



First Experiences With the Use of Targeted and Immunotherapy in the Treatment of Cutaneous Melanoma: a Single Centre Experience

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Abstract

Background / Aim: Up until ten years ago stage four melanoma was considered a disease with extremely poor prognosis. Standard therapy during this period of time was dacarbazine chemotherapy. Patients with better performance status were treated with immunotherapy cytokine IL-2. In the last ten years eight medications have been approved by the FDA for the therapy of melanoma. The goal of this study was to determine objective response rate (ORR), median overall survival (OS), median progression free survival (PFS) and safety in patients with advanced and metastatic cutaneous melanoma treated with targeted therapy and immunotherapy at the University Clinical Centre of the Republic of Srpska (Centre).

Methods: A non-randomised observational retrospective/prospective trial was conducted to investigate first experiences with the use of targeted therapy and immunotherapy at the Centre and compare the results with the literature data. A total of 23 patients received BRAF targeted therapy for the treatment of metastatic cutaneous melanoma in the first line of treatment. Nine patients received vemurafenib, fourteen patients received a combination of BRAF/MEK inhibitor. Nine patients were treated with pembrolizumab immunotherapy. The trial was performed in a period from May 2017 until December 2020.

Results: In patients receiving vemurafenib ORR was 44.4 %, median PFS was 5 months (95 % CI, 1 to 11) and the median OS was 9 months (95 % CI, 2 to 17). In the vemurafenib/cobimetinib group ORR was 71.4 %. Median PFS was 9 months and median OS was 12 months. ORR in patients receiving pembrolizumab was 22.9 %, median PFS was 3 months (95 % CI, 1 to 11) and the median OS was 4.5 months (95 % CI, 2 to 12).

Results in all three groups were inferior compared to the results from the literature except for ORR in patients receiving vemurafenib and vemurafenib/cobimetinib. Adverse events were tolerable and manageable and were similar to those described in the literature.

Conclusion: Based on the experience with the targeted and immunotherapy in the Centre, which was presented in this study, it was concluded that in conditions when there is limited access to drugs, the greatest benefit have the patients who meet the inclusion criteria in clinical trials.

Key words: Melanoma; Immunotherapy; Vemurafenib; Cobimetinib.

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ARTICLE INFO

Received: 1 December 2021
Revision received: 14 March 2022
Accepted: 14 March 2022

Introduction

Up until ten years ago stage four cutaneous melanoma was considered a disease with extremely poor prognosis and most of the patients died 18 months after their initial diagnosis.¹ Standard therapy during this period of time was dacarbazine chemotherapy.² Patients with better performance status were treated with immunotherapy cytokine IL-2.³ Chemotherapy had no overall survival benefit. In the last ten years eight medications have been approved by the US Food and Drug Administration (FDA) for the therapy of melanoma. In other countries around the world similar approvals have been made. These agents are BRAF protein inhibitor or mitogen-activated protein kinase (MEK) inhibitors, antagonistic antibodies against cytotoxic T lymphocyte associated antigen 4 (CTLA 4), antibodies directed at programmed cell death protein 1 (PD 1) and the modified oncolytic herpes virus talimogene laharparepvec (TVEC). Since that time the goals of treatment in stage four melanoma have changed from slowing down the disease progression to durable clinical responses and good disease control. Both BRAF-targeted therapy and immunotherapy lead to improvement of the overall survival in patients with metastatic melanoma.^{4,5}

In 2011 vemurafenib was given a FDA approval for the treatment of adult patients with BRAF V600 mutated locally advanced or metastatic melanoma. Drug was not available in patients in the Republic of Srpska until 2016. Before that all patients received dacarbazine based chemotherapy for the treatment of stage four melanoma. FDA approved cobimetinib in combination with vemurafenib to treat patients with metastatic melanoma in 2014.

