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Taxol and vinorelbine: a new active combination for disseminated malignant melanoma

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We evaluated the activity and toxicity of two sequences of taxol combined with vinorelbine in disseminated malignant melanoma, metastatic beyond regional lymph nodes. Fifteen previously untreated patients, nine males and six females (median age 56 years), were enlisted between May 1994 and February 1995. Eight patients received vinorelbine 30 mg/m^2 (maximum dose 50 mg) first, followed 24 h later by taxol 120 mg/m^2 (maximum dose 240 mg) infused over 3 h (the V/T sequence). Seven patients received the reverse (T/V) sequence. In 79 administered courses there were no anaphylactic episodes, the main toxicity being alopecia (WHO grade 3). Significant neutropenia, emesis or neuropathy was not observed in either schedule (WHO grades 0 or 1). Three major responses, all with the V/T sequence, were seen; one complete (CR) in *nodal* and *cutaneous sites* lasting 13 months and two partial (PR), *omental, ascites* in one and *hepatic, splenic* and *nodal* in the other, lasting 7 and 6 months, respectively. Clinically meaningful tumor regressions, not qualifying strictly for the criteria of major response, were observed in two additional patients in the T/V sequence. Taxol combined with vinorelbine is active against disseminated malignant melanoma. The importance of sequencing the two drugs remains to be determined with accrual of more patients into the study.

Key words: Disseminated, malignant, melanoma, taxol, treatment, vinorelbine.

Introduction

Approximately 15% of patients with disseminated metastases from malignant melanoma are expected to survive beyond 2 years from onset of treatment based primarily on dacarbazine, platinum derivatives, vindesine and related compounds.[1,2] Complete remissions are limited to 6% of patients and only exceptionally are these maintained beyond 5 years.[1–3]

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In the search for newer drugs that could improve these results we recently studied the combination of taxol and vinorelbine.

Methods and patients

Between May 1994 and February 1995, 15 previously untreated patients, nine males and six females, with a median age of 56 years (range 29–68) and widespread metastases beyond regional lymph nodes (MD Anderson stage IV) were treated with taxol combined with vinorelbine. The study had the approval of the Institutional Ethics Committee, and patients gave informed and written consent.

Eight patients received vinorelbine first, at a dose of 30 mg/m^2 (*maximum dose 50 mg*, diluted in 100 ml of normal saline and administered over 30 min) followed 24 h later by taxol 120 mg/m^2 (*maximum dose 240 mg*) infused over 3 h. The cycle was repeated every 3 weeks for six intended courses. The remaining seven patients received taxol first, followed by vinorelbine 24 h later with the same doses. All patients received premedication with dexamethasone 20 mg orally, 6 and 12 h prior to taxol with chlorpheniramine 10 mg i.v. and cimetidine 300 mg i.v., 30–60 min before the onset of the taxol infusion.

This dose of taxol was selected in order to prevent neurotoxicity from the combination with vinorelbine and also because in some *in vitro* experiments in our laboratory some degree of synergy between the two drugs was observed against melanoma cell lines with relatively low drug concentrations (unpublished data).

All patients had more than one anatomical site involved by tumor: cutaneous, five; nodal, eight; pulmonary, seven; hepatic, six; skeletal, five; cere-

bral, three; other, five (ascites, spleen, esophagus). For the responding patients treatment was extended to six additional cycles or to progression.

Results

Toxicity

A total of 79 courses (median 4; range 1–12) were administered to these 15 patients. The median cumulative dose of taxol achieved was 880 mg (range 240–2640 mg) and of vinorelbine 200 mg (range 50–600 mg).

No difference in toxicity was observed between the two schedules.

Treatment was ambulatory, the main toxicity being hair loss. Total alopecia (WHO grade 3) was observed in all patients completing more than two courses of treatment. Hair loss was reversible on withdrawal of taxol. No cardiotoxicity or anaphylactic reactions were seen. Significant emesis or neuropathy was not observed (WHO grades 0 or 1). In the 79 courses administered, the observed nadir white cell count was $4.0 \times 10^9/1$ (WHO grade 0). Peripheral blood counts were routinely performed before each course of treatment at 3 week intervals. No granulocyte colony-stimulating factor was used. Non-neutropenic peritonitis (leucocyte count $24 \times 10^9 1/1$; neutrophils $21.5 \times 10^9/1$) developed after two courses in a patient (case 6) with progressive ilio-inguinal and pulmonary metastases; no visceral perforation was seen at post-mortem.

There was one early death due to pulmonary embolism after one course of treatment (case 9; Table 1).

Responses

Responses were defined as complete (CR) if all measurable and evaluable disease resolved completely, and partial (PR) if all lesions regressed by greater than 50% of their pre-treatment volume according to the accepted criteria of response by the International Union Against Cancer (UICC).

Three major responses, all with the vinorelbine–taxol sequence, were seen; one **CR** in *nodal* and *cutaneous sites* lasting 13 months and two **PR**, *omental, ascites* in one and *hepatic, splenic* and *nodal* in the other, lasting 7 and 6 months, respectively, giving an overall response rate of 20% [95% confidence interval 4–48%].

Of particular interest is the striking resolution in one of these responders (case 4; Table 1) of malignant ascites and regression of omental metastases after two courses of treatment (Figure 1).

All three patients experiencing a major response survived longer than 1 year. The patient who had a complete response (case 1; Table 1) developed cerebral metastases, currently stable on treatment with

Table 1. Patient characteristics.

No.	Sex	WHO performance status	Age	Metastatic sites on entry to study	Drug sequence	Number of cycles	Type of response[a]	Nadir total white cell count ($\times 10^9/l$)
1	F	1	63	skin, nodal	V/T	12	CR	5.3
2	M	1	48	mediastinum, lungs, liver, spleen, nodal	V/T	4	PD	9.3
3	M	2	65	liver, skeletal	V/T	4	PD	11.8
4	M	3	42	ascites, omentum, nodal	V/T	10	PR	7.3
5	M	2	51	nodal (mediastinum), esophagus	V/T	3	PD	10.0
6	F	2	63	nodal, skin, lungs	V/T	2	PD	10.0
7	M	1	64	nodal, liver, spleen, skeletal	V/T	11	PR	5.5
8	M	2	65	brain, skin, nodal, lungs	T/V	6	MR	9.9
9	M	3	48	lungs, liver, spleen	T/V	1	NE	4.0
10	M	1	56	skeletal, soft palate	T/V	7	MXR	8.2
11	F	1	31	lungs, brain	T/V	3	SD	8.2
12	F	3	66	skeletal, skin	T/V	4	PD	5.6
13	M	1	29	nodal, skin, brain	T/V	4	PD	7.7
14	F	1	68	lungs, liver	T/V	2	PD	8.4
15	F	1	39	lungs, liver, skeletal	V/T	6	MXR	5.8

[a]CR, complete response; PD, progressive disease; PR, partial response; MR, minor response; NE, not evaluable; MXR, mixed response; SD, stable disease.

