Docetaxel and Vinorelbine Plus GM-CSF in Malignant Melanoma

By John P. Fruehauf, MD, PhD [2], Kevin M. Kong, PharmD [3], and James G. Jakowatz, MD [4]

Patients having locoregional or metastatic melanoma have a poor prognosis, with 50% to 100% of patients dying from the disease within 5 years. Current chemotherapy regimens offer limited benefits to these patients, and more effective and less toxic treatments are needed. We therefore piloted a study of docetaxel (Taxotere), vinorelbine (Navelbine), granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]), or the DVS regimen, in patients with stage IV melanoma. Eight patients were treated after previous biochemotherapy and two patients were given the regimen as an initial treatment. The DVS regimen consisted of docetaxel at 40 mg/m² IV over 1 hour, vinorelbine at 30 mg/m² IV over 6 to 10 minutes every 14 days, and GM-CSF at 250 mg/m² SC on days 2 to 12. No grade 3 or 4 toxicities were encountered. Of the 10 patients evaluable for response, 5 were partial responders (50% response rate). Time to progression for the 10 cases ranged from 2 to 26+ months (median: 8 months). The DVS regimen was active against advanced melanoma in both previously treated and untreated patients. A larger study to confirm the activity of the DVS regimen for stage IV melanoma is currently under way.

FIGURE 1

The incidence of melanoma has increased more rapidly than any other cancer, except lung cancer in women, during the past decade. There are an estimated 53,600 new cases of malignant melanoma and 7,400 deaths annually in the United States.[1] Although curable in its early stages, melanoma is the most common fatal form of skin cancer. Patients having locoregional or metastatic disease have a poor prognosis, with 50% to 100% of patients dying from the disease within 5 years.[2]

Although malignant melanoma is relatively resistant to systemic treatment, chemotherapy can induce response rates of 30% to 50% and provide palliation for some patients. Combination chemotherapy regimens that have demonstrated activity in phase II studies include the three-drug combination of cisplatin, vinblastine, and dacarbazine (CVD)[3] and the four-drug combination of cisplatin, dacarbazine, carmustine (BiCNU), and tamoxifen (CDBT).[3,4] Interferon and interleukins also produce responses in 10% to 20% of patients with metastatic melanoma.[5,6] The modest therapeutic effectiveness of chemotherapy and cytokine treatment given separately has prompted study of the two treatments given in combination, referred to as biochemotherapy.

Eton et al conducted a phase III prospective, randomized trial to compare the effects of CVD alone with sequential biochemotherapy (CVD plus interferon alfa-2b and interleukin-2 [IL-2]) for patients with advanced melanoma. Ten percent of the patients were alive at a median of 52 months from the start of therapy. Response rates were 48% for biochemotherapy and 25% for chemotherapy ($P = .001$). Six patients given biochemotherapy and two given chemotherapy had complete responses. The median time to progression was 4.9 months for the biochemotherapy group and 2.4 months for the chemotherapy group ($P = .008$); median survival was 11.9 and 9.2 months, respectively ($P = .06$). However, biochemotherapy produced substantially more constitutional, hemodynamic, and myelosuppressive toxic effects in this trial.[7]

Atkins et al randomly assigned 416 patients to receive CVD, either alone or concurrent with IL-2 and interferon, and found no statistically significant differences in efficacy between the two arms. The response rate in CVD-only group was 11.4% vs 17.1% in the biochemotherapy group. The overall survival rates were 8.7 and 8.4 months, respectively. Grade IV toxicity occurred in 37% of patients on CVD vs 63% on CVD plus IL-2 and interferon. Side effects seen more frequently with
biochemotherapy included hypotension, metabolic abnormalities, fatigue, nausea, hepatic dysfunction, leukopenia, thrombocytopenia, anemia, and infection. Five treatment-related deaths were reported: two in the CVD-only group and three in the biochemotherapy group. Although biochemotherapy produced a slightly higher response rate and progression-free survival in this trial (5.3 vs 3.6 months), it was not associated with an improved quality of response or longer overall survival.[ 8] More effective and less toxic treatments are clearly needed.

Docetaxel, Vinorelbine, and GM-CSF

In preclinical studies, we observed that docetaxel (Taxotere) and vinorelbine (Navelbine) showed significant independent in vitro activity against melanoma specimens. Using the Oncotech extreme drug resistance assay to study the in vitro response of melanoma specimens, we found low drug resistance for docetaxel in 32 of 104 cases (31%) and for vinorelbine in 36 of 104 cases (35%) (personal communication, Ing-Ru Yu, 1997). Similarly, Photiou et al reported that the taxane paclitaxel and vinorelbine act synergistically in vitro against melanoma cell lines, with both agents active in the nanomolar range at clinically achievable concentrations.[9] Using an ex vivo adenosine triphosphate (ATP)-based chemosensitivity assay, Neale et al demonstrated that 43% of vinorelbine-treated and 33% of paclitaxel-treated cutaneous melanomas showed sensitivity in the assay.[10]

