TITLE PAGE

Title

Intralesional PV-10 for in-transit melanoma – a single centre experience.

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Shortened title

PV-10 for intransit melanoma

DISCLOSURES AND FUNDING SOURCES

The study authors have no financial support to disclose for this research

SYNOPSIS FOR TABLE OF CONTENTS

This paper reviews a single metropolitan cancer hospitals experience with PV-10 for the treatment of intransit melanoma. Over a 4 year period we have treated 19 patients with PV-10 for melanoma and achieved disease control in 68% of patients. We find it a helpful tool in our armory for local control of this often-difficult clinical scenario.

ABSTRACT

Background and Objectives

Patients with intransit melanoma metastasis have longer median survival than patients with distant metastatic disease. Furthermore, local disease control is an important endpoint for symptom management. The treatment of unresectable loco-regional recurrence or intransit disease has been historically managed with a combination of treatments including surgery, radiotherapy, isolated limb infusion or perfusion as well as systemic therapies.

Intralesional PV-10 has been used at Peter MacCallum Cancer Centre since 2010, and the current report presents a retrospective analysis of patient outcomes, reporting the response rates, durability of responses and observed toxicities.

Methods

Records were analyzed retrieving details of 19 patients treated with PV-10 over a 4 year period from 2010 to 2014. Medical records were reviewed for these patients and data extracted.

Results

Nineteen patients with intransit melanoma were treated with intralesional PV-10 between 2010 and 2014. Disease control (complete or partial response or disease stability) was achieved in 68% of with 26% having a complete response. This was achieved with minimal associated toxicity and low cost.

Conclusions

PV-10 is an effective, durable, well-tolerated and cost effective treatment tool with an acceptable side effect profile for the management of unresectable intransit melanoma.

KEY WORDS

PV-10, Rose Bengal, melanoma, locoregional, metastasis

INTRODUCTION

Management of unresectable local recurrence and in-transit metastasis (ITM) of cutaneous melanoma (American Joint Committee on Cancer - AJCC Stage IIIB and IIIC [1]) can present a therapeutic challenge. These patients have a longer survival than patients with AJCC Stage IV disease [1] and local symptoms, particularly ulceration, bleeding and pain can be associated with significant debility and impact on quality of life.

Treatment options for patients with ITM, can be categorised as loco-regional or systemic. Loco-regional treatments include surgery, injectable and topical therapies [2], isolated limb infusion, isolated limb perfusion and electrochemotherapy as well as radiotherapy [3-5]. Systemic therapies for melanoma include chemotherapy, immunotherapy and molecular targeted therapies (primarily directed at the MAP kinase pathway). Patients with unresectable stage IIIB and IIIC disease were eligible

for many of the recent trials of novel targeted and immune modulating agents for patients with advanced disease which have demonstrated survival benefit [6-8].

PV-10 (Provectus Biopharmaceuticals) is a 10% preparation of Rose Bengal in 0.9% normal saline. Rose Bengal (RB) is a water soluble xanthine dye which historically had a role in ophthalmology and in the assessment of hepatic function but has more recently been identified as a potential anti-neoplastic agent [9]. It is preferentially taken up by tumour cells into lysosomes causing rapid lysis and is subsequently excreted by normal healthy tissues [10]. A T and B cell stimulated local immune response occurs which in some patients is associated with tumor necrosis in both adjacent non-injected lesions and occasionally in distant metastases [11].

This study reviews the institutional experience of intralesional PV-10 in a single high-volume melanoma unit.

MATERIALS AND METHODS

Patients were identified from the pharmacy dispensing records for PV-10 injected intra-lesionally for patients with melanoma. Patient data was obtained from the medical record. Results of treatment were recorded at the time of treatment using a standard data sheet supplemented with clinical photographs. Patient demographics, pathology, prior treatments, number and size of injected lesions, toxicity, disease progression and survival outcomes were collected and analysed.

Intra-tumoural injection was performed either in an outpatient setting or in the operating theatre using intravenous sedation. All patients were treated by one of two surgeons (DS and DG). Patients were injected with up to 4mls of PV-10 in a single treatment with the dose determined according to lesion size. Where too many lesions

were present the largest lesions were injected first then subsequent lesions distributed within the field of disease with priority given to the most proximal and the most distal lesions. Patients selected for PV-10 had been discussed previously at the unit multidisciplinary meeting.

The number of treatments administered and timing of treatments was individualized on an as-required and prior response basis. Patients were followed up every 3-6 months after injection also on an individualized basis.

Patients were considered to have a complete response if all lesions (including un-injected lesions) were eradicated by the treatment. Figure 1 an example of a complete response. A partial response was defined as a reduction in size of injected lesions or eradication of some but not all lesions injected and stability of other non-injected lesions. Stable disease was defined as no significant change to injected and/or uninjected lesions. Disease progression was growth of injected lesions or the development of new lesions.

