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The effect of combined chemotherapy with or without potentiation with interferon alpha or tamoxifen for melanoma

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BACKGROUND: *Metastatic melanoma has shown only limited responsiveness to chemotherapy or immunotherapy. The most commonly used single-agent chemotherapy comes from the nitrosourea group of agents and provides response rates of less than 20%. Several cytotoxic agents have been combined with no dramatic benefit. The incorporation of tamoxifen or interferon in chemotherapy regimens has proven effective in some trials.*

METHODS: *From July 1998 to March 2002, 45 patients with metastatic melanoma were enrolled for the study. None of the patients had previously received chemotherapy. The aim of the study was to compare the activity of three combined regimens: CVD (cisplatin, vinblastine, dacarbazine) chemotherapeutic combination, CVD with interferon (IFN) alpha-2 - biochemotherapy, and CVD with tamoxifen. The study was conducted as a single center, controlled, prospective, randomized phase II study directed toward the disease.*

RESULTS: *The best response rate (RR) was observed in the CVD+IFN (6/15) group related to the CVD (4/15) and CVD+TAM (3/15) groups, without significant difference though. In 29 patients with 1 to 2 metastatic lesions, RR was 44.82% (CR-1, PR-12, SD-13, PD-3), while in 16 patients with 3 or more metastatic lesions RR was 0.0 % (CR-0, PR-0, SD-9, PD-7). The difference was statistically significant ($p<0.005$). The best responding metastatic sites were the lymph nodes (in 10 patients), but patients with lung, skin and liver lesions also responded. All patients experienced mild adverse effects. No treatment-related deaths occurred. The median survival was 12, 12, and 11 months in CVD+IFN, CVD and CVD+TAM group, respectively. Time to progression was about 8 months in all treated groups.*

CONCLUSION: *Combined chemotherapy, biochemotherapy or chemohormonal therapy all showed some activity in metastatic melanoma. However, it is not yet possible to define standard therapy for this disease. Due to a limited number of patients evaluated so far in this investigation the results should be clearer and more conclusive with larger cumulative number of cases enrolled.*

KEY WORDS: *Melanoma; Neoplasm Metastasis; Treatment Outcome; Tamoxifen; Inteferon Alfa-2A*

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INTRODUCTION

Metastatic melanoma has shown only limited responsiveness to chemotherapy or immunotherapy. The median of overall survival (OS) is 6 to 9 months and systemic therapy induces complete response in a minor number of cases.

The most commonly used single-agent chemotherapy comes from the nitrosourea group of agents and provides response rates of less than 20%. Dacarbasine (DTIC), as the most active of these compounds, remains the chemotherapy standard for metastatic disease (1). Several cytotoxic agents have been combined with no dramatic benefit (1). The incorporation of tamoxifen in chemotherapy regimens has proven effective in some trials (2). However, combinations of therapy, for example DTIC with other cytotoxic agents, tamoxifen or cytokines, have largely proven to add toxicity with no significant survival benefit (3). Interferon alpha (IFN

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alpha) as a single agent has been extensively studied in advanced melanoma. When used as monotherapy, IFN alpha produced overall response rates comparable with those achieved with single-agent DTIC. The improvement when IFN alpha and chemotherapy were used in combination was negligible or very moderate in randomized phase III trials (4). The rationale for combining cytostatics with IFN in melanoma lies in the assumed different antitumor mechanism. The wide spectrum of IFN-induced immunomodulatory and antiproliferative effects together with the antitumor activity of cytostatic agents may be additive or synergistic (5).

Aim of the study was to compare the activity of three combined regimens (one of them containing the CVD chemotherapeutic combination; one CVD with IFN alpha-2 - biochemotherapeutical; and one CVD with tamoxifen).

PATIENTS AND METHODS

Patients. From July 1998 to March 2002, 45 patients (15 patients per each group) with metastatic melanoma were enrolled for the present study (Table 1). The treatment required 10 days hospital admittance. None of the patients had previously received chemotherapy.

Table 1. Patients' characteristics

	CVD*	P	CVD*+IFN*	P	CVD*+TAM	p
Age, median (min-max)	55 (35-65)	p<0.10	52 (30-65)	p<0.10	53 (24-64)	N.S.
PS						
0	2	p=1.00	2	p=1.00	2	N.S.
1	3	p>0.10	6	p>0.25	4	N.S.
2	10	p>0.10	7	p>0.30	9	N.S.
Metastatic site						
Skin	4	p>0.25	6	p>0.10	3	N.S.
Lymph nodes	10	p>0.70	9	p>0.25	11	N.S.
Lung	9	p=1.00	9	p=1.00	10	N.S.
Liver	9	p>0.10	6	p>0.10	9	N.S.
Other	3	p>0.10	0	p>0.20	2	N.S.
Number of metastases						
1	1	p>0.10	4	p>0.10	1	N.S.
2	8	p>0.70	7	p>0.70	8	N.S.
3	6	p>0.25	4	p>0.25	6	N.S.