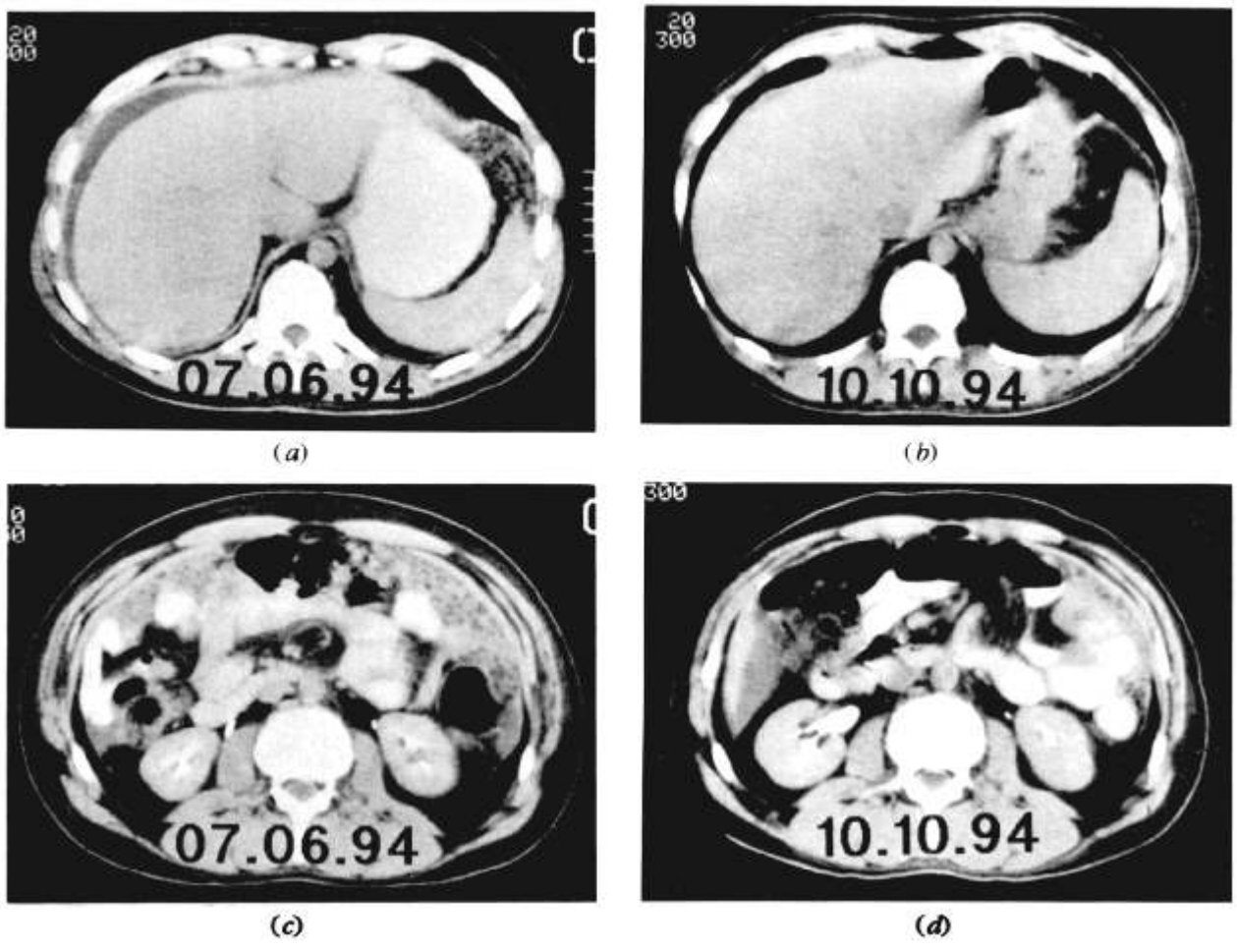

Figure 1. Resolution of ascites (a and b) after two courses of vinorelbine and taxol (V/T sequence) and regression of omental metastases (c and d) in case 4 (Table 1). Before treatment, 7 June 1994; after treatment, 10 October 1994.

vinblastine, carboplatin, vindesine, dacarbazine, vincristine and fotemustine, the DJV3-F combination as previously described.[1,4]

The first relapse in the second objective responder (PR) was recorded in a previously regressed splenic metastasis. This patient (case 7) is currently in second remission, induced with the DJV3 (no fotemustine) regime, also previously described.[1,4]

At the time of preparing this manuscript these two responders (case 1 and 7) were alive 19 and 15 months, respectively, from onset of the study protocol.

The third responding patient (case 4)(PR) developed leptomeningeal carcinomatosis after the 10th cycle of taxol and vinorelbine, confirmed cytologically in the cerebrospinal fluid. This has been the only manifestation of progressive disease for which he was also treated with the DJV3-F combination.[4] He survived for 14 months from onset of the study protocol.

No significant neuropathy has been observed with the DJV3 or the DJV3-F combinations introduced after taxol and vinorelbine.

