Original Article

Patient-Reported Outcomes During Checkpoint Inhibition: Insight into Symptom Burden in Daily Clinical Practice

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Abstract

Context. While praised for inducing durable anti-tumour responses, immune checkpoint inhibitors (ICI) also cause immune-related adverse events (irAEs) that can vary in severity and affect health-related quality of life (HRQL).

Objectives. This study was performed to provide insight into the course of symptoms and the influence of irAEs on HRQL measured with the treatment-specific Utrecht Symptom Diary Immunotherapy (USD-I).

Methods. In this observational cohort study, melanoma or non-small lung cancer (NSCLC) patients treated with PD(L)1-inhibitors between February 2016 and December 2018 were included. Data on symptoms, wellbeing and influence of side effects on HRQL were obtained using the patient-scored, treatment-specific USD-I, which was completed as part of routine care. Patients scored symptom intensity on a 0-10 numeric rating scale (NRS); NRS≥3 considered clinically relevant.

Results. A total of 162 melanoma (55%) or NSCLC (45%) patients completed 1493 USDs (median seven per patient). Most common patient-reported clinically relevant symptoms were: inactivity, fatigue, pain, cough and sleeping problems. Symptom prevalence decreased during treatment. Patients generally reported a low influence of side effects on HRQL. A higher number of clinically relevant symptoms at a certain time point correlated with poorer wellbeing.

Conclusions. These data illustrate that ICI-treatment is generally well tolerated. However, especially the number of clinically relevant symptoms can impact patients wellbeing. Systematic use of an ICI-tailored PROM could create a window to discuss symptoms in a structured way which may promote personalized care during treatment. J Pain Symptom Manage 2022;63:997−1005.

Key Words

Cancer immunotherapy, melanoma, non-small cell lung carcinoma, patient-reported symptoms, supportive care, symptom assessment

Key Message

This observational cohort study describes patient-reported symptoms and health-related quality of life (HRQL) measured with the Utrecht Symptom Diary Immunotherapy. Although patients experienced a multitude of symptoms during treatment with immunotherapy, it is generally well tolerated. Especially the number of clinically relevant symptoms can impact patient's wellbeing.

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Introduction

Immunotherapy with immune checkpoint inhibitors (ICI) has radically changed perspectives for many cancer patients, such as patients with advanced melanoma or non-small cell lung cancer (NSCLC). Antibodies against the immune checkpoint programmed cell death protein-1 (anti-PD1), like pembrolizumab and nivolumab, and its ligand (anti-PD-L1) such as durvalumab and atezolizumab, reinvigorate effective anti-tumour immune responses.

Unfortunately, ICI can cause immune-related adverse events (irAEs), ranging from mild to life-threatening. IrAEs may start sub clinically, can affect multiple organs simultaneously, and may occur at any moment during treatment up to several weeks after stopping treatment.[1,2] Most common irAEs are dermatitis, myalgia, arthralgia, and fatigue. Other irAEs, such as colitis, pneumonitis, hypophysitis and myocarditis are generally more severe and potentially life-threatening.[3] IrAEs often require active immunosuppressive treatment to prevent serious complications.[1,2] Early recognition of irAEs is considered essential to adequately treat symptoms and to maintain health-related quality of life (HRQL).[4]

Although patients with cancer rank survival as their highest priority, they also value symptom control and the ability to continue daily life during and after treatment.[5] Little is known about patient-reported symptom prevalence, symptom intensity and HRQL during ICI in daily clinical practice. Insight into HRQL over time is especially relevant for ICI treated patients, because of the durable responses and longer treatment duration.[6] Since it is known that healthcare professionals tend to underestimate symptoms and family members ratings of symptoms are often higher than patient ratings, symptom reporting by patients themselves is considered the most reliable indicator of symptom presence and intensity.[7,8] Application of patient reported outcome measurements (PROMs) enhances early recognition of symptoms and, improves clinician −patient communications, quality of care and overall survival.[9,10] This has led to an increase in the use of PROMs in clinical trials and to a lesser extent in daily clinical practice. Unfortunately, most PROMs were developed for use in the clinical trial setting, before the introduction of ICI and focus on other symptoms than usually encountered during ICI.[11−13]

Consistent and meaningful use of PROMs requires an easy-to-use and to the point symptom assessment system maximised for clinical use.[14] Worldwide, the most frequently used brief PROM to routinely asses and monitor symptoms in advanced cancer patients is the Edmonton Symptom Assessment System (ESAS), which has been proven to be a strong and highly sensitive tool for assessing/monitoring symptom experience.[7,15] We developed and validated an adapted version of the ESAS, named the Utrecht Symptom Diary (USD).[16,17] In 2016 we implemented the treatment-specific USD-module immunotherapy (USD-I) for cancer patients in our tertiary referral centre for melanoma and immunotherapy.

