# A Clinical Trial of Intravenous Vinorelbine Tartrate plus Tamoxifen in the Treatment of Patients with Advanced Malignant Melanoma

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**BACKGROUND.** The aim of the current trial was to assess the efficacy and toxicity of weekly intravenous vinorelbine tartrate with daily oral tamoxifen in the treatment of patients with advanced or metastatic malignant melanoma.

**METHODS.** Thirty-one patients were treated with vinorelbine tartrate, 30 mg/m$^2$ intravenously, weekly every 13 weeks and then every 2 weeks thereafter until progression of disease or severity of toxicity warranted discontinuation. Tamoxifen, 10 mg orally, twice a day was administered daily starting on Day 1 of chemotherapy with vinorelbine tartrate. Thirty patients had cutaneous melanoma with metastases and 1 patient had ocular melanoma with metastases. Eight patients had received prior chemotherapy.

**RESULTS.** Of the 30 evaluable patients with cutaneous melanoma, 6 achieved a partial response, for an overall response rate of 20% (95% confidence interval, 7–38%). There was no response in the patient with ocular melanoma. Major sites of response include the adrenal gland, lung, tonsil, and cutaneous/subcutaneous tissues. Three patients had a prolonged duration of response lasting $\geq$ 12 months. Side effects generally were mild and tolerable. Grade 3 or 4 hematologic toxicity occurred in 26% and 13% of patients, respectively. Nonhematologic toxicity included mild fatigue, paresthesia, and local arm discomfort from infusion.

**CONCLUSIONS.** Weekly intravenous vinorelbine tartrate plus daily oral tamoxifen appears to be active in the treatment of patients with malignant melanoma. Further clinical trials in malignant melanoma patients treated with vinorelbine tartrate and tamoxifen appear warranted. ***Cancer* 2000;88:584–8.**


**KEYWORDS: melanoma, vinorelbine tartrate, tamoxifen, efficacy, toxicity.**

Treatment for advanced melanoma remains unsatisfactory. Patients with metastatic melanoma survive an average of 4–6 months. Single agent chemotherapy with drugs such as dacarbazine (DTIC) have a response rate of generally $<$ 20%.[1] Combination therapy including carmustine (BCNU), DTIC, cisplatin, and tamoxifen have increased response rates of 40–50% with significantly more toxicity.[1,2] However, a recent randomized study[3] showed this drug combination to have a response rate (16.8%) that was not significantly different from that of DTIC alone (9.9%). New agents for advanced, metastatic melanoma therefore clearly are needed.

Vinorelbine tartrate is a vinca alkaloid that inhibits microtubule assembly. A Phase I trial of vinorelbine included one patient with melanoma.[4] It is interesting to note that this patient had a partial response for $>$ 30 weeks. Vinorelbine also is structurally related to vinblastine and vindesine, which have demonstrated antitumor ac-

tivity in melanoma[5–10] and it potentially could be more active in this disease. Furthermore, vinorelbine has demonstrated antitumor activity in a variety of human tumor cell lines including melanoma[11] as well as activity in murine B16 melanoma.[11]

Tamoxifen is an antiestrogen compound that appears to have modest antitumor activity in melanoma[12–17] and to potentiate the antitumor activity of several chemotherapeutic agents.[2,18–20] When tamoxifen was added to the combination of BCNU, DTIC, and cisplatin the response rate increased from $< 15\%$ to 40–50%.[21] However, other investigators have not observed an increase in response rates with the addition of tamoxifen.[22–24] Tamoxifen's mechanism of action on the antitumor activity of chemotherapy is unclear, but currently is being explored.[20] Tamoxifen also may potentiate the effect of vinorelbine. In hormonally sensitive and insensitive breast carcinoma cell lines, tamoxifen increased the activity of vinorelbine by nearly 50% (unpublished data), suggesting the drugs' interactions are not dependent on the presence of a functional estrogen receptor. It is noteworthy that estrogen receptors may be found on melanoma cells,[25] which may explain the observation that antitumor activity in melanoma has been reported with tamoxifen alone.[12–17] For these reasons, we conducted a Phase II trial of vinorelbine with tamoxifen in patients with advanced, metastatic melanoma.

## MATERIALS AND METHODS

The eligibility criteria for the trial included the following clinical parameters: microscopically confirmed diagnosis of melanoma, no previous cytotoxic therapy for advanced disease or no more than one prior chemotherapy regimen, bidimensionally measurable disease by physical examination or radiologic studies, and a Karnofsky performance status $\geq 70\%$. Prior irradiation was permitted; however, the measurable disease must have been completely outside the radiation portal. Patients had to be at least 3 weeks from radiation therapy and/or chemotherapy (6 weeks from nitrosoureas or mitomycin C). Patients with metastatic central nervous system involvement that was not controlled, patients with preexisting clinically significant peripheral neuropathy not due to cancer, or patients with a history of another malignancy within the past 5 years (except basal cell carcinoma of the skin or carcinoma in situ of the cervix) that could affect the diagnosis of metastatic melanoma were excluded. Required laboratory parameters were as follows: serum bilirubin $< 2.0$ mg/dL, serum creatinine $< 2.5$ mg/dL, platelet count $\geq 100{,}000/\text{mm}^3$, and total granulocyte count $\geq 2000/\text{mm}^3$.

