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ORIGINAL ARTICLE

Patient-reported treatment-related symptom burden for patients with advanced melanoma in Canada

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Abstract

Background Little is known on the impact of emerging treatments for advanced melanoma (stages III and IV) on patients' functioning and well-being. The objective of this study was to describe the patient-reported treatment-related symptom (TRS) burden in advanced melanoma.

Method Twenty-nine in-depth, qualitative interviews were conducted among adult patients with advanced melanoma in Canada using a semi-structured interview method. Interviews were transcribed verbatim, and key concepts were identified using a grounded theory analytic approach.

Results The 29 patients reported 13 unique treatment journeys involving the following drug therapy categories: cytotoxic chemotherapies, CTLA-4 inhibitors, BRAF or MEK inhibitors, and PD-1 inhibitors. Patients typically underwent multiple treatment episodes over time. Common TRSs included nausea, fatigue, diarrhea or constipation, and skin rashes. Patients described these as impacting their physical functioning, ability to perform activities of daily living, social functioning, and overall quality of life.

Conclusion Our findings provide a description of the patient's experience with treatment for advanced melanoma. Our sample included patients typically diagnosed in mid-life, facing an urgent sequence of medical procedures and a pharmacological treatment journey that was burdensome. There is a need for less toxic and more efficacious treatments earlier in the patient journey to alleviate the impact of advanced melanoma treatment on patients' health-related quality of life.

Keywords Melanoma · Qualitative · Health-related quality of life · Cancer · Burden of treatment · Patient interviews · Patient-reported · Treatment-related symptoms

Background

Despite accounting for fewer than 5% of all skin cancer cases, melanoma is by far the most deadly [1]. Melanoma is an aggressive cancer originating in pigment-producing cells known as melanocytes and is typically diagnosed among people aged 55–74 [2]. In the past decade, Canada and the United States (US) each have seen the incidence of melanoma rise by more than 2% per year, with incidence rates for 2016 estimated at 17.8 and 21.8 cases per 100,000 individuals respectively [3, 4]. Five-year survival rates for melanoma overall range from 88% in Canada to 92% in the US but this rate drops precipitously to below 20% for patients whose melanoma has metastasized, for whom median survival is only between 6 and 7 months [5, 6].

Treatment for advanced melanoma has made rapid progress in recent years, with some experts suggesting we are in the midst of "a golden era for advanced melanoma treatment," [7]. Since 2011, promising new immunotherapies and targeted therapies have been developed based on an improved understanding of the biology of advanced melanoma and the discovery of novel mechanisms of action [8]. These are the first major developments since dacarbazine (DTIC) was approved by the US Food and Drug Administration (FDA) in 1976. DTIC has demonstrated very low response rates (< 10%)

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and no survival benefit [9–11], while the new generation of immunotherapies such as CTLA-4 and PD-1 inhibitors as well as targeted therapies such as BRAF- and MEK-inhibitors have each demonstrated increased treatment benefits compared to traditional therapies [7, 12–15].

Beyond the clinical benefits afforded by newer treatments, the patient perspective has been increasingly factored into regulatory decision making in Canada and the US [16–18]. Recommendations to publicly fund cancer treatments in Canada follow careful consideration of input from patient advocacy groups on patients' experiences with the relevant cancer and treatment under review [17, 19, 20]. The impact of adverse side effects, as reported by patients, can be used to differentiate alternative treatments that are otherwise similar in terms of clinical benefits and cost-effectiveness [17].

Little is currently known of the patient-reported treatment-related symptom (TRS) burden associated with emerging treatments for advanced melanoma and the impact on patients' functioning and well-being [21]. Melanoma itself has been associated with physical and mental health deficits that impair patients' functioning, known as the humanistic burden on patients' health-related quality of life (HRQL), particularly in the domains of fatigue and physical functioning [11, 21–26]. Worse HRQL, including domains of physical, social, and role functioning, has been shown to predict faster disease progression and lower survival [27–29].

