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TOXIC EFFECTS OF CHEMOTHERAPY, IMMUNOTHERAPY AND CHEMOIMMUNOTHERAPY IN PATIENTS WITH CUTANEOUS MELANOMA

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Abstract

Many systemic therapies for the treatment of metastatic melanoma are diponible in this moment. Several reports have suggested that the administration of chemotherapy in combination with IL-2 and interferon alpha-2b can improve the percent of favorable response.

Based on data provided by the scientific literature, in this study we aimed to evaluate comparatively the side effects of 3 and 4 degree, produced by classical chemotherapy (Dacarbazine), immunotherapy (Interferon alfa-2b) and chemo-immunotherapy (Dacarbazine and Interferon alpha-2b). Study was conducted on a total of 133 patients diagnosed with thick metastatic melanoma, that were randomized into three groups: 45 patients received chemotherapy, 44 received immunotherapy and 44 patients received chemo immunotherapy. Each treatment consisted of two cycles of three days of chemotherapy, followed at the group of patients randomized to receive also immunotherapy - 4 days of treatment with interferon alfa-2 and at the group of patients with immunotherapy - two cycles of 4 days with interferon alfa-2. The toxic effects of therapy were monitored during treatment in all the three groups and were statistically processed.

From the point of view of toxicity, the use of immunotherapy associated with chemotherapy in treating patients with metastatic melanoma is not recommended.

Key words: cutaneous melanoma, systemic therapy, toxicity, chemotherapy, immunotherapy, chemo immunotherapy.

INTRODUCTION

Cutaneous melanoma is a serious and unpredictable disease; although curable in the early stages it has a devastating evolution in the disseminated stage.

In scientific literature there are many systemic therapies for the treatment of patients with metastatic melanoma. Chemotherapeutic agents such as dacarbazine, cisplatin alone determine objective responses in 10% - 20% of cases, and the combinations of these agents with nitrosoureas or vinca alkaloids reported favorable response rates in 30% - 40% of cases (Balch CM, et al 1997; Mastrangelo MJ.et al 1991)

Recently, several reports have suggested that the administration of chemotherapy in combination with IL-2 and interferon alpha-2b can improve favorable response rates at 55% - 60% (Richards JM., et al 1992; Antoine EC. et al 1997 Legha SS. et al, 1998)

Based on data provided by the scientific literature, in this study we aimed to evaluate comparatively the side effects of 3 and 4 degree produced by classical chemotherapy (Dacarbazine), immunotherapy (Interferon alfa-2b) and chemo-immunotherapy (Dacarbazine and Interferon alpha-2b).

MATERIAL AND METHOD

This observational study prospectively randomized was conducted on a total of 133 patients diagnosed with thick metastatic melanoma in the Oncology Clinic of the Municipal Clinical Hospital "Dr. Gabriel Curtenu "Oradea over a period of four years respectively 2010-2013.

The inclusion criteria were: patients with cutaneous melanoma with intermediate Breslow (1-4 mm) - thick metastatic melanoma respectively stage Ib, II, III and IV > Leucocytes 3,000 / mm3 Platelet > 100,000 / mm3; Serum creatinine <1.7 mg / dl; Bilirubin <1.6 mg / dl; Patients seronegative for HIV and hepatitis B antigen.

The exclusion criteria were: patients with primary ocular or mucosal melanoma ; Patients who had previously received chemotherapy or had previously received immunotherapy dacarbazine interferon alfa-2b; patients with evidence of brain metastases, cardiovascular or respiratory diseases or renal insufficiency.

Chemotherapy consisted in the administration of Dacarbazine. A course of treatment consisting of two cycles, starting in the days 2 and 23 lasted two months. The first cycle consisted in administering chemotherapy in the days 2, 3, and 4 and in the days 23, 24 and 25 Dacarbazine 220 mg/m^2 intravenously for 1 hour.

Immunotherapy consisted in the administration of Interferon alfa-2b 6,000,000 U /m^2 subcutaneously starting with the days 5 and 26 of 4 days for 2 months. .