Pembrolizumab was given approval in the same indication in 2015. Both of these treatment option became available in the Republic of Srpska in 2018. These drugs are available only for limited number of patients, others are still receiving chemotherapy. The use of these drugs has led to improvements in progression free survival (PFS) and overall survival (OS) in patients with melanoma treated in the first line and their efficacy has been confirmed through clinical trials.

BRAF targeted therapies

Half of all patients have BRAF mutated melanoma at exon V600.⁶ The first approved agent for

the therapy of BRAF mutated metastatic melanoma was vemurafenib. Vemurafenib is a selective inhibitor of V600E mutant BRAF. This drug provided a benefit not previously seen in stage four melanoma.⁷ BRIM3 was a phase III randomised trial and in this trial vemurafenib was compared against dacarbazine chemotherapy. Objective response rate (ORR) was 48 % compared to 5 % and the median PFS was 5.3 months compared to 1.6 months respectively.⁷ Data from the extended follow up study showed OS was 13.3 months in the vemurafenib group compared to 10.0 months in the dacarbazine group (hazard ratio (HR) 0.75; $p = 0.0085$).⁸ BRAF signalling pathway depends on a downstream activation of MEK1/2. Therefore, it was a priority to develop a MEK inhibitor. In a phase I study combination of vemurafenib and cobimetinib, MEK1/2 inhibitor, had a very good efficacy.⁹ This study included both treatment naïve patients and those who progressed to previously administered BRAF inhibitors. In patients who were naïve to prior treatment with a BRAF inhibitor ORR was 87 % and the median PFS was 13.7 months. These data were the basis for the phase III coBRIM trial.^{4, 10, 11} In this trial 495 patients were treated with vemurafenib and cobimetinib, or vemurafenib and placebo. ORR was 70 % in the vemurafenib/cobimetinib group versus 50 % in the vemurafenib/placebo group. PFS was 12.3 months compared to 7.2 months and OS was 22.3 months compared to 17.4 months (HR 0.70; $p = 0.005$) respectively. Based on these data BRAF and MEK inhibitor combination therapy became a standard treatment of BRAF mutated metastatic melanoma.^{4, 10, 11}

Immunotherapy

Discovery of immune checkpoint inhibitors improved the use of immunotherapy in the treatment of melanoma. Ipilimumab was the first monoclonal antibody to be approved for the treatment of stage four melanoma. Ipilimumab blocks the CTLA 4 and activates immune system against cancer.¹² Monotherapy directed against CTLA4 has increased survival rate in metastatic melanoma up to 22 %.¹³ PD-1 inhibitors pembrolizumab and nivolumab activate the anticancer immune response by blocking the interaction between PD-1 on T cells and its ligands PD-L1 and PD-L2 who are expressed on antigen presenting cells and tumour cells.^{14, 15} In KEYNOTE 001, 002 and 006 trials pembrolizumab monotherapy provided durable response rates of 30 – 40 %.^{5, 16, 17} These trials included previously treated and treatment-naïve patients.^{5, 16-21} In phase I CA209-003 study treatment

with nivolumab resulted in a cumulative response rate of 28 % and OS rate of 34 %, in the advanced melanoma cohort of patients.^{22, 23} Later phase III studies of nivolumab monotherapy in treatment naive and previously treated patients with metastatic melanoma provided durable response rates of 32 % and 40 %, respectively.^{24, 25} Results from these trials led to approval of pembrolizumab and nivolumab for the treatment of patients with advanced melanoma.

The goal of this study was to determine efficacy profile (ORR, OS and PFS) and safety profile of targeted therapy and immunotherapy in patients with advanced metastatic cutaneous melanoma treated at the Oncology Clinic, University Clinical Centre of the Republic of Srpska (UCC RS) and compare obtained results with the literature data.

Methods

A non-randomised observational retrospective/prospective trial was conducted to investigate first experiences with the use of BRAF targeted therapy and immunotherapy for cutaneous melanoma patients and compare the results with the literature data. The trial was performed in the period from May 2017 until December 2020 at the Oncology Clinic, University Clinical Centre of the Republic of Srpska. This trial included total of 32 patients. Patients were 18 years and older Caucasians, had unresectable stage IIIC or stage IV melanoma and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-3. The patients who were treated with BRAF/MEK targeted therapy had pathohistologically confirmed BRAF mutated metastatic melanoma. Distribution of metastatic sites is shown in Table 1. Every patient was presented to and their treatment protocol was approved by a multidisciplinary tumour board.

Table 1: Distribution of metastatic sites

	N	%
Affected organs/vemurafenib		
Lung	6	66.6
Liver	5	55.5
Skin / Subcutaneous tissue	2	22.2
Brain	4	44.4
Bones	2	22.2
Lymph nodes	6	66.6
Affected organs/vemurafenib/cobimetinib		
Lung	7	50.0
Liver	6	42.8
Skin / Subcutaneous tissue	5	35.7
Brain	5	35.7
Bones	6	42.8
Lymph nodes	9	64.2
Affected organs/pembrolizumab		
Lung	8	88.8
Liver	4	44.4
Skin / Subcutaneous tissue	2	22.2
Brain	3	33.3
Bones	1	11.1
Lymph nodes	9	100.0

In the period from June 2017 until December 2020, a total of 23 patients received BRAF targeted therapy for the treatment of metastatic melanoma in the first line of treatment. Nine patients received vemurafenib (four men and five women with average age of 51 years) at a dose of 960 mg twice daily continuously until disease progression. Fourteen patients received a combination of BRAF/MEK inhibitor (nine men and five women with average age of 54 years) at a dose of vemurafenib 960 mg twice daily continuously and cobimetinib 60 mg once daily for 21 days until disease progression (Table 2).

In the period from May 2017 until December 2020, nine patients were treated with pembrolizumab immunotherapy. Eight patients had BRAF wild and one patient BRAF mutated melanoma. All patients received the drug at a dose of 200 mg

Table 2: Baseline demographics and clinical characteristics of patients with cutaneous melanoma

Characteristics	Target therapy		Immunotherapy pembrolizumab
	Vemurafenib	BRAF/MEK (vemurafenib/cobimetinib)	
Number of patients	9	14	8 with BRAF wild and 1 with BRAF mutated
Average age	51	54	56
Sex			
Men	4	9	5
Women	5	5	4
Therapy regimen	960 mg twice daily	vemurafenib 960 mg twice daily continuously and cobimetinib 60 mg once daily for 21 days	200 mg every three weeks

every three weeks. Five patients were men and four were women with an average age of 56 years (Table 2).

The drugs were administered according to the indication for the treatment of locally advanced and metastatic melanoma in the first line of treatment.

It was used MedCalc statistical software for processing collected data. The Kaplan–Meier (KM) method was used to estimate the OS curve in each treatment population. Also, KM method was used to calculate the PFS curve in each patient group. ORR was calculated as the sum of patients who had a partial or complete response to therapy.

Tumour assessments were conducted by the investigators according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1.²⁶ Tumour assessments were conducted every three months. AEs were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, NCICTCAE v4.²⁷ A data cut-off date was 15 December 2020.

Results

Efficacy and safety profile of targeted therapy

Vemurafenib

Total of nine patients were treated in vemurafenib group. The ORR was 44.4 %. Four patients (44.4 %) had partial regression and five patients (55.6 %) had disease progression. The median PFS was five months (95 % CI, 1 to 11) and the median OS was nine months (95 % CI, 2 to 17). KM estimates of PFS and OS are presented in Figure 1.

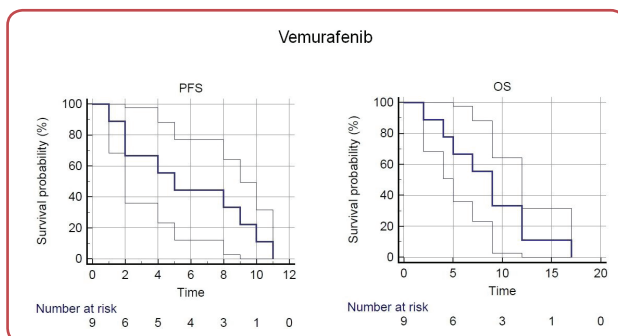


Figure 1: Kaplan–Meier curves - Kaplan–Meier survival estimates of median progression free survival (PFS) and median overall survival (OS) in patients with cutaneous melanoma treated by vemurafenib

Four out of nine patients experienced adverse events (AEs) 44.4 %. In three patients the dose was reduced to 50 % of the starting dose due to Grade (Gr) 2 and Gr 3 erythema. None of the patients had Gr 4 AEs and total percentage of Gr 3 AEs was 33.3 %. Vemurafenib safety profile in observed group of patients was persistent with the safety profile described in the literature. All AEs were manageable and tolerable. AEs are listed according to grade and percentage in Table 3.

Table 3: Adverse events in patients receiving targeted therapy

Vemurafenib						
Adverse events	G1	G2	G3	G4	Total (N)	(%)
Rash	2				2	33.3
Erythema			2		2	33.3
Arthralgia		1			1	16.6
Fatigue		1			1	16.6
Vemurafenib/Cobimetinib						
Adverse events	G1	G2	G3	G4	Total (N)	(%)
Itching	1				1	4.1
Acneiform dermatitis		3	4		7	29.1
Erythema			1		1	4.1
Muscle pain		1			1	4.1
Hypertension			1		1	4.1
Diarrhoea		1	1		2	8.2
Nausea	3	1			4	16.4
Vomiting	1				1	4.1
Arthralgia		1			1	4.1
Loss of appetite			1		1	4.1
Fatigue	1	2	1		4	16.4

Vemurafenib/cobimetinib

Total of fourteen patients were treated in vemurafenib/cobimetinib group. ORR overall response rate was 71.4 %. Eight patients had partial regression (57.1 %), two patients had complete regression, two had stable disease and two had disease progression. Median PFS was 9 months (CI 95 % 7 to 13) and median OS was 12 months (CI 95 % 9 to 28). KM estimates for PFS and OS are presented in Figure 2.

Ten out of fourteen patients experienced a AEs (71.4 %). Due to AEs both vemurafenib and cobimetinib doses were reduced in 8 patients (50 % dose reduction). After the resolution of the AEs three patients continued therapy in the initial full dose. Five patients continued therapy in the reduced dose. There was no treatment discontinuation.

The incidence of Gr 3 AEs was 37.5 %. There were no Gr 4 AEs. The largest number of patients in the

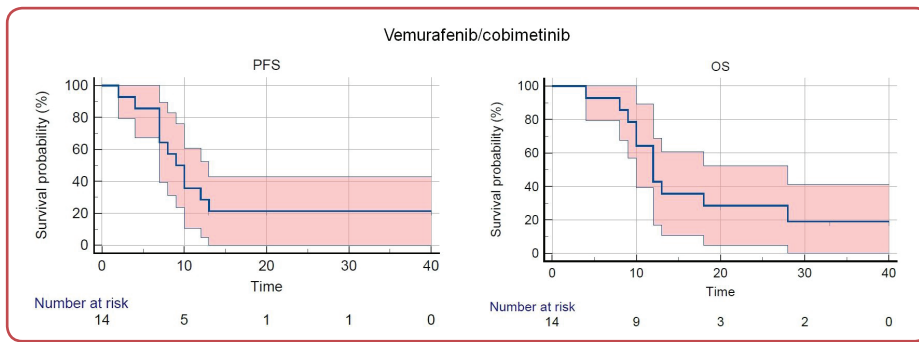


Figure 2: Kaplan–Meier curves - Kaplan-Meier survival estimates of median progression free survival (PFS) and median overall survival (OS) in patients with cutaneous melanoma treated by vemurafenib and cobimetinib

present analysis had acneiform dermatitis, 29.1 %, when compared to total number of AEs (Table 3).

Pembrolizumab

The ORR in nine patients receiving pembrolizumab was 22.9 %. Eight patients had BRAF wild and one patient BRAF mutated melanoma. Two patients had partial regression (22.9 %) five patients had stable disease (55.5 %) and two had disease progression (22.9 %). The median PFS was 3 months (95 % CI, 1 to 11) and the median OS was 4.5 months (95 % CI, 2 to 12). KM estimates for PFS and OS are presented in Figure 3.

Adverse events occurred in six out of nine patients

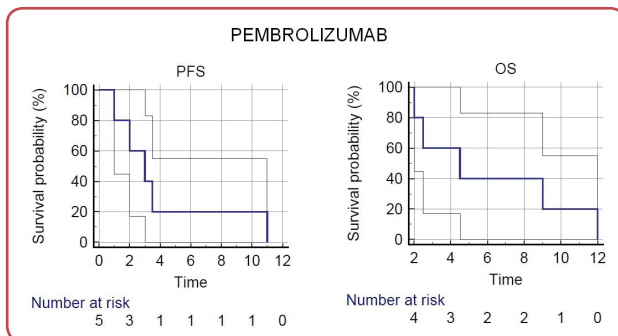


Figure 3: Kaplan–Meier curve - Kaplan-Meier survival estimates of median progression free survival (PFS) and median overall survival (OS) in patients with cutaneous melanoma treated by pembrolizumab

Table 4: Adverse events in patients with cutaneous melanoma receiving immunotherapy

Adverse events	Pembrolizumab				Total (N)	(%)
	G1	G2	G3	G3		
Anaemia		1			1	16.6
Thrombocytopenia					1	16.6
Thyroiditis		1	1		1	16.6
Hepatitis				1	1	16.6
Nausea		1			1	16.6
Fatigue			1		1	16.6

(66.6 %). The total number of Gr 3 and Gr 4 AEs was 33.2 % and 16.6 %, respectively. In one patient pem-

brolizumab was discontinued due to hepatitis Gr 4. In Table 4 adverse events are listed according to grade and percentage.

Discussion

Results in this analysis, in all three groups, were inferior compared to the results from registrational clinical trials except for ORR in patients receiving vemurafenib and vemurafenib/cobimetinib. AEs were tolerable and manageable and are similar to those in clinical trials. There were no treatment delays or dose reduction due to limited access to drugs.

In BRIM study ORR was 48 % in vemurafenib treatment group and 5 % in patients receiving dacarbazine.⁸ The median PFS was 6.8 months and the median OS was 13.2 months in patients receiving vemurafenib. The median PFS and OS in patients receiving dacarbazine were 1.6 and 9.7 months. The results obtained in this analysis matched the data from this registrational trial for ORR. In this analysis ORR was 44.4 %. Median PFS was five months and median OS was nine months, both inferior to the PFS and OS in the BRIM trial. Safety of vemurafenib was assessed in an open-label multicentre study in patients with untreated or previously treated melanoma and a BRAF (V600) mutation. In this trial common AEs of all grades included rash (49 %), arthralgia (39 %), fatigue (34 %), photosensitivity reaction (31 %), alopecia (26 %) and nausea (19 %). A total of 46 % of patients reported Gr 3 or Gr 4 adverse events, including cutaneous squamous cell carcinoma (12 %), rash (5 %), liver tests abnormalities (5 %), joint stiffness (3 %) and fatigue (3 %).²⁸ Vemurafenib safety profile in observed group of patients was persistent with the safety profile described in the literature. All adverse events were manageable and tolerable.

