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Short communication

Treatment of advanced malignant melanoma with coumarin and cimetidine: a pilot study

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Summary. Based on previous results demonstrating that coumarin and cimetidine render objective tumor regressions in renal cell carcinoma, we conducted a pilot study to determine whether these drugs possess activity against malignant melanoma. A total of 22 patients with advanced melanoma received 100 mg coumarin p.o. daily for 14 days; on day 15, cimetidine was added at an oral dose of 300 mg four times daily. Both drugs were continued until progression of disease. In all, 12 patients had previously been treated, but all patients had a favorable performance status. No response was observed in 19 patients. Two patients with a low tumor burden achieved a partial response and a third showed a minor response. There was no toxicity from this regimen. Although coumarin and cimetidine at this dose and schedule did not display significant activity in this study population, further studies are warranted to explore higher doses and focus on patients with relatively low tumor burdens.

Introduction

The currently available therapies for advanced malignant melanoma are unsatisfactory. Chemotherapeutic agents in single or multiple-drug regimens have yielded disappointingly low response rates and have been associated with significant toxicity [1, 2, 4, 8]. Observed responses to chemotherapy have not been durable and survival has not been significantly prolonged. Promising preliminary results in the treatment of malignant melanoma have been reported with the use of biologic response modifier agents such as the interferons and interleukin-2 plus lymphokine-activated killer cells [3, 10]. However, these agents also produce significant toxicity. The optimal dosing and scheduling of these biologic therapies have not yet been defined.

In a previously reported pilot study [5], the combination of coumarin (1, 2-benzopyrone) and cimetidine produced significant antitumor responses in patients with advanced renal cell carcinoma. A number of anecdotal reports have suggested that these drugs may have some degree of activity against advanced melanoma [11–13, 15]. Based on our earlier results in renal cell carcinoma, we conducted a pilot study using our previously reported regimen to determine whether coumarin and cimetidine possess activity against advanced malignant melanoma.

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Materials and methods

A total of 22 patients with advanced malignant melanoma were treated with coumarin and cimetidine. All patients gave written informed consent to participate in this study, and all were evaluable for response and toxicity. All patients had measurable and/or evaluable disease. Patient characteristics are summarized in Table 1. None of the patients were excluded from treatment on the basis of prior treatment history, extent of disease, or performance status. Most of the patients (19) had extensive, multi-site, bulky metastases, with only 3 exhibiting relatively limited disease. Ten patients had not previously been treated, whereas five had received prior chemotherapy (with no response), two had received prior bacille Calmette-Guérin (BCG) (with no response), and 8 had undergone prior radiation therapy to sites of symptomatic disease or CNS metastases. Patients who had received prior radiation therapy were required to have measurable disease in nonirradiated sites.

Patients were given 100 mg coumarin (Schaper and Brummer, West Germany) p.o. daily for 14 days; on day 15, cimetidine was added at an oral dose of 300 mg four times daily. Both drugs were continued until disease progression. Patients were monitored for disease status and toxicity at 2 and 4 weeks, then monthly during therapy. Monitoring consisted of a history and physical examination, complete blood counts, measurement of serum electrolytes, blood urea nitrogen, and creatinine, and a full panel of liver function tests. Standard response criteria were used.

Results

In all, 22 patients received an adequate trial, arbitrarily defined as at least 4 weeks of therapy. Two patients achieved a partial response (PR), defined as a reduction of $\geq 50\%$ in measurable disease. Both of these patients had a relatively small tumor burden, one having only small lung metastases and the other, only palpable adenopathy. One PR lasted 3 months, and the other patient was lost to follow-up after 2.5 months. A third patient with a small tumor burden achieved a minor response (defined as a re-

Table 1. Patient characteristics

Characteristics	Number of patients
Entered	22
Men/Women	12/10
Mean age in years (range)	50.9 (29–84)
Performance status (ECOG):	
0	9
1	9
2	4
3	0
4	0
Prior treatment:	
None	10
Chemotherapy	5
BCG	2
Radiation	8
Major sites of disease:	
Lung	14
Liver	8
Bone	7
Soft tissue:	
Palpable adenopathy	12
Abdominal adenopathy	12
Cutaneous	7
Brain	6
Response:	
Complete response	0
Partial response	2
Minor response	1
No response	19
Toxicity:	
Symptomatic	0
Hematologic	0
Organ Dysfunction	0

duction of $\geq 25\%$ but $\leq 50\%$ in disease) that lasted 3 months. Treatment with coumarin and cimetidine was not associated with any symptomatic, hematologic, or organ dysfunction toxicity.

Discussion

The results of the present pilot study indicate that at the dose and schedule used, coumarin and cimetidine do not possess significant activity in patients with advanced malignant melanoma. It must be noted that the dose and schedule used in this study were empirically derived and that little is currently known of the dose-response relationship for coumarin against human malignancies. The results of the present study, showing two PRs and one minor response, indicate that further trials with these drugs are warranted. It is biologically significant that some activity was observed in three patients with relatively small tumor burdens. Although Pedersen et al. [9] observed no activity with these drugs in melanoma, no correlations were made with regard to tumor burden.

We have previously shown [6, 7] that coumarin can augment certain cellular immune functions in vivo and in vitro. We have also shown that coumarin inhibits growth in a dose-dependent fashion in vitro against a number of human malignant cell lines (unpublished data). Moreover, Tseng et al. [14] have shown that coumarin inhibits tumorigenesis in an EJ-*ras* oncogene-containing tumor in an animal model.

The dose of coumarin used in this study and previously reported clinical trials may ultimately prove to be suboptimal. The dose and schedule used in this study were derived from those reported in the literature. Future clinical trials with coumarin, with or without cimetidine, should await the completion of formal phase I trials. Indeed, the maximally tolerated dose and dose-limiting toxicity of coumarin are unknown. Future clinical trials with these drugs should also be designed to correlate response to the degree of tumor burden, as patients with lesser tumor burdens may prove to be more likely to respond to therapy than those with extensive, bulky disease. The delineation of subsets of patients who have a greater likelihood of responding to this therapy is needed.

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