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OUR EXPERIENCE WITH DACARBAZINE IN THE TREATMENT OF PATIENTS WITH INOPERABLE SKIN MELANOMA

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ABSTRACT:

Objective: The standard treatment for inoperable skin melanoma is chemotherapy. The aim of this study was to explore the efficacy and safety of therapy with dacarbazine in patients with advanced melanoma.

Methods: Twenty- seven consecutive patients with inoperable stage III or IV skin melanoma were treated with chemotherapy. Treatment schedule consists of dacarbazine 150 mg/ m2 days 1- 5 administered every 3- 4 weeks.

Results: Overall response rate was 14,8% with four partial remissions. The main toxicity were neutropenia and vomitus.

Conclusions: These data confirm that advanced skin melanoma is resistant of chemotherapy with dacarbazine.

Key words: Chemotherapy, Skin melanoma, Survival

INTRODUCTION

The skin melanoma accounts apparently 1%- 3% of all malignant tumors and is increasing in incidence annually by 6% to 7% in the last years. The World Health Organization estimates 132,000 new cases each year and an associated 46,000 deaths from melanoma worldwide (1).

Melanoma is curable with surgical resection in a high percentage of cases. Prognosis in cutaneous melanoma depends strongly on the primary stage according to TNM; thus 5- and 10- year survival rates in operable stage IA are 97% and 93% respectively, while in stage IIIC they are only 53% and 39%. Stage IV- melanoma with metastasis to distant organs- is characterized by the worst prognosis, and the outlook for these patients remains dismal, with 1- year survival 62% for M1a, 53% for M1b and 33% for M1c stage (2). A minority of patients respond to treatment, remissions are generally only short- lived. The largest meta- analysis of historical data (2,100 patients, 42 phase II studies), found a median overall survival (OS) time of 6,2 months and 1- year survival rate of 25,5% for both pretreated and untreated stage IV melanoma patients (3). Furthermore, Howlader et al. suggested that 5- year survival for patients with metastasized melanoma was <16%, whereas others estimated this proportion to be < 5% depending of the cancer spreads to distant sites (4, 5, 6).

The standard treatment for advanced disease has been with chemotherapy. Over the years, a variety of chemotherapeutic drugs combinations have been explored with the hopes of improving the response rates. Examples include dacarbazine (DTIC), vinblastine, cisplatin, bleomycin, carmustine and others. The response rates and duration of responses to currently available chemotherapy have been poor. DTIC is considered the most active single agent and is often used as the standard chemotherapy. When used as a single agent, DTIC has produced objective response in 15% to 20% of patients with a complete response (CR) rate of less than 5%. Toxicities, primarily gastrointestinal and haematologic, were manageable (7, 8).

The aim of this study was to explore the efficacy and safety of the chemotherapy using DTIC in patients with inoperable stage III and IV skin melanoma.

PATIENTS AND METHODS

We performed a retrospective analysis on 27 patients with inoperable stage III or IV skin melanoma, aged 42- 76 years, comprising 21 men and 6 women. Some patient's baseline characteristics are listed on table 1. All patients started systemic treatment in the Department of Chemotherapy, Oncological center, Medical University, Pleven, Bulgaria in the years 2001- 2009. The analysed group included only patients with histologically confirmed diagnosis of skin melanoma. Patients with ocular melanoma and these with unknown primary site were not included in the analysis. Complete information on tested clinical factors, survival and treatment method was gathered from the medical files. Evaluation of time- varying clinical parameters such as stage of the disease (stage III or IV), affected sites, performance status, and biochemical parameters was performed when diagnosing inoperable metastasis or disqualifying from surgical treatment. For each patient the basic epidemiological information was recorded, such as age, sex, and the date of histological diagnosis, but also the date of dissemination of the disease (or qualifying changes as inoperable) and date of death or last follow- up.

The disease stage was assessed on the basis of the medical reports of clinical and imaging examinations (chest/ bone X- ray, bone scan, ultrasonographic tests and CT/MR scans).