Newer immunotherapies have brought on unique toxicities referred to as "immune-related adverse events" that affect primarily the skin, gastrointestinal tract, endocrine system or liver, though they are generally reversible if quickly treated and carefully monitored [30–32]. The risk of these adverse events highlights the need to understand the patient's experience with these newer therapies.

A recent qualitative study reported on the humanistic burden of disease for patients with advanced melanoma [33]. The objective of this study was to describe TRSs for advanced melanoma from the patient's perspective.

Methods

Study design and rationale

This was a qualitative, non-interventional study to explore patients' experiences of treatment for advanced melanoma (stages III and IV) in Canada, conducted in the winter of 2014/2015. During the study time period, CTLA-4, BRAF, and PD-1 inhibitors were only available as single agents in cases of advanced disease. PD-1 inhibitors were introduced just as this study was initiated so its uptake was low in the patient population. Neither the use of these single agents in the curative/adjuvant setting nor the use of combination regimens in any setting were reimbursed by the publicly funded healthcare system. Thus, their use was limited to patients who were participating in clinical trials.

Target population and recruitment

Recruitment was facilitated by Canadian patient advocacy associations who made initial contact with members and determined study eligibility. Patients were recruited from seven provinces: Alberta, British Columbia, Manitoba, New Brunswick, Ontario, Quebec, and Saskatchewan. Patients met all of the following inclusion criteria: had advanced melanoma (stage III or IV, self-report of doctor diagnosis), 18 years of age or above, spoke English or French, and were willing and able to participate in the study and give written informed consent.

Study procedures

Individual interviews were conducted in either English or French by one of five trained interviewers and were conducted in a single session lasting 45 to 60 min, during which patients shared their stories and answered questions about their experiences with treatment for advanced melanoma. Interviews conducted in French were translated by a professional translation service provider to ensure proper language translation of the French-Canadian language into English. The interviews were audio-recorded and transcribed verbatim using a professional linguist and superior machine-assisted rapid translation that ensures accuracy and consistency in the translation process.

Most interviews ($n = 18$; 62%) took place in one of two central locations (Montreal or Vancouver), scheduled to align with an advocacy group forum. These interviews took place in an office suite. Seven others (24%) took place at locations convenient to patients within each of the five remaining provinces, and these interviews were scheduled directly with the interviewers. Four interviews (14%) were conducted by telephone with patients who were unable to travel to any interview location. Each patient received a standard stipend.

Prior to the interview, patients received an overview of the study, the patient information letter, and the informed consent form. Patients completed a demographic health information form including detailed questions related to diagnosis and treatment course. The interview was guided by open-ended questions (see Table 1) from a semi-structured interview guide.

Interview questions for this study were designed based on a literature review and collaboration with clinical experts and patient advocacy groups. The interview guide is a set of questions exploring patients' general experience of the effects of melanoma and its treatment in terms of symptoms and quality of life. Questions designed to elicit personal experience without leading the patient were developed to allow patients to describe their experiences spontaneously. For example, "First, will you describe what it has been like for you since

Table 1 Semi-structured interview questions

Topic/questions
Experiences with advanced melanoma
▪ *First, will you describe what it has been like for you since you were diagnosed with advanced melanoma?*
▪ *Please describe any changes in how your body feels or functions since you were diagnosed with advanced melanoma?*
Experiences with advanced melanoma symptoms
▪ *What symptoms have you experienced, due to your melanoma, if any?*
▪ *How often do you experience your [symptom]?*
▪ *How long does your [symptom] last?*
▪ *What is a good day like with your [symptom]? What is a bad day like with your [symptom]?*
Experiences with treatments for advanced melanoma
▪ *What has it been like for you [patient's current treatment]?*
▪ *What treatments, if any, have you previously been on for your melanoma?*
▪ *What side effects, if any, did you experience with [given drug]?*
▪ *Please describe any chemotherapy that you have had?*
▪ *Have you been on any biologic (targeted) therapy or immunotherapy for your melanoma? What was this treatment like for you?*
▪ *What side effects, if any, have you noticed with the biologic (targeted) therapies you have been or are on? Can you describe the side effects for me?*
▪ *Have you had any issues with getting the medication that you want to treat your melanoma? Please describe.*
▪ *Have you ever considered stopping a treatment because it was affecting your quality of life?*

you were diagnosed with advanced melanoma?" and, "Please describe any changes in how your body feels or functions since you were diagnosed with advanced melanoma?" Patients were queried about specific symptoms and impacts on functioning or well-being if not mentioned spontaneously.