*CVD – cisplatin, vinblastine, dacarbazine; IFN – interferon alfa-2a

Study type. Prospective, controlled randomized phase II disease-directed study. The study was conducted in accordance with the Helsinki Declaration standards of ethics (1964) amended in 1975, 1983, and 2000 by the World Medical Association.

Inclusion criteria. Histologically confirmed malignant melanoma; metastatic disease with metastatic lesions inappropriate for radical surgery; measurable or assessable lesions; performance status 0-2; expected survival over 2 months; and oral consent of the patient.

Exclusion criteria. Patients who do not fulfill the inclusion criteria; choroidal primary disease site; presence of unresectable CNS metastases; voluminous liver metastases associated with hyperbilirubinemia or liver insufficiency; and other contraindications for any of the planned drugs.

Treatment schedule. The patients were randomized in three groups. The treatment regimen A consisted of dacarbazine 800 mg/m^2 IV day 1, vinblastine 1.6 mg/m^2 IV days 1-5, and cisplatin 20 mg/m^2 IV days 1-4 (CVD). The cycle was repeated on day 22. The treatment regimen B consisted of CVD chemotherapy plus IFN alpha-2a (Roferon A, Roche) 1.5x10^6 IU/m^2 days 1-10. The treatment regimen C consisted of CVD chemotherapy plus tamoxifen 20 mg/m^2, all the time. The total number of cycles/day was 6 at the most. Those with progressive disease were excluded from the program after two cycles, while all the rest received six cycles, including those with stable disease, partial and complete remission.

Evaluation of response and toxicity. Pretreatment evaluation included physical examination, complete blood count and organ function tests. Staging was based on clinical and radiological examinations. Physical status and adverse effects were recorded and laboratory tests were taken every 4 weeks. Overall response was evaluated every 6 weeks. The responses and adverse effects were evaluated according to the World Health Organization criteria.

Statistical methods. The results obtained were evaluated according to the methodology of descriptive and analytic statistics. For hypothesis checking adequate parametric and non-parametric statistic tests were used (Pearson χ^2 test). Survival analysis was done according to Kaplan-Meier, with log-rank test of comparison of two or more factors (6). The 95% confidence limits for response rate were calculated using the normal approximation.

RESULTS

Patients' characteristics (Table 1) indicated that there was no significant difference among the groups for the factor of patient age, performance status (PS), and the number of anatomic sites involved by metastatic process.

Table 2. Response rate

	CR	PR	SD	PD
CVD	0 (0.0%)	4 (26.7%)	7 (46.7%)	4 (26.7%)
CVD+IFN	1 (6.7%)	5 (33.3%)	7 (46.7%)	2 (13.3%)
CVD+TAM	0 (0.0%)	3(20.0%)	8(53.3%)	4 (26.7%)

CR - complete remission; PR - partial remission; SD - stable disease; PD - progression disease

Therapeutic response is shown in Table 2. One complete remission (CR) was achieved in B group (CVD+IFN) in a female patient with bilateral multiple metastatic lesions in the lungs; the remission lasted 14 months, with consequent lung relapse (up to the evaluation time, total survival was 19 months).

Response rate was the highest best in CVD+IFN group (6/15) compared to CVD (4/15) and CVD+TAM (3/15) groups, but the difference was not significant (Figure 1).

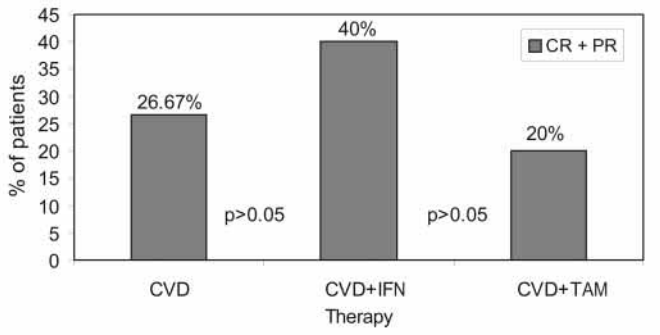


Figure 1. Response to therapy

Response to treatment related to the number of involved anatomic sites is shown in Figure 2. Out of 29 patients with 1-2 metastatic sites, RR was 44.82% (CR-1, PR-12, SD-13, PD-3) while in all groups with three or more involved sites 16 patients, RR was 0.0% (CR-0, PR-0, SD-9, PD-7). The difference was of high statistical significance ($p<0.005$).

