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Phase II Study of Bleomycin, Actinomycin D, DTIC and Vindesine in Disseminated Malignant Melanoma

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Abstract—*Twenty-seven patients with disseminated malignant melanoma were treated with combination chemotherapy consisting of bleomycin, actinomycin D, DTIC and vindesine. There were 4 complete responses in patients with pulmonary metastasis, 5 patients had a partial remission, 2 of them had mainly lung lesions. Toxicity consisted mainly of leuco- and thrombocytopenia of short duration and sporadic severe mucositis.*

INTRODUCTION

DISSEMINATED malignant melanoma has a dismal prognosis, despite attempts at chemotherapeutic intervention. Most drugs that have been applied in this disease have at best modest response rates when given as single agents, among them DTIC, CCNU, actinomycin D and the vinca derivatives [1]. Bleomycin has been reported to synchronize melanoma cells *in vitro* [2] and might therefore be of some use in combination chemotherapy. It is hoped that such combinations, consisting of otherwise marginally active drugs could eventually improve the results of chemotherapy. We have studied response rates and duration in a regimen combining bleomycin with actinomycin D, DTIC and vindesine in 27 patients with disseminated malignant melanoma.

MATERIALS AND METHODS

Patients who had not previously received chemotherapy who had histologically proven disseminated malignant melanoma were eligible if bidimensional measurable disease was present. The only exclusion criterion used was the clinical presence and CT scan confirmation of CNS disease. Patients were entered between 1981 and 1985.

Initial diagnostic workup, repeated before a new treatment course, included physical examination, Smac 16, ultrasound of abdomen and liver and CT scan if lesions were suspected, chest X-ray and tomography. In case of remission this workup was repeated every 6–8 weeks. Lung tomography was performed only if chest X-rays gave cause for suspicion. Brain CT was done if clinical indications of brain metastasis were present.

Chemotherapy consisted of 30 mg bleomycin daily for 4 days by continuous i.v. infusion. DTIC was given as a slow i.v. push of 300 mg/m^2 on the same days. On day 5 vindesine was given, 3 mg/m^2 in an 8-hr infusion, followed by actinomycin D 2 mg/m^2.

Cycles were repeated after 6 weeks, unless progressive disease was diagnosed. After 2 cycles, treatment was discontinued in case of complete remission, tumor progression, or if no further response had occurred during the second compared to the first course. Otherwise a third course was given.

Complete response was defined as the disappearance of all signs of disease for at least one month. Partial response was defined as a decrease by at least 50% in the product of the greatest perpendicular parameters of all measurable tumor lesions, for at least 1 month. No change was defined as less than 50% increase or decrease in the parameters and progressive disease as more than 50% increase in the parameters. Response duration was defined as the period between the moment of diagnosis of tumor regression compatible with response and the moment that signs of tumor progression were identified. Patients were evaluated for tumor response and toxicity after each cycle.

Toxicity was graded according to the WHO criteria [3].

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RESULTS

Twenty-seven patients were entered in the study, 14 male and 13 female. Median age was 43 yr (range 24–59). Five patients had a Karnofsky score below 60, 20 patients scored 80 or above. The sites of indicator lesions and their responses are given in Table 1. In addition to these lesions 4 patients also had evidence of bone involvement.

Nine responses occurred in the group of 27 patients, 4 were complete. These 4 patients all had mainly pulmonary disease. In 2 of them only 2 respectively 4 small pulmonary lesions were present, in the third patient 1 lesion was detected plus a hilar lymph node. The fourth patient had extensive lung and abdominal tumors. In these 4 patients the remission was complete after the second course, while tumor regression was at least 50% after the first course.

Five patients had a partial remission. In 1 patient, 3 courses were given. In the others a partial remission was seen after the first course and no additional decrease of tumor was seen after the second course.

Two patients with complete responses were male, all other responders were female. All nonresponding patients had progressive disease after the first or second course (11 and 5 patients, respectively).

Two patients died during the first course of treatment with chemotherapy. Both presented with extensive pulmonary disease with dyspnea at rest and a Karnofsky performance score of 50. The cause of death was rapidly progressive disease, no relation with treatment was assumed.

Table 1. *Responses by indicator site*

	Patients	CR	PR
Lung	14	4	2
Liver	5	—	—
Lymph nodes	7	1	1
Subcutaneous	11	—	3
Abdominal mass	2	1	—
Cutaneous	3	—	—
Kidney	1	—	—
Pancreas	1	—	—

Table 2. *Toxicity (number of courses)*

WHO grading	0	1	2	3	4
Thrombocytopenia	31				
Leucocytopenia	11	11	10	5	3
Mucositis	21	15	2	1	1
Diarrhoea	24	7	7	2	0

In the group of 9 patients responding to therapy, 6 had symptomatic disease. In 4 of these patients the tumor response coincided with a relative normalization of the life pattern of the patient without symptoms due to tumor or treatment for the duration of the remission, respectively 18, 12, 4 and 4 months.

The toxicity of this treatment was quite variable. Table 2 gives the most important toxicity in all 40 evaluable courses. All patients experienced nausea and vomiting related to the DTIC, and fever related to the bleomycin treatment. No neurotoxicity was seen. The most discomforting toxicity for the patient was the oropharyngeal mucositis, grade 2 or higher in 10% of all courses, and the diarrhoea grade 2 or higher in 23% of all courses.

Leucopenia and thrombocytopenia did not require special treatment and were of short duration.

DISCUSSION

The remission rate of this regimen is 33%, 95% confidence range 17–54%. The complete remission rate is 14%, range 4–34%.

When these results are compared with the literature on monochemotherapy with DTIC, the overall response rate of our combination may not be better than the 23% described for the single agent [1]. Nevertheless, the relatively long-lasting complete responses, when compared with DTIC [4] may render the combination worthwhile, especially in view of the short treatment period required to obtain these results. The suggestion that a fair result as far as response and duration are concerned can be reached in patients with predominant lung disease without liver involvement (remissions in 6 of 12 patients who completed 5 days of therapy) should be further investigated.

The combination regimen described increases the toxicity that is experienced with DTIC alone. This is especially true for mucositis that is rarely found with monotherapy. This side effect is probably mainly due to actinomycin D. The incidence of the other side effects is comparable, although the intensity may be higher [5]. The continuous infusion of bleomycin requires hospitalization.

The role of bleomycin in combinations remains equivocal. In some reports its addition suggests improvement of overall results [6–10]. Other studies however could not confirm this impression [11,12].

It remains difficult to ascribe a place to single agent chemotherapy or combination chemotherapy in the treatment of disseminated malignant melanoma. Even among the responders in this study only 50% had alleviation of symptoms, the others were either asymptomatic on entrance to the study or had no benefit from their response. On the other

hand toxicity of this combination is manageable and the duration of ineffective treatment can be limited as it will be evident after the first course if no response will occur.

We conclude that the regimen described here has some activity in disseminated melanoma, in particular in patients with pulmonary metastatic disease.

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