Factors associated with clinical response were analysed using Wilcoxon rank sum test and Fisher exact test.

RESULTS

Between 2010 and 2014, 19 patients treated with intra-lesional PV-10 for melanoma and constitute the study group (2 additional patients were treated for Kaposi's sarcoma and recurrent angiosarcoma of the leg respectively). The median age was 79.5 years (42-94yrs) and 11 (58%) were male, the site of in transit disease was upper limb 2 (11%), lower limb 10 (53%), trunk 2 (11%) and head and neck 5 (26%). Most patients had stage IIIC disease (74%) (Table 1).

Most patients (n= 12, 63%) received only one treatment however one patient had nine treatments and six patients had two treatments (34 treatments in total). Initially lesions were injected in the clinic under local anaesthetic, however it proved to be highly uncomfortable to inject multiple lesions and subsequently all but 2 patients had their lesions injected under intravenous sedation in the operating room.

Thirteen patients (68%) had less than 10 lesions present at the time of first treatment (Table 2), four patients (21%) had more than 10 lesions and accurate data was not available for the remainder (n=2).

For the 17 patients with complete tumour data, the median injected lesion diameter was 5.5mm. Twelve patients had an average lesion diameter of less than 1cm diameter, 3 patients had an average lesion diameter 1-2cm and 2 patients had an average lesion diameter greater than 2cm in diameter.

Toxicity

The majority of treatments (73%, 24/33) were well tolerated without any reported side effects. Oedema, pain and erythema were the most common side effects although these were minor in severity, limited in duration and easily managed by simple analgesia. Five patients required opiate analgesia for pain associated with PV-10 injection.

One patient was readmitted to hospital one week following treatment with lower limb cellulitis requiring intravenous antibiotics for 2 days. This patient was obese and elderly and the cellulitis arose in the area of recent injection.

Treatment response

After a median follow up of 11.7 months, disease control was achieved in 63% of patients. Five patients (26%) achieved a complete response, another five (26%) patients achieved a partial response and two patients had stable disease (11%) at the time of last follow up. 74% (14/19) of patients had a clinical response at time of first follow up (median time 21 days); range 8-91 days. Younger patients and those with smaller lesions were more likely to respond to treatment (Table 3). The number of injected lesions and the time from primary diagnosis to treatment were not predictive of response.

Ten patients did not have all lesions injected, primarily due to the number of lesions present. A bystander response was noted in un-injected lesions in 50% of patients who did not have all their lesions directly injected (Table 2).

After a median follow up of 11.7 months, 8 patients had died from metastatic melanoma.

DISCUSSION

This single-centre retrospective review demonstrates that intralesional PV-10 is an effective, safe and well tolerated treatment option for patients with in transit metastases and loco-regional recurrence of melanoma. Treatment was delivered to a group of patients who were elderly (median age 82 years) and in many cases considered inappropriate for more aggressive and potentially toxic therapies such as ipilimumab or isolated limb infusion.

There have been several previous reports of success with intra-tumoral injection of PV-10, providing local control in this group of patients with an acceptable toxicity profile [12-14]. There is still a lack of data about durability of PV-10 as well as a lack of long term survival data. The largest published study assessing the use of PV-10 in

the setting of refractory melanoma published in 2014 analysed 80 patients from 7 international sites [15]. In this study a 52% overall response rate and 26% complete response rate were described which is comparable to the overall response rate of 63% and complete response rate of 26% in the current series as well as in another previously published single centre series [14] (Table 4).

The effective treatment options for metastatic and loco-regional inoperable disease melanoma have rapidly improved over the last 5 years [6-8, 16-19]. With the introduction of novel systemic agents targeting immune checkpoints (ipilimumab, pembrolizumab, nivolumab), and mutations in the MAP kinase pathway (dabrafenib and trametinib) the treatment options for patients with unresectable metastases have increased and the prognosis for these patients has significantly improved [6-8, 16-19]. However, these agents may be associated with significant toxicity and in the case of PD-1 targeted therapy require frequent hospital visits for infusions [16]. Intralesional PV-10 compares favourably with other intralesional therapies including talimogene laherperpvec (T-VEC) which in the recently published OPTiM study demonstrated on overall response rate of 26.1% [20]. It is important to note that the patient population in the OPTiM study had more advanced disease than the population in the current study, and the response rate for patients with all lesions injected lesions with T-VEC was 33%. For an elderly patient with in transit metastasis a simple and effective local therapy with minimal side effects is an attractive option. In our centre the use of ILI has steeply decreased with the availability of PV-10.

In the modern era of effective systemic therapies, patient selection for intra-lesional therapy is critical. Previously described factors predictive of response include the presence of ulceration, blistering, eschar or pain following injection [13,15]. In the current study, lesion size was also found to be predictive. Of the 5 patients who achieved a complete response the average lesion diameter was 3mm compared to

the cohort average size of 6.3mm. We did not specifically collect data on eschar formation but anecdotally have seen significant ulceration and eschar in most responders which may represent a brisk immune response to treatment or a direct toxic effect.