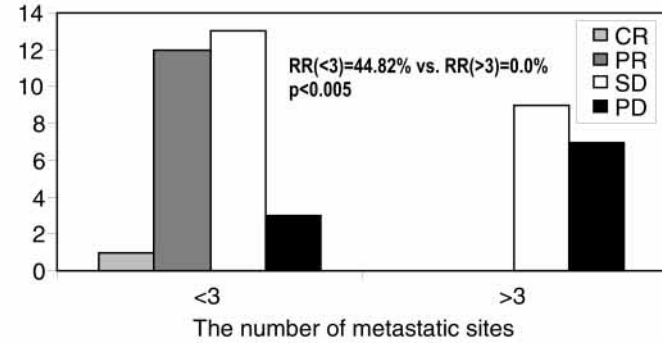


Figure 2. Response to therapy depending on the number of metastatic sites

The best responding metastatic sites were the lymph nodes (in 10 patients), but the patients with lung, skin and liver metastatic deposits also responded (Table 3).

Table 3. Characteristics of responding patients

Age (years)/sex	Metastat. site	Response Overall	Duration (months)	Survival (months)
57/female	Skin, node	PR	9	13+
39/female	Node	PR	9+	11+
35/male	Liver, lung	PR	8	12
40/male	Node, lung	PR	10+	12+
30/female	Skin, node	PR	10	14
61/female	Skin	PR	10+	12+
62/female	Lung	CR	12+	14+
61/female	Node, liver	PR	7+	9+
35/male	Node, lung	PR	8	12
40/male	Node, lung	PR	10+	12+
31/male	Node, lung	PR	10+	12+
36/female	Node	PR	10+	13+
55/female	Node, liver	PR	7+	10+

The reported toxicities associated with the treatment are shown in Tables 4, 5, and 6. All patients experienced mild adverse effects. Toxicity grade 3 and 4 were common in all the groups. The occurrence of nausea is understandable in view of the emetic agents used, above all of cisplatin. Serotonin receptor (5-HT3) antagonists and metoclopramide were routinely given to prevent nausea and vomiting during chemotherapy. Fever and arthralgias were characteristic for the IFN group. One patient from the tamoxifen

Table 4. Treatment toxicity in group A - CVD

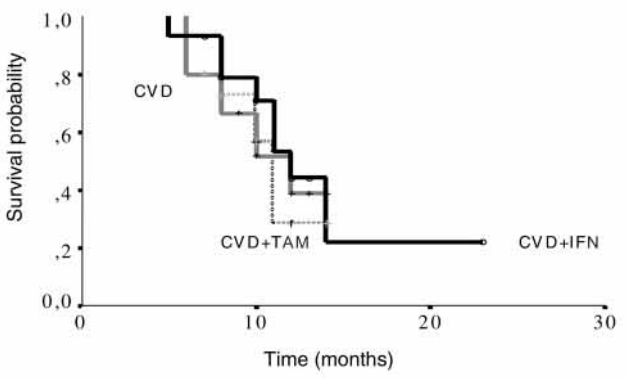
	WHO Grade, No. of patients				
	0	1	2	3	4
Hematol. tox.					
Hb	5	6	3	1	0
Plt	11	2	1	1	0
WBC	3	5	4	2	1
ANC	3	3	5	2	2
Non-hematol. tox.					
Nausea/vomiting	1	5	7	2	0
Fever	10	5	0	0	0
Arthralgia/myalgia	9	5	1	0	0

Table 5. Therapy toxicity in group B - CVD+IFN

	WHO Grade, No. of patients				
	0	1	2	3	4
Hematol. tox.					
Hb	7	4	4	0	0
Plt	10	1	2	2	0
WBC	1	4	5	3	2
ANC	1	4	4	3	3
Non-hematol. tox.					
Nausea/vomiting	1	3	8	3	0
Fever	5	4	3	2	1
Arthralgia/myalgia	3	5	3	3	1