Response to treatment was evaluated according to RECIST- Response Evaluation Criteria in Solid Tumors, version 1,0. The assessment of toxicity in all cases was based on CTCAE - Common Terminology Criteria for Adverse Events, version 3,0. In all cases adverse symptoms from respective organs and systems are scored on a four- point scale. All forms of excision of metastatic lesions in patients

with distant metastasis of melanoma were considered as palliative resection. Those were most commonly resections within soft tissues, brain, and in a few cases resections of metastatic changes from lungs. Radiotherapy of distant metastases (mainly in central nervous system and skeletal system) were considered as palliative radiotherapy.

Chemotherapy regimen consists of DTIC for five days. DTIC was used in a dose of 150 mg/ m2 administered intravenously over 1- 2 hours on days 1- 5. The courses of chemotherapy were repeated at 21- 28 days intervals provided the blood counts had recovered to adequate levels. All patients received premedication with antiemetics. The doses of chemotherapy were reduced in patients who developed neutropenia during chemotherapy.

Time to progression (TTP) was defined as the time from registration to disease progression. Overall survival time (OS) was defined as the time from registration to death. The duration of treatment response was defined as time from the date at which the response was first noted until the date at which disease progression was noted. The duration of the OS and TTP were estimated using the Kaplan- Meier method.

RESULTS

From January 2001 to December 2009 twenty seven patients received DTIC chemotherapy. Some clinical characteristics of these patients are shown in table 1. The median patient's age was 64 years. Twenty one patients were male and six females. Six patients had a WHO PS- 0, fourteen had a PS- 1 and seven had a PS of 2. The dominant sites of metastases were liver and lung.

The resulting antitumor effects are presented on table 2. Four partial remissions were obtained. The overall response rate (ORR) was 14,8 %. No change was observed in 6 (22,2%) and progressive disease in 7 (26,0%) patients. The OS was 6,2 months with PFS of 3,7 months. These results confirm that skin melanoma is resistant to conventional chemotherapy.

Table 3 presents the incidence of adverse drug reactions grade 3- 4 that occurred in all patients. The highest incidence was nausea, vomiting and neutropenia. Treatment-related deaths were not observed.

DISCUSSION

The prognosis of patients with metastatic melanoma remains poor (9). Chemotherapy remains largely palliative, and survival times after diagnosis are short. In the current study we evaluate efficacy and safety of DTIC as first- line chemotherapy for inoperable skin melanoma. Response rate- 14,8 % confirm that skin melanoma is resistant to chemotherapy. Our results are comparable with previously published data. A pooled analysis of 23 randomized, controlled trials showed that the objective response rate (ORR) for 1,390 patients receiving DTIC alone was 15,3%. The majority of these responses were partial (11,2% PR), with 4,2 % CR (10). Both haematological and nonhaematological toxicity was mild to moderate and never was fatal.

CONCLUSIONS

In conclusion, our results indicate that DTIC chemotherapy for advanced skin melanoma is ineffective and needed new alternatives.

Table 1. Patient characteristics

Patient characteristics	Number of patients- 36
Age (years)	43 - 79
Sex	
Males	21 (77,7%)
Females	6 (22,3%)
Dominant site of metastasis	
Liver	12 (44,4%)
Lung	9 (33,3%)
Soft tissue	4 (14,8%)
Other	2 (7,5%)
Performance status WHO	
0	6 (22,2%)
1	14 (51,8%)
2	7 (26,0%)
Stage	
III	4 (14,8%)
IV	23 (85,2%)
Site of primary tumor	
Head and neck	5 (18,5%)
Body	14 (51,8%)
Arms	8 (29,7%)

Table 2. Objective responses

Patients/ Response (N)	CR	PR	NC	PD	ORR%
36	0	4	14	9	14,8%

ORR= CR+ PR

CR - Complete response; PR - Partial response; NC - No change; PD - Progressive disease; ORR - Overall response rate;

Table 3. Adverse drug reactions (grade 3-4 only)

Haematological	Grade 3- 4
Neutropenia	3 (11,1%)
Febrile neutropenia	1 (3, 7%)
Anemia	3 (11,1%)
Thrombocytopenia	1 (3, 7%)
Non- Hematological	
Nausea	4 (14,8%)
Vomitus	4 (14,8%)
Diarrhea	2 (7, 4%)
Oral mucositis	1 (3, 7%)

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