Data analysis

Transcripts were coded and analyzed to identify themes important to patients, using a grounded theory method that identified important concepts from the narrative data without applying an a priori theoretical model [34, 35]. This allowed for the elicitation of patients' described experiences rather than applying themes developed by researchers, as in traditional content analysis [36]. Grounded theory is widely used for analyzing exploratory qualitative data [37, 38].

An initial code book was developed by the research team, reflecting the overall structure of the interview guide. Codes were created to capture key concepts in the guide. For example, for a probe asking about diarrhea as a side effect of treatment, a code for the experience of diarrhea was created. Codes were created separately for symptoms that were mentioned spontaneously and those mentioned in response to a probe.

After the first two transcripts were coded independently by all researchers, the coding scheme was refined to capture new, emerging symptoms, experiences, and HRQL impacts. Each transcript was then coded by one researcher and independently reviewed by another. Discrepancies and changes to the coding scheme were harmonized among the research team, ensuring reliability of coding. All data was analyzed using ATLAS.ti. [39]

Results

Sample characteristics

The study included 29 adult patients with advanced melanoma. Most (n = 18; 62%) were female; mean age 52 (range = 28–69). Twenty patients (69%) reported stages III or IV melanoma at diagnosis. At the time of the interview, 22 (76%) reported stages III or IV, three (10%) reported being in remission, and four (14%) had achieved no evidence of disease (NED). Patients' sociodemographic and clinical characteristics are shown in Table 2.

Treatment journey for different regimens

We observed 13 unique treatment journeys involving drug therapies, and one patient who had radiotherapy only. In the following sections, we summarize the experiences of patients representing four major therapy groups:

1. Cytotoxic chemotherapies
2. CTLA-4 inhibitors
3. BRAF or MEK inhibitors
4. PD-1 inhibitors

Counts and percentages of the treatment experiences represented are shown in Table 3. The TRSs reported by patients in our sample are shown in Table 4 and detailed results are described below.

Cytotoxic chemotherapies (dacarbazine and temozolomide)

Ten patients (34%) received between one and four cycles of cytotoxic chemotherapy (nine DTIC, one temozolomide),[1] and none of these patients experienced remission.

Nausea was the most commonly reported TRS for patients who had received DTIC and was described as being the most severe right after intravenous infusions, often continuing between infusions. Two patients described these infusions as being painful experiences.

Fatigue and flu-like symptoms such as chills were other common TRSs among chemotherapy patients. Patients

[1] One patient had described use of DTIC on the demographic and health information form, but did not confirm or describe it during the interview.

Table 2 Sociodemographic and clinical characteristics of study sample

	N (%)
Age (mean years)	52
Gender	
Female	18 (62.1)
Male	11 (37.9)
Primary language	
English	24 (82.8)
French	5 (17.2)
Province	
Alberta	2 (6.9)
British Columbia	13 (44.8)
Manitoba	1 (3.5)
New Brunswick	1 (3.5)
Ontario	7 (24.1)
Quebec	4 (13.8)
Saskatchewan	1 (3.5)
Education	
Completed secondary school	4 (13.8)
Some college courses (in QC-CEGEP)	1 (3.5)
Completed college (in QC-CEGEP)	8 (27.6)
Some university or technical college	4 (13.8)
Completed university (bachelor)	6 (20.7)
Postgraduate	6 (20.7)
Work	
Employed full-time	6 (20.7)
Part-time	2 (6.9)
Student/part-time	1 (3.5)
On disability or leave of absence	10 (34.5)
Unemployed	1 (3.5)
Retired	9 (31.0)
Marital status	
Married	26 (89.7)
Single/never married	3 (10.3)
Disease stage at diagnosis (patient self-report)	
Do not know/no answer	2 (6.9)
Stage 0	1 (3.5)
Stage I	2 (6.9)
Stage II	4 (13.8)
Stage III (locally advanced cancer)	11 (37.9)
Stage IV (metastatic)	9 (31.0)
Disease stage at interview (patient self-report)	
NED	4 (13.8)
Remission	3 (10.3)
Stage III (locally advanced cancer)	4 (13.8)
Stage IV (metastatic)	18 (62.1)

who reported fatigue described it as debilitating and thus having a significant impact on their overall health-related quality of life:

Table 3 Treatment experiences of study sample

Treatment	*N* (%)
Cytotoxic chemotherapies	10 (34)
Dacarbazine	9 (31)
Temozolomide	1 (3)
CTLA-4 inhibitors (*ipilimumab*)	14 (48)
BRAF and MEK inhibitors	8 (28)
Vemurafenib	4 (14)
Dabrafenib	5 (17)
Binimetinib	1 (3)
PD-1 Inhibitors	4 (14)
Pembrolizumab	3 (10)
Unspecified	1 (3)

Counts and percentages represent the total number of participants who indicated having experienced either of the treatments listed. Percentages are rounded to the nearest whole number

> "I still have the side effects. Some days, I am going back to bed for the entire afternoon, it will make me feel better, I just need to sleep. There is still a lot of fatigue."

A patient who received temozolomide similarly referred to a profound burden on their physical functioning:

> "That was the most physically debilitating part…it actually like physically knocked me on my butt for the entire week that I had to take the pill…I couldn't move. I couldn't function."

Mental health impacts from chemotherapy were less common but included sadness over having to avoid social contact due to germs or feelings of burdening others:

> "…you just feel like you're a burden on the entire world, right? Because there's nothing you can do."

CTLA-4 inhibitors (ipilimumab)

Fourteen patients (48%) had received or were currently receiving ipilimumab. Those on treatment ($n = 10$) either reported good clinical results or were at a stage where they could not report on effectiveness yet. The other four patients switched to a PD-1 inhibitor treatment due to severe side effects or complications, including hospitalization, liver complications, or colitis. Patients typically received four to five treatment cycles, although one patient reported being on ipilimumab for 6 years.

The most commonly reported physical TRSs attributed to ipilimumab were skin rash, diarrhea or constipation, fatigue,

Table 4 Patient-reported treatment-related symptoms (TRSs) for advanced melanoma

Side effect of treatment	Cytotoxic chemotherapies	CTLA-4 inhibitors	BRAF and MEK inhibitors	PD-1 inhibitors
Nausea	44%	7%	50%	
Fatigue	33%	36%	90%	
Chills	33%	7%	20%	
Joint pain	11%	7%	40%	
Diarrhea or constipation		43%	70%	25%
Sun sensitivity	11%		50%	
Lightheadedness	11%	7%		
Skin rash		50%	40%	
Itching		21%	40%	
Headache		7%	20%	
Loss of appetite		7%	30%	
Thyroid problems		7%		50%
Pain from intravenous infusion	22%			
Face swelling	11%			
Muscle atrophy	11%			
Stomach aches		7%		
Dark hair patches		7%		
Pituitary failure		7%		
Liver complications		7%		
Developed colitis		7%		
"Weird" tastes or inability to taste		7%		
Hair loss			70%	
Sleep disturbance			40%	
Pain all over			40%	
Unusual curly hair growth after loss of hair			30%	
Fever			30%	
Sore or painful feet			30%	
Muscular pain			30%	
Difficulty concentrating			20%	
Calluses on feet			20%	
Memory loss			10%	
Warts			10%	
Muscle function problems			10%	
Skeletal problems			10%	
Night sweats			10%	
Nails growing in on themselves			10%	
Keratoacanthoma			10%	
Mouth issues (gums and teeth)			10%	
Eye/vision problems			10%	
Burning palms			10%	
Dry mouth				25%
Itching, inflamed, red toe				25%

Percentages are relative to the number of patients with experience with that treatment

and itching. While most described skin rash and fatigue as annoyances, two patients reported serious fatigue that had a greater impact on their daily functioning, as one patient's quote describes representatively:

"And there was a lot a fatigue, I was always tired. I couldn't spend half a day without lying down. If I got up at 8 a.m., I had to lay down at 10 a.m., then again at 12 p.m. I had to lay down every two hours because I was so tired."