Two additional patients, both treated with the taxol–vinorelbine sequence, experienced clinically meaningful tumor regressions not qualifying strictly for the *UICC* criteria of PR but conferring improvement in quality of life.

In one of these patients (case 8) presenting with hemoptysis, pulmonary, nodal and cutaneous metastases remained stable or regressed by less than 50%, whilst a concomitant large cerebral lesion resolved by greater than 50% in volume after two courses of treatment (Figure 2).

In the fifth patient (case 10), a tumor filling the oral cavity and infiltrating the base of the skull regressed after four courses of treatment allowing free mastication and resulting in 10 kg of weight gain. This patient experienced further tumor regression with the DJV3 regime, introduced after with-

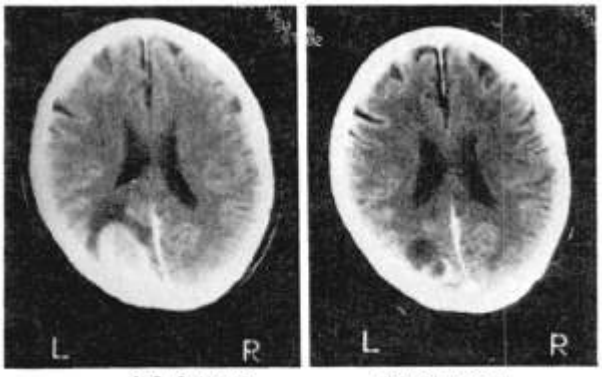

Figure 2. Regression of cerebral metastasis after two courses of taxol and vinorelbine (T/V sequence) in case 8 (Table 1). Concomitant pulmonary, cutaneous and nodal lesions regressed by less than 50% in volume. Before treatment, 4 October 1994; after treatment, 16 November 1994.

drawal of the taxol–vinorelbine combination, and is now surviving with stable disease, 13 months from initial presentation.

Discussion

Taxol is the first representative of a new class of drugs with broad anti-neoplastic activity—the taxanes—targeting tubulin.

Legha *et al.* first reported activity of taxol against malignant melanoma.[5] This was limited to three PRs only, among 25 evaluable patients for a response rate of 12%.

Einzig *et al.* observed a similar 14% response rate among 28 evaluable patients but with three CRs and one PR, concluding that taxol has significant activity against malignant melanoma which merited further studies in combination with other active agents.[6] In both these studies taxol was administered as a 24 h continuous infusion in a dose of 250 mg/m^2

In pooled data of 73 evaluable patients treated with this dose and schedule, Wiernik and Einzig[7] reported CRs and PRs in 12 patients (16.4%).

Vinorelbine, a new semi-synthetic drug belonging to the vinca alkaloid class, was shown to have activity against melanoma cell lines *in vitro* comparable to vindesine.[8] In the clinic, however, vinorelbine was active in only 5% of patients in our phase II study; two PRs were seen, one in 15 previously untreated and one among 28 pre-treated patients.[9]

There are reports in the literature of sequence-dependent interactions between taxol and other cytotoxics—principally cisplatin—when combined for the treatment of other malignancies.[10] With this in mind we elected to use two different sequences of taxol and vinorelbine in our study. No apparent difference in toxicity was recorded between the two schedules. However, all three major responses (one CR and two PRs) were achieved in patients treated with the vinorelbine–taxol sequence.

Because of the small number of patients treated so far, no firm conclusions can be reached about the importance of sequence in the administration of these two drugs. Nevertheless, with major objective responses observed in 20% of the patients in this study and clinical benefit in an additional 14%, the results of combining relatively low dose taxol with vinorelbine denote some degree of synergy between these two agents against malignant melanoma. In the absence of synergy, the logical conclusion from the observed responses must be that taxol is effective against metastatic malignant melanoma but in considerably lower doses than previously reported.[5–7]

These issues can be resolved with the accrual of more patients into the study. This combination has not precluded additional benefit from subsequent treatment with conventional drugs.

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