a tamoxifen-containing regimen [5].

We conclude that this schedule of tamoxifen and fotemustine has manageable toxicity, and may result in long-term complete responses in patients with metastatic melanoma, even when bulky disease is present. The question of whether tamoxifen increases the efficacy of treatment with fotemustine has to be answered in a prospective randomised study.

Hepatic Angiosarcoma in a Patient With Essential Thrombocythaemia and Budd-Chiari Syndrome

C. Marichy, C. Dumontet, Y. Bastion, C. Rieux, J.Y. Blay, G. Salles, P. Biron and B. Coiffier

Hepatic angiosarcoma is a rare tumour, accounting for less than 2% of all hepatic tumours [1]. Various environmental agents have been reported to be associated with this neoplasm, including thorotrast, arsenic and vinyl chloride [2]. We describe the case of a patient who developed essential thrombocythaemia during childhood, Budd-Chiari syndrome 6 years later and hepatic angiosarcoma after another period of 6 years. This is the first observation of angiosarcoma occurring in a patient with chronic visceral venous stasis.

A 24-year-old female was admitted in September 1991 for severe abdominal pain and fever. At the age of 12, she had presented with splenomegaly and thrombocythaemia. Various environmental factors have been reported to be associated with this neoplasm, including thorotrast, arsenic and vinyl chloride [2]. We describe the case of a patient who developed essential thrombocythaemia during childhood, Budd-Chiari syndrome 6 years later and hepatic angiosarcoma after another period of 6 years. This is the first observation of angiosarcoma occurring in a patient with chronic visceral venous stasis.

A 24-year-old female was admitted in September 1991 for severe abdominal pain and fever. At the age of 12, she had presented with splenomegaly and thrombocythaemia. Platelet count reached 1,000 giga/l, but the parents refused anti-mitotic therapy and the child received aspirin only. In April 1986, she presented with Budd-Chiari syndrome and underwent shunting with a mesenterico-caval anastomosis which allowed partial regression of the liver enlargement. Anti-mitotic therapy was initiated with hydroxyurea, and response to mesna, doxorubicin, ifosfamide and dacarbazine (MAID-type regimen) [3], which allowed rapid resolution of the pain and fever and a partial reduction of the liver enlargement. The patient then received intensive chemotherapy with etoposide, ifosfamide and cisplatinum in superficial soft tissues [6, 7]. Two cases of liver angiosarcomas have been reported in patients treated for Hodgkin's disease by radiochemotherapy, including hepatic irradiation [8]. However, this is the first report of angiosarcoma occurring in a patient with a myeloproliferative disease and/or with Budd-Chiari syndrome.

The patient had received for more than 5 years anti-mitotic treatment with hydroxyurea, a drug which has not been reported to be leukaemogenic or carcinogetic. No cases of angiosarcoma have been reported after chemotherapy alone to our knowledge. Finally the patient had, 5 years before, developed Budd-Chiari syndrome. This condition was responsible for chronic venous stasis in the liver which may have contributed to the occurrence of sarcoma, as has been described in patients with postmastectomy lymph oedema developing angiosarcoma. We believe that chronic venous stasis was the most important factor determining the occurrence of angiosarcoma in our patient.