Here, we describe the results of an observational cohort study on patient-reported symptoms measured by USD-I in 162 patients treated with PD(L)1-inhibitors for advanced melanoma or NSCLC. We aim to provide insight into the course of symptoms and wellbeing as well as the influence of side effects on HRQL from a patient perspective.

Patients and Methods

Patients

Patients treated with monotherapy nivolumab, pembrolizumab, durvalumab or atezolizumab with curative or palliative intent for melanoma or NSCLC in the University Medical Centre (UMC) Utrecht between February 2016 and December 2018 and who completed at least two USD-Is were included. As part of standard care, each patient visiting the outpatient clinic for ICI administration was asked to complete the USD-I to tailor supportive care. In compliance with Dutch regulations, the use of these data for research purposes was approved by the medical ethical committee and was not considered subject to the Medical Research Involving Human Subjects Act (METC number 16-755/C).

Definitions & Measurements

The USD-I (Appendix A) - a treatment specific and adapted version of the validated USD[17] - consists of 22 items: lack of appetite, abnormal stool, diarrhoea, blood/mucus in stool, abdominal pain, cough, eye complaints, skin rash, itching, headache, muscle pain, joint pain, numbness or tingling in arms/feet, pain, sleeping problems, nausea, shortness of breath, anxiety, fatigue, depressed mood, inactivity and wellbeing. The items sleeping problems, lack of appetite, abnormal stool, nausea, shortness of breath, fatigue, anxiety, depressed mood and wellbeing have been validated.[17] The other items were added based on generic irAEs with a prevalence of ≥10% and less common but potentially serious irAEs described in clinical trials.[18,19]

Before each treatment episode, patients scored the USD-I items on paper or within the patient environment of the electronic medical files, on a 0−10 numeric rating scale (NRS), with higher values indicating increasing symptom intensity/poorer wellbeing. Patients generally complete the USD-I in less than five minutes, and have the opportunity to add missing items and to assign priority to symptoms which need support

first. Influence of AEs on HRQL was measured by a single-item,[20] answering the question: "To what extent do the side effects of treatment influence your quality of life"? on a 0−7 NRS, with higher values indicating decreased HRQL. Patients are asked to score the intensity of their symptoms over the last period of time (since the last time they visited the outpatient clinic). Nurses reported symptoms with USD-I score ≥3 in the electronic medical files and discussed them with the patients to bring about early recognition of symptoms and symptom intensity, and to objectify the effect of symptom management interventions deployed. Symptom severity from healthcare professional perspective was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[21]

Data Collection and Analysis

Patient characteristics, disease and treatment-related data and USD-I scores were extracted from the electronic medical files. Disease stage of melanoma was classified according to the American Joint Commission on Cancer (AJCC) staging system seventh edition and NSCLC to the TNM, both seventh edition.[22,23] Response Evaluation Criteria in Solid Tumours (RECIST 1.1) were used to define response to treatment.[24]

USD-I scores were analysed per time point: baseline (range -2−2 weeks), week 4 (2−6), week 8 (6-10), week 12 (10−14), week 16 (14−18), week 20 (18−22), week 24 (22−26), third quarter (week 26−40) and fourth quarter (week 40−53). Per time point one USD-I per patient (the one closest to that time point) was selected for analysis.

USD-I symptom scores were categorized to describe symptom prevalence and intensity at baseline and during treatment, absent (0), prevalent (≥1), clinically relevant (≥3), severe (≥6).[17] For the items wellbeing (NRS 0−10) and influence of side effects on HRQL (NRS 0−7) only the intensity was compared in line with the original USD validation study.[17] Patients with a missing value for the studied USD-I item were excluded for analysis for that item.

All item scores (except influence of side effects on HRQL) were summed to calculate a total symptom distress score, as previously done with the ESAS by Hui et al;[25] total score 0−220, higher scores indicate higher total symptom burden. In this score, when a patient did not score an item, we assumed that that specific item was not prevalent (NRS 0).