Although less common, gastrointestinal problems such as chronic diarrhea or constipation were described as particularly bothersome and often limiting of their ability to be away from home, in addition to being painful and irritating. Severe diarrhea was implicated in three of the previously mentioned cases where patients needed to cease ipilimumab treatment and switch to PD-1 inhibitor treatment.

Two patients specifically mentioned that they had experienced far worse side effects with prior treatment and did not feel that the ipilimumab TRSs placed as much burden on their functioning:

> "And that's when he got me into the Yervoy [ipilimumab] trial, and … it was a complete about-face, because taking that drug, it does—didn't make me sick. I could —you know, I was tired from it and had some other physical side effects, but I could still function and—you know, carry on kind of sort of semi-normal, I suppose."

No impacts on mental health functioning or social functioning attributed to ipilimumab were reported.

BRAF and MEK inhibitors (vemurafenib, dabrafenib, and binimetinib)

Eight patients (28%) had received or were currently receiving one or more of the following BRAF inhibitors: vemurafenib ($n = 4$), dabrafenib ($n = 5$), or the MEK inhibitor binimetinib plus dabrafenib ($n = 1$), generally as the second line of therapy after chemotherapy.

Although five patients were told by their doctors that the BRAF inhibitor would be effective for 6 to 9 months, these patients had been taking their medication for up to 3 years with no evidence of cancer at the time of the interview. One patient had serious TRSs from vemurafenib and switched to dabrafenib, which was tolerable. Two patients did not have a successful treatment response to dabrafenib; one switched to ipilimumab and the other switched to dabrafenib plus binimetinib.

A majority of patients reported TRSs of fatigue, hair loss, and diarrhea or constipation as side effects associated with BRAF inhibitors. Additionally, roughly half reported experiencing nausea, sun sensitivity, sleep disturbance, skin rashes, itching, pervasive pain, and joint pain. TRSs unique to vemurafenib were a loss of appetite and callouses on feet, while side effects unique to dabrafenib were muscular pain, headaches, chills, and difficulty concentrating. No unique TRSs were reported for the combination therapy of dabrafenib and binimetinib.

Patients who reported skin rash as a TRS of a BRAF inhibitor described the rashes as being severe and typically developing at the start of treatment, causing patients to stop and re-start the therapy. Five patients experienced severe fatigue and other side effects such as anxiety and memory loss that significantly affected their quality of life, requiring a dose reduction. One patient called the TRSs "horrendous" when at the full dose. Yet, all five were willing to continue treatment given reductions in tumor sizes and other positive treatment responses. The following quote from a patient on dabrafenib is consistent with this majority sentiment:

> "The diagnosis itself didn't really affect my body as much the surgeries and the chemicals that they pumped into me. The latest on the dabrafenib that I had was very painful. It affected my skeletal system and my muscle function. It was very painful and—but it was doing a good job, so you tolerate it. You know, and they give you pills to help counter everything else, but it—but that really did incapacitate me, that one."

With respect to BRAF and MEK inhibitors, patients reported fewer effects on mental health functioning compared to physical health functioning. There were only two reports of a specific mental health side effect, and only five patients reported any at all. One patient reported experiencing anxiety about whether the treatment would continue to be effective after the duration of action suggested by their doctor (6 to 9 months) had passed.

There were two reports of impacts on social functioning that were attributed specifically to side effects from taking a BRAF inhibitor. One lamented about the difficulty of raising a young daughter and participating in activities with her due to aches, pains, fatigue, and sun sensitivity. Another patient related not feeling well enough to drive to a friend's home an hour away and being limited to short visits with friends.

