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## Clinical report

# Phase II trial of 9-nitrocamptothecin (RFS 2000) for patients with metastatic cutaneous or uveal melanoma

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**The camptothecin derivative 9-nitrocamptothecin (9-NC) has demonstrated clinical activity in patients with ovarian and pancreatic carcinomas. Preclinical studies have shown promising activity of 9-NC for melanoma. We have thus conducted a phase II clinical trial of 9-NC for patients with metastatic cutaneous and uveal melanoma. Twenty-eight patients were enrolled in the trial, with diagnoses evenly divided between the two types of melanoma. 9-NC was administered orally at a starting dose of 1.5 mg/m$^2$/day for 5 consecutive days of each week. No complete or partial responses were observed. Stabilization of disease was achieved in four individuals (15%) for durations of 3, 4, 6 and 8 months. Hematologic toxicity was moderate. Gastrointestinal side effects were common with 43% of the patients experiencing grade 3 or 4 diarrhea and 18% reporting grade 3 or 4 vomiting. In contrast to other 9-NC clinical trials, no patients developed chemical cystitis with gross hematuria. We conclude that, in keeping with the general chemoresistance of melanoma, 9-NC at the dose and schedule studied in this trial is significantly toxic and is not active for metastatic melanoma of cutaneous or uveal origin. [© 2002 Lippincott Williams & Wilkins.]**

*Key words:* 9-Nitrocamptothecin, camptothecin, cutaneous melanoma, RFS 2000, uveal melanoma.

## Introduction

Metastatic melanoma, whether of cutaneous or uveal origin, is one of the most refractory malignancies to treatment with the available systemic cytotoxic drugs. Response rates of metastatic cutaneous melanoma to chemotherapy are generally less than 25% and the responses are of poor quality.[1] Durable responses are occasionally seen to treatment with cytokines such as interferon-α or interleukin-2, but occur in less than 10% of patients.[1] Uveal melanoma, with its predilection for liver metastasis, may be even more refractory, with response to any intervention and long-term survival seen only in rare cases.[2] There is an unquestionable need for research into new drugs for metastatic melanoma of either origin.

Camptothecin is a plant alkaloid derived from *Camptotheca acuminata*. This compound and its analogs are being developed as cytotoxic drugs for a variety of malignancies. Camptothecins have been shown to exert their anti-tumor effects by stabilization of topoisomerase I–DNA complexes, thus inhibiting DNA replication and RNA synthesis.[3–5] The analog 9-nitrocamptothecin (9-NC) has shown clinical activity for ovarian and pancreatic cancer.[6–8] In preclinical studies focusing on melanoma, 9-NC has been shown to induce S phase cell cycle arrest and apoptosis in cultured human melanoma cells,[9] bring about regression of established human melanoma xenografts in nude mice,[10] and reduce the number of experimental pulmonary metastases formed by murine B16F10 melanoma cells.[11] Based on these encouraging clinical and *in vitro* data, we initiated a trial of 9-NC for patients with metastatic cutaneous or uveal melanoma. The objectives of this trial were to assess the response rate and the toxicity of 9-NC in this patient population.

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## Patients and methods

### Patients

The study was conducted by the Department of Melanoma Medical Oncology, University of Texas MD

Anderson Cancer Center and was approved by the MD Anderson Institutional Review Board. Informed consent was obtained from all subjects. 9-NC (RFS 2000) was supplied by SuperGen (Dublin, CA). Eligible patients included those with metastatic melanoma of cutaneous or uveal origin, with bidimensionally measurable disease. Prior treatment with up to three regimens of cytotoxic therapy was permitted. Other criteria included Zubrod performance status $\leqslant 2$, life expectancy $> 8$ weeks, absolute granulocyte count $\geqslant 1000/\mu$l, platelet count $\geqslant 100\,000/\mu$l, creatinine $\leqslant 2.0$ mg/dl, bilirubin $\leqslant 1.5 \times$ upper limit of normal (ULN) and transaminases $\leqslant 3 \times$ ULN. Patients with brain metastasis were eligible if the disease was treated and asymptomatic.