Table 6. Therapy toxicity in group C - CVD+TAM

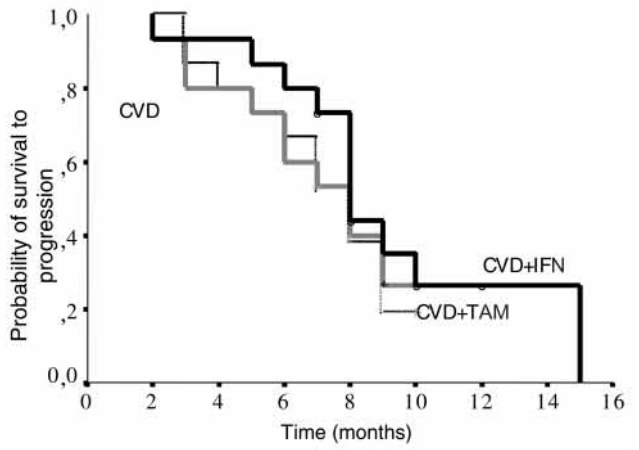
	WHO Grade, No. of patients				
	0	1	2	3	4
Hematol. tox.					
Hb	6	5	3	0	0
Plt	10	2	2	1	0
WBC	3	4	6	1	1
ANC	1	5	3	4	2
Non-hematol. tox.					
Nausea/vomiting	2	4	6	3	0
Fever	8	4	3	0	0
Arthralgia/myalgia	8	6	1	0	0
* DVT	1				



	No. of deaths /total No.	Average survival	Survival median	Log Rank
CVD+IFN	8/15	13.51 (9.7; 17.3)	12.0 (9.9; 14.1)	
CVD	7/15	10.75 (9.1; 12.4)	12.0 (7.8; 16.2)	
CVD+TAM	7/15	10.47 (8.9; 12.0)	11.0 (9.9; 12.1)	0.39 p=0.824

Figure 3. Overall survival. Heavy line represents CVD + IFN group; Fine line represents CVD group; Interrupted line represents CVD + TAM group (p=0.824, N.S.)

group had deep vein thrombosis. No treatment-related deaths occurred. Total patients survival is shown in Figure 3, and time to progression (TTP) is shown in Figure 4.



	No of progressions / total No	Average time to progression	Median to progression	Log Rank
CVD+IFN	11/15	9.31 (7.2; 11.5)	8.0 (7.1; 8.9)	
CVD	11/15	7.07 (5.7; 8.4)	8.0 (5.5; 10.5)	
CVD+TAM	11/15	7.17 (6.0; 8.4)	8.0 (6.2; 9.8)	0.56 p=0.758

Figure 4. Time to progression. Heavy line represents CVD + IFN group; Fine line represents CVD group; Interrupted line represents CVD + TAM group (p=0.758 N.S.)

DISCUSSION AND CONCLUSION

Response rates in this study ranged between 20% and 40% (CVD+IFN 6/15, CVD 4/15, CVD+TAM 3/15), i.e., 28.8% if all the cases were analyzed together. This is comparable with many studies performed during the 1990s. One of the most marked deviations from these results was a Finish phase II study with the response rate of 62% achieved with combined chemotherapy and human leukocyte interferon alfa (7). Liver metastases accounted for more then 50% in our study, as opposed to 21% in Pyrhoenen's study. Liver metastases are shown to be more resistant to any kind of chemotherapy or immunotherapy, especially liver metastases of ocular melanoma.

In two prospective randomized trials, a therapeutic advantage in the response rate or in the duration of response has been reported with the combination of IFN and dacarbazine compared to dacarbazine alone (8). The results of our study correspond to a later phase III study by Falkson et al. (4). However, it should be emphasized that response rates were higher with combined IFN-alpha and chemotherapy compared to chemotherapy alone and, two times higher than with combined chemotherapy and tamoxifen. Extra toxicity was not observed, at least with these IFN alpha-2a doses.

The MD Anderson study, comparing biochemotherapy to combination therapy, demonstrated doubling of objective response rates (48% versus 25%; p=0.001) and time to progression of disease (4.9 months versus 2.4 months: p=0.008) but no advantage for overall median survival (18.7 months versus 15.4 months: p=0.99) (9). These findings generated renewed enthusiasm for biochemotherapy. The results of our study agree with these results. Time to progression in our study was somewhat higher (7.17 to 9.31 months) with overall median survival somewhat lower (10.47 to 13.51) though without significant difference among the groups for TTP as well as for OS. The United States intergroup study of IL-2/IFN + CVD versus CVD was closed after randomizing 397 patients (10). Primary end points included response, survival, and time to progression. The median OS was 8.1 months for biochemotherapy compared with 8.7 months for chemotherapy alone (p=0.439); time to progression was about 4 months for biochemotherapy and approximately 2 months for chemotherapy (p=0.082). Significantly more toxicity was noted the biochemotherapy arm.

In view of a small number of examinees, we may point out as a conclusion that standard systemic therapy still cannot be defined for metastatic melanoma.

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