The safety and clinical activity of the docetaxel/vinorelbine combination have been demonstrated in patients with locally advanced and metastatic non-small-cell lung cancer[11] and metastatic breast cancer.[12,13] Retsas et al evaluated the activity and toxicity of two sequences of paclitaxel combined with vinorelbine in disseminated malignant melanoma. Of 15 previously untreated patients, eight received vinorelbine at 30 mg/m² (maximum dose 50 mg) first, followed 24 hours later by paclitaxel at 120 mg/m² (maximum dose 240 mg) infused over 3 hours (VT sequence). Seven patients received the reverse sequence (TV).[14]

There were no anaphylactic episodes, and the main toxicity noted was alopecia. No significant neutropenia, emesis, or neuropathy was observed with either schedule. Three major responses were seen, all in patients who received the VT sequence. Clinically meaningful tumor regressions that did not qualify as major responses were observed in two additional patients who received the TV sequence.[14]

Granulocyte-macrophage colonystimulating factor (GM-CSF, sargramostim [Leukine]) may have adjuvant benefit in melanoma. GM-CSF is integral to the functioning of the immune system, such as activation of macrophages, an important consideration in adjuvant therapy of cancer. Activated macrophages distinguish tumor cells from normal cells and, consequently, target only the tumor cells.[15] In vitro, GM-CSF stimulates peripheral blood monocytes to become cytotoxic to human melanoma cells.[16,17] The in vivo administration of GM-CSF results in an increase in the functional capacity of monocytes, as reflected by increased cytotoxicity.[18,19] Additionally, GM-CSF, through its action on tumor infiltrating macrophages, causes the production of angiostatin, an angiogenesis inhibitor.[20,21]

In two separate melanoma models, GM-CSF was found to be the most effective of the cytokines studied for induction of long-term protective immunity.[22,23] GM-CSF was first studied as an adjuvant to surgery in patients with metastatic melanoma by Spitler and colleagues. In a phase II openlabel study, patients with aggressive malignant melanoma (n = 48) received GM-CSF at 125 mg/m²/d for 14 days followed by 14 days of no treatment. The cycle was repeated every 28 days for a total of 12 cycles (12 months). The survival rate at 1 year for patients receiving GM-CSF was almost double (89% vs 45%) that of historically matched controls (P < .001).[24]

The evidence of vaccine immunopotentiation by GM-CSF and the welldescribed array of T-cell targets that are candidate intermediate end points for clinical trials in melanoma, along with the data reviewed above, support more extensive evaluation of the possible immune effects of GM-CSF in this setting. Therefore, an evaluation of the activity of the DVS combination (docetaxel, vinorelbine, and GM-CSF [sargramostim]) for the treatment of patients with stage IV melanoma was undertaken.

Patients and Methods

Treatment

TABLE 1
Time to Progression of 10 Patients Treated With the DVS Regimen

A regimen of docetaxel at 40 mg/m$^2$ IV over 1 hour, vinorelbine at 30 mg/m$^2$ IV over 6 to 10 minutes every 14 days, and GM-CSF at 250 mg/m$^2$ SC daily on days 2 to 12 was administered to 10 patients with stage IV melanoma with measurable disease, either after biochemotherapy (n = 8) or as an initial treatment (n = 2).

**Study Design**

Response rates were determined by CT scans using criteria for partial response of ≥ 50% reduction in one dimension of the dominant mass that lasted > 4 weeks. Time to progression was determined from the time DVS treatment was initiated until radiologic evidence of an increase of > 25% in one dimension of the dominant mass.

**Results**

No grade 3 or 4 toxicities were encountered for the initial 10 cases. Response rate for 10 evaluable patients was 50%, with 5 partial responses. Time to progression for the 10 cases is shown in Table 1. The median time to progression was 8 months, which is a minor improvement over the median survival of 7.5 months reported by Atkins et al for a biochemotherapy regimen that substituted oral temozolomide (Temodar) for dacarbazine.[25] A CT scan showing evidence of a partial response in one study subject is shown in Figure 1.

**Conclusions**

The DVS regimen in this study was active in delaying time to progression for both previously treated and untreated patients with advanced melanoma. Toxicities demonstrated were substantially less severe than those reported for other biologic agents, such as IL-2 and interferon alfa. No grade 3/4 toxicity was noted, allowing normal daily activities. These preliminary results suggest that the docetaxel/vinorelbine combination may offer a new treatment option for patients with malignant melanoma, and that GM-CSF may be a valuable component of this regimen. A larger, phase II study to confirm the activity of the DVS regimen for stage IV melanoma, using time to progression as the primary end point, is currently under way.

**Financial Disclosure:** Dr. Fruehauf has received grant and/or research support from Berlex Laboratories and Pfizer. He has served as a consultant to Oncotech, and has owned stock in Oncotech.
References:


Source URL:

Links: