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A Very Well Tolerated and Active Protocol in Advanced and Metastatic Melanoma for Developing Countries in the Immunotherapy Era!

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Abstract

Here we report our experience with a new protocol consisting of bevacizumb, paclitaxel and carboplatin for metastatic melanoma, which has been shown to be active and well tolerated. In a phase II trial, we treated 22 consecutive patients with metastatic melanoma with this protocol and observed a very low toxicity, a response rate of 23% and a median survival of 15 months. Survival data in pretreated and non-pretreated patients were similar. This protocol could be an alternative treatment option in metastatic melanoma patients, especially in countries with lower income.

Introduction

Metastatic melanoma is very hard to treat and has a very poor prognosis. Here we report our experience with a new protocol, including bevacizumab, an antivascular endothelial growth factor for metastatic melanoma, which has shown to be active and well tolerated. Metastatic melanoma is a highly vascularized tumor with strong expression of vascular endothelial growth factor (1). Many chemotherapeutic agents, Interferon gamma and combinations have been used and before the new immunotherapies like the check point inhibitor ipilimumab or the PD1 inhibitors nivolumab and pembrolizumab (2-4) metastatic melanoma was a lethal disease with a long-term remission rate of less than 10%. Single-agent was palliative in some patients and there was no advantage of combination or chemo-immunotherapy in randomized trials (5).

The first published report in metastatic melanoma with a protocol consisting of bevacizumab, paclitaxel and carboplatin, was published by Perez et al. in 2009 (6), showing a response rate of 17 %, a stable disease in 53% of the patients. The median overall survival was 12 months and we used a modification of this protocol to see whether it is applicable to our patients.

Patients and methods

Our protocol consisted of Bevacizumab 5 mg/m2 day 1 and 15, Paclitaxel 80 mg/m2 day 1, 8 and 15, Carboplatin AUC x 6, day 1 and G-CSF 300 mcg x 2 days after each treatment day.

Our first patient was a 79year old patient with a history of melanoma in her left little finger in 2009. She underwent an amputation of her little finger and received an adjuvant treatment with Interferon alpha 3 million units three times a week (standard adjuvant treatment at that time). She was well until she developed multiple axillary lymph node metastases in 2013. She had a core needle biopsy revealing that the metastases were of melanoma origin. The surgeon declared the metastases as being non-operable. We started this protocol and after three courses of the axillary metastases had shrunk massively. The patient underwent an axillary lymphadenectomy and received 3 courses of adjuvant treatment with the same protocol and is well now 6 years after the operation.

Having treated 22 consecutive patients 15 male, 7 female age between 36 and 82 (median 56) with metastatic melanoma in our phase II trial, we report our safety and response data.

Results

No hematological and non-hematological grade III/IV toxicities were observed.

We observed a pathological response in 5 patients (23%) and a stable disease in 10 patients (67%).

Survival analysis

Of 22 patients enrolled, 12 had died at the time of data cut off and 10 were censored in the analysis.

At cutoff date (3/19/2022), the median survival was estimated 15 months for the whole population (95% CI 12.3-17.6). The median survival in patients with prior treatment was 14 (95% CI 11.7-16.2) and the median in patients without prior treatments was 15 (95% CI 12.3-17.6-23). of 12 patients with prior treatments, 7 had immunotherapy and 5 had chemotherapy.

Figure. 1 protocol

Bevacizumab 5 mg/m2 day 1 and 15

Paclitaxel 80 mg/m2 day 1, 8 and 15

Carboplatin AUC x 6 day 1

G-CSF 300 mcg x 2 days after each treatment day

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
30.973	5.216	20.750	41.196	15.000	1.339	12.375	17.625

a. Estimation is limited to the largest survival time if it is censored.

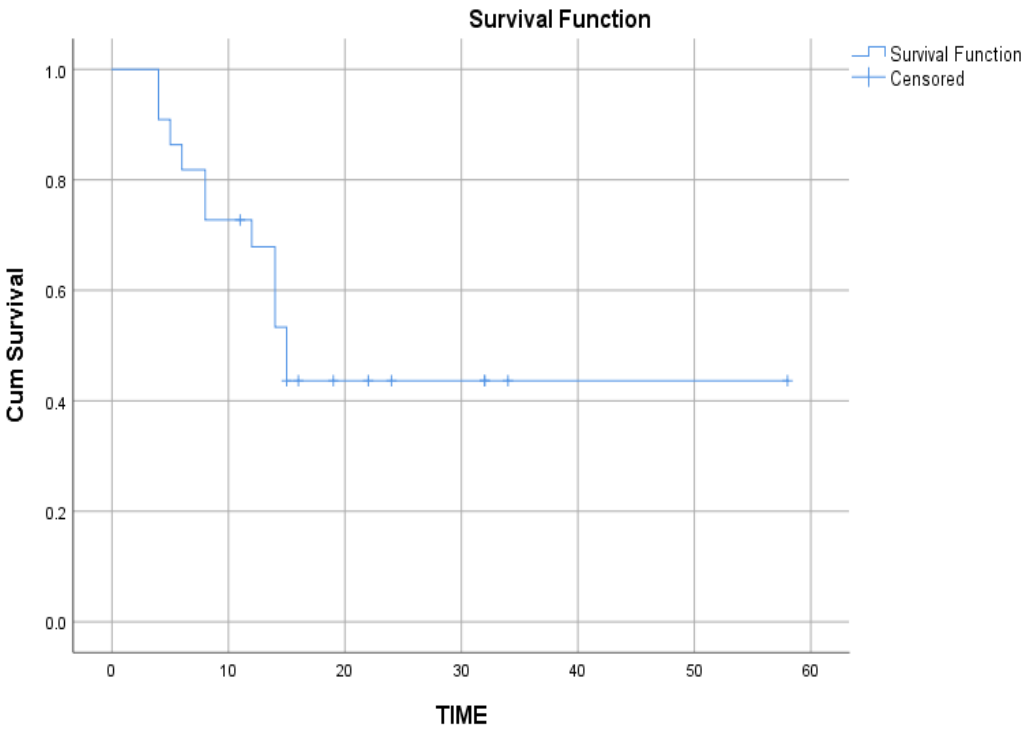

Figure 02

Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
VAR00002	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
prior treatment	20.083	3.513	13.198	26.968	14.000	1.139	11.768	16.232
no prior treatment	32.367	7.964	16.757	47.977	15.000	.	.	.
Overall	30.973	5.216	20.750	41.196	15.000	1.339	12.375	17.625

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.091	1	.763
Breslow (Generalized Wilcoxon)	.102	1	.750
Tarone-Ware	.103	1	.749

Test of equality of survival distributions for the different levels of VAR00002.

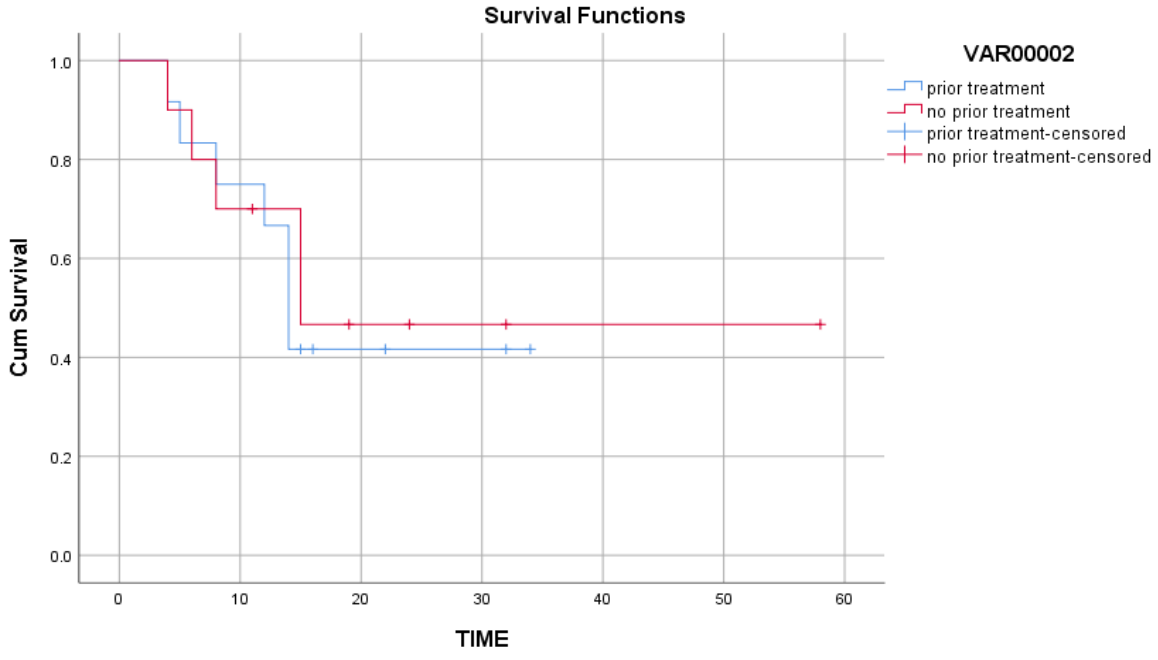

Figure .3 Survival curve based on Prior treatment status

The median survival in patients with prior treatment was 14 (95% CI 11.7-16.2) and the median in patients without prior treatments was 15 (95% CI 12.3-17.6-23).

Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
VAR00003	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Chemotherapy	14.400	4.644	5.297	23.503	12.000	4.382	3.412	20.588
immunotherapy	23.000	4.066	15.031	30.969	.	.	.	.
Overall	20.083	3.513	13.198	26.968	14.000	1.139	11.768	16.232

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	2.253	1	.133
Breslow (Generalized Wilcoxon)	2.211	1	.137
Tarone-Ware	2.246	1	.134

Test of equality of survival distributions for the different levels of VAR00003.