Patients randomized to receive ***chemoimmunotherapy*** received the same chemotherapy regimen followed, starting with the days 5 and 26 of 4 days of interferon alfa-2b 6.000.000 U / m^2 subcutaneously.

Therefore, each treatment consisted of two cycles of three days of chemotherapy followed, in those patients randomized to receive immunotherapy also, of 4 days of treatment with interferon alfa-2b and for patients with immunotherapy two cycles of 4 days with interferon alfa-2b (Table no. 1).

Table 1

Treatment schedule

The cure and the day	**Treatment**		
Abbreviations and doses: DTIC, dacarbazine, 220 mg /m^2 IV for 1 hour; IFNα, interferon alfa-2b, 6,000,000 U / m^2 subcutaneously.			
The first cure	Chemotherapy	Immunotherapy	Chemoimmunotherapy
1			
2	DTIC		DTIC
3	DTIC		DTIC
4	DTIC		DTIC
5		IFNα	IFNα
6		IFNα	IFNα
7		IFNα	IFNα
8		IFNα	IFNα
9-22			
The second cure			
23	DTIC		DTIC
24	DTIC		DTIC
25	DTIC		DTIC
26		IFNα	IFNα
27		IFNα	IFNα
28		IFNα	IFNα
29		IFNα	IFNα
57	Evaluation of the clinical response; re-treatment if the tumor has decreased or regressed		

Data were prospectively collected, stored and processed using Microsoft Excel® 2010 (Microsoft Corporation, USA) representing the statistical study database in which we followed the toxicity of the therapy.

RESULTS AND DISSCUSIONS

The 133 patients included in the study were randomized into three groups: 45 patients received chemotherapy, 44 received immunotherapy and 44 patients received chemo immunotherapy (Figure 1).

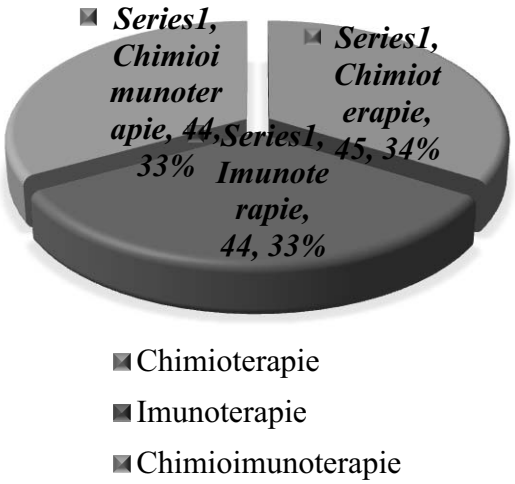

Chart no. 10 The distribution of patients with cutaneous melanoma distribution based on systemic therapy

The results concerning the studied toxic effects (side effects degree 3 and 4) are shown in Table 2 and the graph in Figure 2.

Table 2

The toxicity of the treatment

	Chemotherapy (n = 45,98 cure)		**Immunotherapy (n = 44, 88 cure)**		**Chemoimmunotherapy (n = 44, 88 cure)**		
	No.	**%**	**No.**	**%**	**No.**	**%**	
3 and 4 degree side effects							
Shivering	2	2%	21	24%	22	24%	***p<0,0001****
Pruritus	1	1%	8	9%	8	10%	
Anaphylaxis	0	0%	1	1%	1	1%	
Mucositis	0	0%	4	4%	4	4%	
Nausea	4	3%	11	12%	11	13%	
Diarrhea	0	0%	17	20%	18	20%	
Edema	0	0%	1	1%	1	1%	
Respiratory distress	0	0%	2	2%	2	2%	
Bronchospasm	0	0%	2	2%	2	2%	
Pleurisy	0	0%	1	1%	1	1%	
Drowsiness	0	0%	4	4%	4	4%	
Coma	0	0%	1	1%	1	1%	
Orientation	0	0%	14	15%	14	16%	
Hypotension	0	0%	20	23%	21	23%	

Angina	0	0%	3	3%	3	3%	
Arrhythmias	0	0%	5	6%	6	6%	
Infection	1	1%	4	4%	4	4%	
Sepsis	0	0%	2	2%	2	2%	
General malaise	0	0%	35	40%	37	41%	