In the coBRIM trial patients receiving vemurafenib/cobimetinib had ORR 70 %, median PFS

was 12.6 and median OS was 22.5 months.⁴ In this analysis 14 patients received vemurafenib/cobimetinib. ORR for those patients was 71.4 %. Three patients did not reach PFS and two of them had complete responses. Median PFS was nine months and median OS was 12 months. Results for ORR match the results from registrational COBRIM trial and results for PFS and OS are inferior to those in the trial. In this trial, the most common AEs reported were gastrointestinal disturbances in more than 10 % of patients (diarrhoea 60 %, nausea 41 %, vomiting 24 % and stomatitis 14 %), skin and subcutaneous tissue disorders (photosensitivity reaction 46 %, acneiform dermatitis 16 %), hypertension 15 %, bleeding 13 %. All of the listed AEs reported in this analysis are among the most common AEs reported in this trial.

Estimated 5-year OS in KEYNOTE-001 trial in patients receiving pembrolizumab was 34 % in all patients and 41 % in treatment naive patients, median OS was 23.8 months and 38.6 months, respectively. In all patients estimated 5-year PFS rates were 21 %. In treatment naive patients estimated 5-year PFS rates were 29 %. Median PFS for all patients was 8.3 months and 16.9 months for treatment naive patients.²⁹

Compared to data from this trial these results were inferior. Median PFS was 3 month and median OS was 4.5 months. The ORR in patients receiving pembrolizumab was 22.9 %. In the group of nine patients two are still in treatment without the disease progression. The reasons for these results can be explained by the fact that six out of nine patients had high volume disease, with three or more metastatic sites affected. Patients with high volume disease and BRAF mutated melanoma could be better candidates for BRAF/MEK combination therapy because of the need for fast treatment response. Three patients had brain metastases and two patients were ECOG PS 3, both of these were exclusion criteria in the KEYNOTE 001 trial and contributed to the inferior results in this analysis. Safety of pembrolizumab in a treatment of melanoma was assessed in KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006 trials. Total of 1567 patients had AEs (median follow-up, 42.4 months). Most AEs were mild/moderate. Gr 3 and Gr 4 AEs occurred in 17.7 % of patients. 23.0 % of patients had immune mediated AEs of any grade. Most common AEs were hypothyroidism (9.1 %), pneumonitis (3.3 %) and hyperthyroidism (3.0 %). A total of 6.9 % of patients had Gr 3 and Gr 4 immune mediated AEs. In presented analysis an equal percent of Gr 2 (3/6) and Gr 3/4 (3/6) adverse events were present. The

data obtained are not consistent with data from the study where the highest number of AEs were Gr 1 and Gr 2. These results are not conclusive and not statistically significant due to the small number of patients receiving pembrolizumab.

Results in this analysis, in all three groups, were inferior compared to the results from registrational clinical trials except for ORR in patients receiving vemurafenib and vemurafenib/cobimetinib. Reasons for these are small number of patients that were included in this analysis, insufficient selection of patients because of the limited drug availability and shorter follow up period. Adverse events were tolerable and manageable and are similar to those in clinical trials. First experiences with the application of immunotherapy and targeted therapy suggest that this is a therapy that is highly effective in well selected patients with an acceptable safety profile.

Limited access to drugs is related to the number of patients who have access to the drugs. Only limited number of patients have access to the drug each year. The others are put on the waiting list or are receiving chemotherapy. Based on the experience with the targeted and immunotherapy in the centre, which was presented in this study, it could be concluded that in conditions when there is limited access to drugs, the greatest benefit have the patients who meet the inclusion criteria in clinical trials.

Conclusion

First experiences with the application of immunotherapy and targeted therapy suggest that this is a therapy that is highly effective in well selected patients with an acceptable safety profile. In conditions when there is limited access to drugs, the greatest benefit have the patients who meet the inclusion criteria in clinical trials.

Acknowledgements

This work was supported by the Ministry for Scientific-Technological Development, Higher Education and Information Society of the Republic of Srpska, as a part of the Projects No 19/6-020/961-54/18.

Conflict of interest

None.

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