Pretreatment evaluation included a complete history and physical examination, complete blood count (CBC) with differential and platelet count, full serum chemistry profile, urinalysis, and electrocardiogram. Baseline staging consisted of a chest radiograph, computed tomography (CT) scan of the chest and abdomen, magnetic resonance imaging or CT scan of the brain, and imaging of any other known or suspected sites of disease. During the course of the study, CBCs with differential and platelet counts were repeated weekly. Urinalyses and chemistry profiles were performed every 4 weeks. Radiographic imaging to determine disease status was repeated every 8 weeks or two cycles of therapy.

### Treatment plan

The starting dose (level 0) of 9-NC was 1.5 mg/m$^2$/day taken orally for 5 consecutive days of each week. Dose adjustments were made for granulocyte nadirs $< 1000$ cells/$\mu$l, platelet nadirs of $< 100\,000$ cells/$\mu$l or grade 3 or 4 non-hematologic toxicity. Dose escalation was permitted for patients with a granulocyte nadir $> 2000$ cells/$\mu$l if accompanied by a platelet nadir $> 150\,000$ cells/$\mu$l. Dose levels are shown in Table 1. One course of therapy was defined as 4 weeks.

Responses were defined as follows: complete response, disappearance of all clinical evidence of tumor for a period of $\geqslant 4$ weeks; partial response, a $\geqslant 50\%$ decrease in the sum of the products of the largest perpendicular diameters of measurable lesions, lasting for a period of $\geqslant 4$ weeks; progression, a $\geqslant 25\%$ increase in the size of any measurable lesion, the appearance of any new lesion or clinical deterioration felt to be a consequence of disease progression; stability, any outcome falling between partial response and progression, lasting for $\geqslant 4$ weeks. Patients were removed from the study for progression of disease, unacceptable toxicity or at their request.

**Table 1.** Dose levels

| Dose level | Dose (mg/m$^2$/day) | Treatment days per week |
|---|---|---|
| (+)1 | 2.0 | 1–5 |
| 0 | 1.5 | 1–5 |
| (−)1 | 1.5 | 1–4 |
| (−)2 | 1.0 | 1–4 |

### Statistical design

The statistical design of the study was based on a modified two-stage Simon's design.[12] Response data from patients with cutaneous melanoma and from those with uveal melanoma were to be analyzed separately. A response rate of 20% or greater was targeted, with a 5% rejection error. The design called for initial treatment of 14 patients in each group. If no responses were seen among the first 14 patients, the trial would be terminated for that group. If at least one response were to occur among the first 14 patients treated, the study would continue for that group to an enrollment total of 37 subjects.

## Results

### Patients

Twenty-eight patients were enrolled in the trial, including 14 with cutaneous melanoma and 14 with uveal melanoma. Patient characteristics are described in Table 2. All 28 patients were evaluated for toxic effects; response determinations could be made for 26. A total of 78 courses of treatment were administered: 56 at the starting dose level 0, seven at level (+)1, seven at level (−)1 and eight at level (−)2.

### Response

No complete or partial responses to treatment with 9-NC were observed in either group of patients. Stabilization of disease was achieved in four individuals (15%) for durations of 3, 4, 6 and 8 months; two of these patients had uveal primaries and two

**Table 2.** Patient characteristics

| | No. | (%) |
|---|---|---|
| No. registered | 28 | |
| Eligible for response | 26 | |
| Age (years) | | |
| median | 59 | |
| range | 28–79 | |
| Sex | | |
| male | 19 | (68) |
| female | 9 | (32) |
| Melanoma type | | |
| cutaneous | 14 | (50) |
| uveal | 14 | (50) |
| Performance status (Zubrod) | | |
| 0 | 7 | (25) |
| 1 | 14 | (50) |
| 2 | 7 | (25) |
| Prior therapy | | |
| chemotherapy | 23 | (82) |
| immunotherapy | 13 | (46) |
| radiotherapy | 11 | (39) |

had cutaneous primaries. Disease progressed in spite of treatment in 22 individuals (85%). Response could not be determined for the remaining two patients due to rapid clinical deterioration in one with cutaneous melanoma and unacceptable toxicity during the first course experienced by the other, a uveal melanoma patient, resulting in early withdrawal from the protocol.