†p < 0,05 shows a significant statistically difference between the studied groups
**Friedman test*

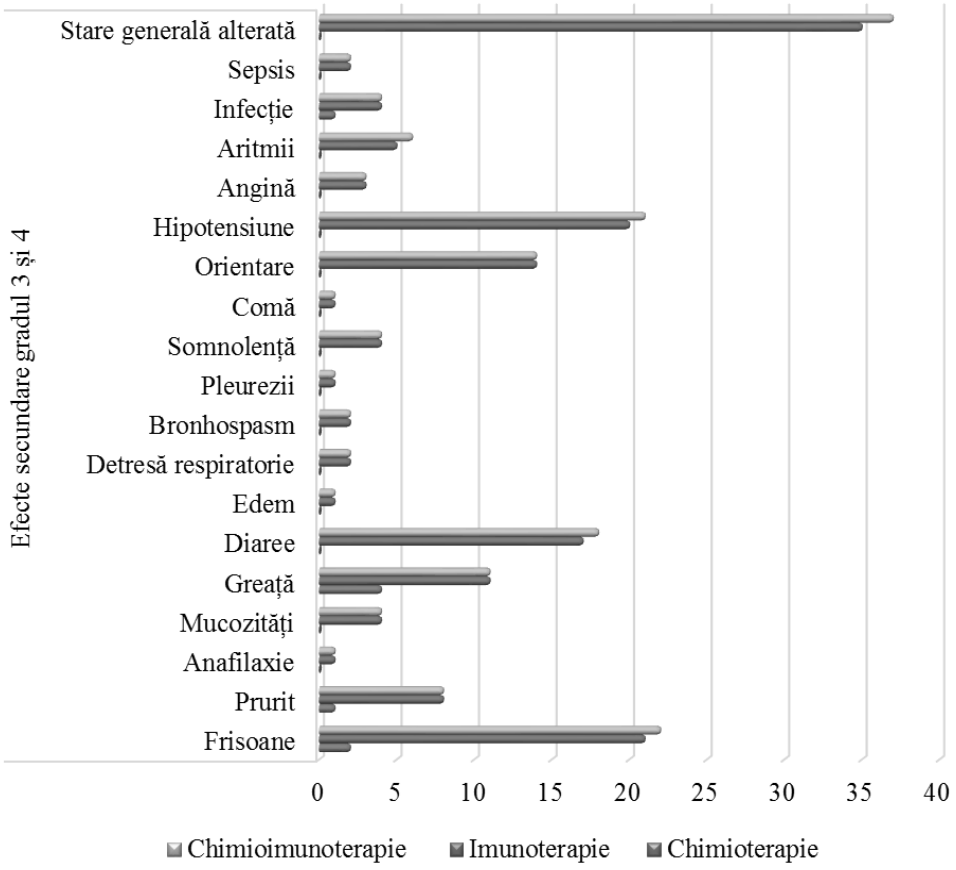

Fig.2 The distribution of the side effects of the treatment of melanoma in the three groups of patients

Analyzing the toxicity of the administered treatment we can observe that most adverse effects were recorded when chemotherapy and immunotherapy regimens were combined compared to the other two groups, with significant statistically difference (p <0.0001).These results are consistent with the results of studies from literature that say that the administration of Interferon alfa-2b in combination with Dacarbazine led to

the development of hypersensitivity reactions to chemotherapeutic agents, including itching, erythema, edema, eosinophilia, and hemodynamic instability (GR Heywood . et al 1995). Hypotension was recorded in 46% of the patients.

CONCLUSIONS

Adding interferon alfa-2b does not lead to improvements in the treatment of patients with metastatic melanoma compared to chemotherapy regimen used in monotherapy.

It should be emphasized however that the Dacarbazine doses used in this study have been used in many studies that support with enthusiasm the use of chemotherapy in the treatment of these patients.

Subcutaneous treatment with interferon alfa-2b is often used in combination with chemotherapy.

Because of the high toxicity observed the use of immunotherapy associated with chemotherapy in treating patients with metastatic melanoma is not recommended.

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