PD-1 inhibitors (pembrolizumab)

Four patients (14%) received a PD-1 inhibitor, three of whom received pembrolizumab, and the other was unspecified. All four received the treatment as second- or third-line therapy and either through a clinical trial or an early access program because the drugs had not been approved in Canada at the time of this study. All of these patients had previously received DTIC and/or ipilimumab, during which their advanced melanoma either did not respond or had returned.

All PD-1 inhibitor patients reported a positive response to treatment in terms of reduced number and size of tumors.[2] Patients attributed few TRSs to PD-1 inhibitor treatment and described them as mild. One patient reported diarrhea and dry mouth after the seventh pembrolizumab treatment. Another mentioned itchy, inflamed toes. A third patient spoke of

[2] Note that we are reporting the patients' statements about treatment effectiveness, not clinical observations about disease progression.

fatigue that was concurrent with pembrolizumab therapy, but could not be certain it had been caused by the treatment. Two of the pembrolizumab-treated patients reported damage to the thyroid, which they understood to be a consequence of "amping up" the immune system to treat the melanoma.

Patients described their overall experience with PD-1 inhibitors as generally tolerable, separately reporting that they felt "good," "great," or "healthy" throughout. One patient was surprised and very pleased about feeling better early in the pembrolizumab treatment regimen:

> "And so, you know, actually, before the second infusion three weeks later, I felt symptom-free."

Another patient expressed pleasure that the administration of pembrolizumab was less burdensome than their previous therapy:

> "The ipilimumab was an hour and a half infusion. This [pembrolizumab] is a half hour. So time-wise, it has been beautiful."

In terms of mental health functioning, one patient reported a change in mood concurrent with their pembrolizumab treatment, but they could not attribute it specifically to the drug or to the cumulative impact of advanced melanoma. No other impact on mental health functioning was specifically associated with PD-1 inhibitors. When prompted, all patients reported that they had not felt any impact of PD-1 inhibitor treatment on cognition, feeling depressed or sad, or feeling anxious. Additionally, there were no specific reports of impacts on social functioning, even after probing questions were asked.

Discussion

Across the 29 patients, we observed 13 unique treatment journeys involving drug therapies, and one patient who had received only radiotherapy. Patients typically had multiple treatments for advanced melanoma, usually starting with chemotherapy, then a BRAF inhibitor or ipilimumab or one followed by the other, and in four cases, a PD-1 inhibitor. Many TRSs were reported that impacted physical health functioning. Fatigue was the most commonly reported TRS across all treatments, followed by nausea, diarrhea, or constipation. These TRSs often were severe and had debilitating effects on physical functioning and quality of life. Individual treatments were associated with specific TRS patterns such as flu-like symptoms (DTIC), skin rash and diarrhea (ipilimumab), and pain (BRAF inhibitor). Patients did not report significant mental health or social functioning side effects attributed to specific treatments.

While the study did not specifically target patients who were treated with PD-1 inhibitors, it included four such patients; three with experience on pembrolizumab and one with an unspecified PD-1 inhibitor. In this treatment category, patients reported positive experiences, describing a high level of clinical benefit with little or no TRS impacts on functioning and well-being. Limitations of this study include the relatively small sample size, though it is typical of qualitative research studies, particularly studies involving patients with rare diseases.

Nonetheless, we provide a characterization of the patient's experience with treatment for advanced melanoma. Our sample included patients diagnosed in mid-life who reported facing an urgent sequence of medical procedures and a pharmacological treatment journey that was burdensome. Thus, we see a need for improved communication with patients about the likely treatment journey and different treatment options.

Although the treatment landscape has changed since the completion of this study, namely with the introduction of CTLA-4/PD-1 as well as BRAF/MEK combinations in the treatment of advanced disease, the individual agents that constitute these doublet regimens are not new per se. Therefore, the patient experiences with these drugs as monotherapy are still likely to resonate with patients diagnosed and treated today with multi-agent regimens.

We conclude that there is an ongoing need for less toxic and more efficacious treatments earlier in the patient journey which would help to alleviate the humanistic burden of advanced melanoma and bring benefits to patients across all aspects of their lives, as well as the lives and livelihoods of their families.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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