### Toxicity

Moderate hematologic toxicity was observed (Table 3). Five patients (17.9%) developed grade 4 neutropenia and two (7.1%) developed grade 4 thrombocytopenia. Granulocyte colony stimulating factor was administered to three patients to facilitate granulocyte recovery. There were no hospitalizations for febrile neutropenia. A total of 21 units of blood were administered to eight patients; two patients required platelet support.

Gastrointestinal side effects were the most common non-hematologic toxic effects (Table 4). Twelve of the 28 patients (43%) experienced grade 3 or 4 diarrhea and five (18%) reported grade 3 or 4 vomiting. Dehydration secondary to gastrointestinal toxicity lead to four hospitalizations. Myalgias and fatigue were also common, but were usually described as mild to moderate in intensity. There were no instances of significant renal or hepatic toxicity, based upon serum creatinine or transaminase levels.

**Table 3.** Hematologic toxicity for 28 patients[a]

| | Grade 3 [*N* (%)] | Grade 4 [*N* (%)] |
|---|---|---|
| Neutropenia | 1 (3.6) | 5 (17.9) |
| Thrombocytopenia | 4 (14.3) | 2 (7.1) |
| Anemia | 9 (32.1) | 0 (0) |

[a]Highest grade of hematologic toxicity experienced by each patient.

**Table 4.** Gastrointestinal side effects for 28 patients

| | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) | Total |
|---|---|---|---|---|
| Diarrhea | 5 (17.9) | 9 (32.1) | 3 (10.7) | 17 (60.7) |
| Nausea alone | 4 (14.3) | 0 (0) | 2 (7.1) | 6 (21.4) |
| Nausea with vomiting | 14 (50.0) | 2 (7.1) | 3 (10.7) | 19 (67.9) |

In contrast to other published clinical trials of 9-NC, there were no instances of chemical cystitis with gross hematuria. Microscopic hematuria (greater than 5 red blood cells per high power field) complicated five (6.4%) courses for four patients, two of whom reported mild dysuria.

## Discussion

This phase II trial was conducted to determine if the reported *in vitro* activity of 9-NC for melanoma would translate into clinical efficacy. Our study population of 28 subjects was divided evenly between patients with cutaneous and uveal primaries. The toxicity that we observed was similar to that reported from other clinical trials,[6–8] the exception being the absence of clinically significant chemical cystitis in our study. Unfortunately, no complete or partial responses were seen, with stability of disease being the most favorable outcome observed. These findings are consistent with the general chemoresistance of melanoma.[1] Furthermore, our results are similar to those of an early study of camptothecin for patients with advanced melanoma, in which no responses were observed in 15 treated patients, although one melanoma response had been reported in the preceding phase I trial.[13,14] Similarly, there have been two published trials testing the activity of topotecan, another camptothecin analog, for melanoma; in these two studies combined, only one partial response was seen among 43 evaluable patients.[15,16]

Contributing to the lack of responses in our trial may have been the relatively brief exposure of the patients to 9-NC, with 18 of the 28 patients taken off therapy for progression after 8 or fewer weeks of treatment. It has been suggested that prolonged exposure to 9-NC is necessary to achieve response.[8] Melanoma tends to be rapidly progressive, once metastatic, and these patients are unlikely to remain stable for many months while waiting for responses to occur.

## Conclusion

The toxicity that we observed in this trial of 9-NC was not justified by the negligible antitumor activity. Further investigation of 9-NC at this dose and schedule for patients with melanoma of cutaneous or uveal origin is therefore not warranted.

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