Before the initiation of therapy, all patients were required to undergo screening assessments for eligibility and to have tumor measurements within 4 weeks prior to entry on to the study. Voluntary written informed consent was obtained from all patients registered on the study.

Antiemetic therapies were administered at the discretion of the the treating physician. Tamoxifen was given at a dose of 10 mg orally, twice a day daily starting on the first day of vinorelbine chemotherapy. Vinorelbine at a starting dose of 30 mg/m$^2$ was administered by the intravenous route over 6–10 minutes. Patients were encouraged to have a central line placed (i.e., Port-a-Cath) for chemotherapy infusion. Doses of vinorelbine were repeated weekly for 13 weeks and once every 2 weeks thereafter until progression of disease or severity of toxicity warranted discontinuation.

During therapy, patients were required to undergo a complete blood count with differential and platelet count weekly for 13 weeks and then once every 2 weeks thereafter.

Tumor evaluation was performed after the first 4 weeks of therapy and every 8 weeks thereafter. The length of 1 course of therapy was considered to be 8 weeks.

Response to chemotherapy was assessed using the standard criteria for response. Complete response was defined as the total disappearance of all malignant lesions and evaluable clinical evidence of tumor without the development of any new malignant lesions. Partial response was defined as an at least 50% reduction in the size of all measurable tumor areas as indicated by the sum of the products of the largest perpendicular dimensions of all measurable lesions. No lesion could progress (products of bidimensional measurements increased by 25%) and no new lesions could appear. Stable disease was defined as at least 2 evaluations separated by at least 4 weeks in which no increase in the size of any lesion was apparent. Minor response was defined as a reduction in size $< 50\%$ in any lesion. The duration of response was measured from the date of the initiation of chemotherapy until the date of progression of disease.

## RESULTS

The patient characteristics are shown in Table 1. There were 30 patients entered on to the study at the Sylvester Cancer Center and Jackson Memorial Hospital. In addition, one patient at the VA Medical Center was treated.

Overall, 6 of 30 patients with cutaneous melanoma (20%) had a response to the combination of vinorelbine plus tamoxifen (Table 2). All six were partial responses. The characteristics of the responding

**TABLE 1**
**Patient Characteristics**

| | |
|---|---|
| No. of patients | |
| Median age (yrs) (range) | 61 (27–74) |
| Karnofsky performance status | |
| 0 | 26 |
| 1 | 5 |
| Gender | |
| Male | 18 |
| Female | 13 |
| Metastatic sites | |
| Skin/soft tissue only | 9 |
| Lung | 19 |
| All visceral | 15 |
| Hepatic | 12 |
| No. of sites | |
| 1 | 10 |
| 2 | 10 |
| 3 | 11 |
| Prior therapy[a] | |
| Prior biologic therapy | |
| None | 15 |
| Adjuvant | 12 |
| Advanced | 2 |
| Adjuvant and advanced | 2 |
| Prior chemotherapy | 8 |

[a] Patients received more than one therapy.

patients are outlined in Table 2. Sites of response include the lung, tonsil, adrenal gland, and subcutaneous tissues. One patient with a tonsillar mass underwent a biopsy and the mass was proven to be melanoma. A partial response was documented both by the medical oncologist and otolaryngologist. Another patient with extensive subcutaneous and cutaneous nodules achieved a partial response documented by two medical oncologists. In addition, one patient had objective regression of cutaneous and subcutaneous nodules, which was considered a minor response. No complete responses were observed. The 95% confidence interval for the response rate was 7–38%. The duration of response ranged from 2+–20(+) months (median, 12 months). One patient with ocular melanoma and liver metastases was treated. No response was observed in this patient. One patient had mixed response in liver metastases and another patient had objective regression of subcutaneous lesions although his pulmonary nodules increased. Three patients has stable disease for 4 months, 10 months, and 12 months, respectively.

### Side Effects

The most common side effect noted in the patients was mild fatigue, which may have been due to their disease (Table 3). Several patients had mild arm discomfort from the vinorelbine infusion and one patient had chest discomfort after infusion into a central Port-a-Cath. Five patients had mild (Grade 1) paresthesia. Only one patient had Grade 2 peripheral neuropathy requiring discontinuation of the treatment. This patient had received prior cisplatin chemotherapy for 7 months. One patient had Grade 4 diarrhea, but diarrhea or constipation were otherwise uncommon. Grade 3 neutropenia occurred in 26% of patients and Grade 4 neutropenia developed in 13% of patients with febrile neutropenia reported in 2 patients. No Grade 3 or 4 thrombocytopenia or anemia occurred in any patient.