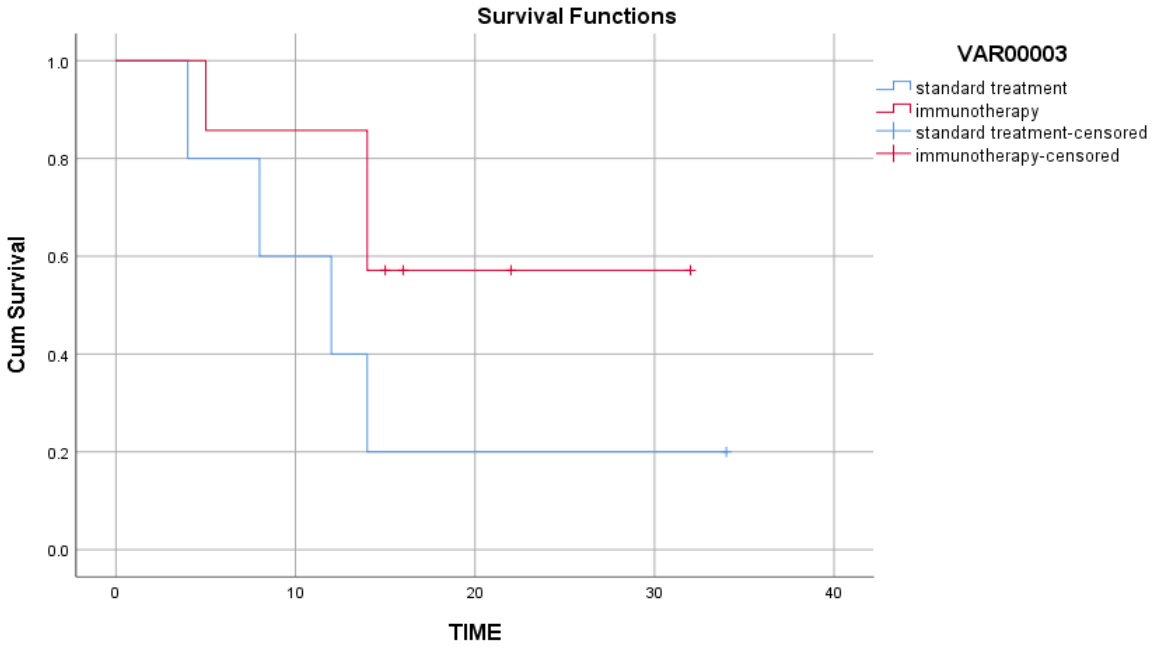

Figure .4 Survival curve based on the prior treatment type

12 patients had undergone prior treatment for metastatic disease, 7 had immunotherapy and 5 had standard treatment The mean survival in patients with prior treatment with chemotherapy was 14.4 (95% CI 5-23) and the mean in patients with prior immunotherapy was 23.0 (95% CI 15-30). No statistically significant relationship was found between the two groups.

Conclusion

Having our positive experience with this protocol, we conclude that this treatment which is very much cheaper than the recently available immunotherapies (50 times less expensive!) is a very good therapeutic option for patients in developing countries especially in the palliative setting and should be further investigated in phase II and III trials.

We observed similar efficacy in terms of response and survival in both pre-treated and treatment naïve patients. Especially the low toxicity and good survival data are promising.

Other new treatment options in metastatic melanoma.

Though a handful of mutations involved in melanoma development may be inherited, the majority of melanomas arise from somatic mutations acquired later in life. One of the most commonly mutated pathways in melanoma, and one that is interesting for targeted therapeutic purposes, is the MAP kinase signaling pathway. Mutations in BRAF and other MAPK mutational events are thought to be early oncogenic events. ~50% of melanomas contain activating BRAF mutations, the most common of which is the V600E mutation (>85% of BRAF mutations), which lead to constitutive activity of downstream MAPK signaling.

Multiple targeted therapies have been developed to combat molecular defects present in melanoma. The most promising of these include the BRAF inhibitors, vemurafenib and dabrafenib, that were approved for the treatment of metastatic and unresectable BRAF-mutated melanomas in 2011 and 2013 respectively (7,8). However, though these drugs are highly effective for approximately half of patients with BRAF mutated melanomas, a majority of patients develop secondary resistance within a relatively short amount of time (7,8,9)

There are three immune checkpoint inhibitor drugs that have been approved for use in melanoma treatment: the anti-CTLA-4 antibody ipilimumab and two anti-PD-1 antibodies nivolumab and pembrolizumab (10). There are also several PD-L1/2 antibody drugs currently in clinical trials, and a few that have been approved for clinical use, though not for melanoma (10).

Treatment with iplimumab showed durable survival of up to 10 years in 20% of cases; compared to the median survival rate of less than one year in stage IV melanoma patients, this is a great advancement (10-14). Pembrolizumab has a response rate of ~37–38% in patients with metastatic melanoma, and an overall survival of 74% at 12 months (14). Treatment with nivolumab showed a ~40% response rate with a 12 month overall survival rate of 73% compared to 43% of patients treated with dacarbazine (15).

While checkpoint inhibitors are promising, there are necessarily complications involved in inhibiting mechanisms that promote tolerance of self-cells. Therefore, the side-effects of checkpoint inhibitors can be severe. The side effects are typically immune-related inflammatory conditions of the skin, GI system,

and endocrine organs (14). Recognizing and managing side effects of these treatments is important, and though the toxicity of these drugs can be offset in some cases by treatment with corticosteroids, some patients cannot tolerate the side-effects and treatment must be terminated (16).

Though immune checkpoint inhibitors have been a breakthrough for cancer therapeutics and have revolutionized the treatment of metastatic melanoma, a significant subset of patients still does not respond to these drugs, and many patients who do respond develop a secondary resistance. Research into why some patients respond and other do not is ongoing.

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