Aside from the local toxicity of pain and oedema and an isolated report of photosensitivity [21], PV-10 remains a very safe treatment option. As compared to radiotherapy, PV-10 has the advantages of allowing a wider field of treatment which may be repeated if necessary. A successful combination of radiotherapy and intralesional PV-10 has been reported and may warrant further investigation [13].

The limitations to this study is the retrospective nature and the variable treatment regimens which were tailored to patients according to social, geographic and oncological factors. As our cohort consisted of elderly and comorbid patients we often limited their required visits to hospital which is reflected in the short follow up intervals.

There are a growing number of options for the treatment of unresectable in transit disease [5] and choice depends on many factors including availability of treatment, patient suitability and disease factors. Intralesional PV-10 compares favorably in that it is well tolerated especially in an elderly patient or one with significant comorbidities.

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FIGURE LEGENDS

Figure 1: A 93 year old patient presenting two years following a wide local excision for a T2B melanoma on the calf.

A) Initial pre treatment photograph demonstrating extensive in transit disease, arrows demonstrate lesions to be injected.

B) Partial response 2 months following initial treatment, arrows demonstrate further lesions to be injected.

C) Complete response 4 months after initial treatment with resolution of all injected and uninjected lesions.

Table I – Patient demographics

Characteristic		N	%
Gender			
	Male	11	58
	Female	8	42
Age			
	<70	3	16
	>70	16	84
Time from diagnosis to first treatment			
	<6 months	3	16
	6-12 months	4	21
	1-2 years	3	16
	2-3 years	1	5
	>3 years	8	42
BRAF status	V600E	4	21
	Wild type	12	63

	Unknown	3	16
Disease stage at first treatment			
	IIIB	2	11
	IIIC	14	74
	IV – M1a	2	11
	IV – M1c	1	5
Treatment history			
	Surgery for intransit disease	16	84
	Radiotherapy	2	11
	Isolated limb infusion	2	11
	Systemic therapy	3	16
	Topical 0.01% DCP	1	5

Table II – Lesion and treatment characteristics

Characteristic	N	%
Site of disease		
Lower limb	10	53
Upper limb	2	11
Head and neck	5	26
Trunk	2	11
Number of lesions		
<10	13	68
>10	4	21
Unknown	2	11
Number of treatments		
1	12	63
2	6	32
>2	1	5
Median lesion diameter		
<5mm	6	32
5mm - 1cm	6	32
>1cm	5	26
Unknown	2	11
Extent of treatment		
All lesions treated	8	42
Not all lesions treated	11	58

Table III: Predictors of complete response

Variable	Statistic	CR (n=5)	PR+SD+PD (n=14)	p-value
Age	Mean (SD)	62.60 (14.83)	82.43 (7.76)	0.004[a]
	Median [range]	61 [42 - 82]	85 [71 - 94]	
	Interquartile range	58 - 70	74.8 - 88	
Time diagnostic to treatment	Mean (SD)	25.64 (19.56)	42.70 (46.54)	0.849[b]
	Median [range]	21.5 [7.9 - 56.8]	23.2 [3.2 - 155.8]	
	Interquartile range	11.4 - 30.6	8.5 - 50.4	
	Missing	0	1	
Lesion size	Mean (SD)	3.40 (0.89)	9.22 (6.20)	0.004[b]
	Median [range]	3 [3 - 5]	7 [5 - 25]	
	Interquartile range	3 - 3	6 - 10	
	Missing	0	5	
Lesion size (grouped)	<5	4 (80.0%)	0 (0.0%)	0.008[c]
	5-9	1 (20.0%)	6 (66.7%)	
	10 or more	0 (0.0%)	3 (33.3%)	
	Missing	0	5	
Number of lesions	Mean (SD)	15.80 (19.18)	7.70 (8.38)	0.266[b]
	Median [range]	8 [5 - 50]	6 [1 - 30]	
	Interquartile range	7 - 9	3 - 8.5	
	Missing	0	4	
Number of lesions (grouped)	1-5	1 (20.0%)	3 (30.0%)	>0.999[c]
	6-10	3 (60.0%)	6 (60.0%)	
	>10	1 (20.0%)	1 (10.0%)	
	Missing	0	4	

[a] t-test; [b] Wilcoxon rank sum test; [c] Fisher exact test

Table IV: Publications for comparison

Authors	Year	Number of patients	Median patient age	Best overall response rate	Complete response rate	Predicto
Thompson JF et al.	2014	80	70	51%	26%	Locoreg
Thompson JF et al.	2008	11	83	48%	36%	Dos
Foote MC et al	2010	3	70	100%	100%	
Current Series	2015	19	80	68%	26%	Y Sma