## DISCUSSION

Vinorelbine plus tamoxifen was selected for clinical investigation in patients with malignant melanoma because vinorelbine has demonstrated activity in this disease in a previous Phase I study[4] and in human murine melanoma cell lines.[11] Tamoxifen was added to vinorelbine for several reasons. Tamoxifen appears to potentiate the activity of certain drugs such as cisplatin in melanoma[19,21] as well as potentiate the activity of vinorelbine in breast carcinoma, independent of hormonal sensitivity (unpublished data). Therefore, it appeared reasonable to combine vinorelbine with tamoxifen to treat patients with advanced malignant melanoma.

The overall response rate in this study was 20% in patients with advanced cutaneous melanoma, which compares favorably with that reported for other single agents in melanoma.[1] A recent review[1] list 14 agents considered active for metastatic melanoma and only DTIC[1] fotemustine,[26] cisplatin,[27] and piritrexim[28] were found to show a response rate of $\geq$ 20%. In addition, the response rate for the combination of DTIC, cisplatin, and BCNU with tamoxifen recently was reported to be only 16.8%.[3] We treated one patient with ocular melanoma and extensive liver metastases in our study. It currently is believed that ocular melanoma patients should be excluded from chemotherapy trials designed for cutaneous melanoma because chemotherapy and immunotherapy regimens that have produced major responses in cutaneous melanoma have been found to show little activity in ocular melanoma.[29] In the one patient with ocular melanoma in this study no objective response occurred.

Responses were observed in patients with cutaneous/subcutaneous lesions as well as pulmonary, tonsillar, and adrenal metastases. Metastases in these sites are known to be more likely to respond to chemotherapy than other visceral lesions such as those occurring in the liver. Liver metastases generally are considered to be more resistant to chemotherapy and

**TABLE 2**
**Characteristics of Responding Patients**

| Patient | Age (yrs) | Gender | Sites of metastases | Response | Duration (most) |
|---|---|---|---|---|---|
| | 42 | F | Adrenal 6 × 4 cm | PR | 4 |
| | 43 | M | Tonsillar mass 2.5 × 2 cm | PR | 2 (+) |
| | 67 | M | Lung, 7 nodules (1–2 cm) | PR | 9 |
| | 72 | F | Lung, multiple (1–2 cm) | PR | 12 |
| | 63 | F | Lung, multiple (1–2 cm) | PR | 20 (+) |
| | 63 | M | Sub Q, Extensive | PR | 14 |

F: female; PR: partial response; M: male; Sub Q: subcutaneous tissues.

**TABLE 3**
**Toxicity Data**

| | Grade 3 | | Grade 4 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Neutropenia | 8 | 26 | 13 | 4 |
| Diarrhea | — | — | 3 | 1 |
| Fatigue | 3 | 1 | | |

this was the experience in the current study. We did not observe major responses in the liver (one patient had a mixed response) and no complete responses were noted. However, responses often were durable, with 3 patients having responses for ≥ 12 months.

The response rate of 20% for the combination of vinorelbine plus tamoxifen compares favorably with that reported for vinca alkaloids. Vincristine has a response rate of 12% in metastatic melanoma, vinblastine a response rate of 13%, and vindesine a response rate of 15%.[1] However, the confidence intervals for response for these drugs[1] generally were found to overlap with that reported for the combination of vinorelbine plus tamoxifen in the current study.

The advantage of combining vinorelbine with tamoxifen may be the ease of administration as an outpatient regimen and the generally tolerable side effects. With the exception of one patient who developed Grade 2 neuropathy, no major toxicities were observed in the current study that required discontinuation of the drugs. In addition, other side effects such as severe nausea and emesis or significant alopecia were not observed, which contributed to patient compliance with the treatment. The degree of myelosuppression reported in the current study is somewhat less than that reported for combination therapy with BCNU, DTIC, cisplatin, and tamoxifen, in which Grade 3 or 4 hematologic toxicities ranged from 56–63%.[30] The combination of vinorelbine plus tamoxifen might be an alternative for elderly patients with advanced melanoma in whom drug toxicity and quality of life is of particular concern.

Because this drug regimen has shown activity in melanoma, it may be worthwhile to consider adding the combination of vinorelbine and tamoxifen to other active agents. Drugs such as DTIC or temozolomide may be used in multiagent combination therapy to attempt to improve the response rate. We believe that further studies to confirm the activity of this regimen in melanoma, as well as in combination with other drugs, are indicated.

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