Differences in symptom prevalence between time points and tumour types were analysed by using the $\chi 2$ (or Fisher exact test in case of cell frequencies ≤1 or ≥20% or expected cell frequencies between 1 and 5). Differences in medians were analysed by using the Mann-Whitney U test.

To test whether a high number of clinically relevant symptoms (NRS ≥3) was correlated with experiencing a poorer wellbeing, a higher influence of side effects on HRQL, and a higher total symptom distress score we used the Spearman's rho coefficient (ρ).

Due to the group size in relation to the number of statistical tests, the differences found will be considered as hypothesis generating. Statistical analysis were performed using SPSS 25.0 for Windows software (©2018 IBM SPSS Inc.).

Results

Demographics/Patient Characteristics

During the selected period 203 patients with melanoma or NSCLC started treatment with anti-PD(L)1 monotherapy and could have had completed at least two USD-Is. A total of 162 out of 203 (80%) patients with melanoma (55%) or NSCLC (45%) completed at least two USD-Is and were included for analysis. Patient characteristics are depicted in Table 1. Median age was 66, 59% of the patients were men, and 90% patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. Most (90%) patients were treated with nivolumab or pembrolizumab.

Treatment Duration and Healthcare Professional-Reported AEs

At time of analysis, which was May 2021, all patients had stopped treatment. Median follow up from start of treatment was 116 weeks (interquartile range (IQR) 31−171 weeks). Overall median treatment duration was 30 weeks (IQR 10-61), which was 33 weeks for melanoma patients and 18 weeks for NSCLC patients. Most common reasons for treatment discontinuation were: progressive disease (49%), completed treatment or confirmed response to treatment (26%) and irAEs (19%). Six percent of the patients stopped treatment for other reasons such as bleeding or infection.

CTCAE grade ≥3 (severe) irAEs occurred in 14% of the patients, and more often in patients previously treated with ICI (53%) vs. 10% in patients receiving ICI for the first time; $P<0.001$). Most reported grade ≥3 irAEs were: pneumonitis (4%) and hepatitis (3%) (Table 2). Twelve percent of the patients were admitted to the hospital for irAEs and systemic steroids were required for irAE management in 17% of the patients.

Patient-Reported Symptoms

Patients completed a total of 1493 USD-Is, with a median of seven (IQR 4−13) per patient. At baseline, 116 out of 162 patients (72%) completed a USD-I vs. 55/64 (86%) patients on treatment in quarter 4 (Fig. 1).

Every USD-I item was scored present (NRS ≥1) at a certain time point by ≥20% of the patients, except for

Table 1
Demographics and Patient Characteristics

Variable (*n*, %)			*n* = 162 (100)
Age (yrs), median (range)			66.4 (33–90)
	Categorized	<50	21 (13)
		50–69	75 (46)
		≥70	66 (41)
Gender, male			95 (59)
ECOG performance status	0		51 (31)
	1		95 (59)
	2		15 (9)
	3		1 (1)
Tumour type	Melanoma, all stages[a]		89 (55)
	Melanoma, per stage[a]	III	3 (3)
		IV	86 (53)
	Non-small cell lung carcinoma, all stages		73 (45)
	NSCLC, per stage	III	10 (14)
		IV	63 (39)
Brain metastasis present			40 (25)
		Symptomatic	25 (15)
Comorbidity present[b]			102 (63)
	Cardiovascular		57 (35)
	COPD		16 (10)
	Diabetes mellitus		11 (7)
	Auto-immune disease		6 (4)
	Other		63 (39)
Type of immunotherapy	Anti-PD1		145 (90)
		Nivolumab	45 (28)
		Pembrolizumab	100 (62)
	Anti-PD-L1		17 (10)
		Durvalumab	8 (5)
		Atezolizumab	9 (6)
Any previous treatment			82 (51)
Any previous immunotherapy			17 (10)
		Ipilimumab	11 (65)
		Pembrolizumab	1 (6)
		Ipilimumab/ nivolumab	5 (29)

[a]AJCC 7th edition
[b]Comorbidities: Patients could have been diagnosed with multiple comorbidities. Other comorbidities such as other malignancies, obesity, impaired renal function, Of seven patients the comorbidity was unknown

blood/mucus in stool (5%–13% of patients at different time points) (Fig. 1).

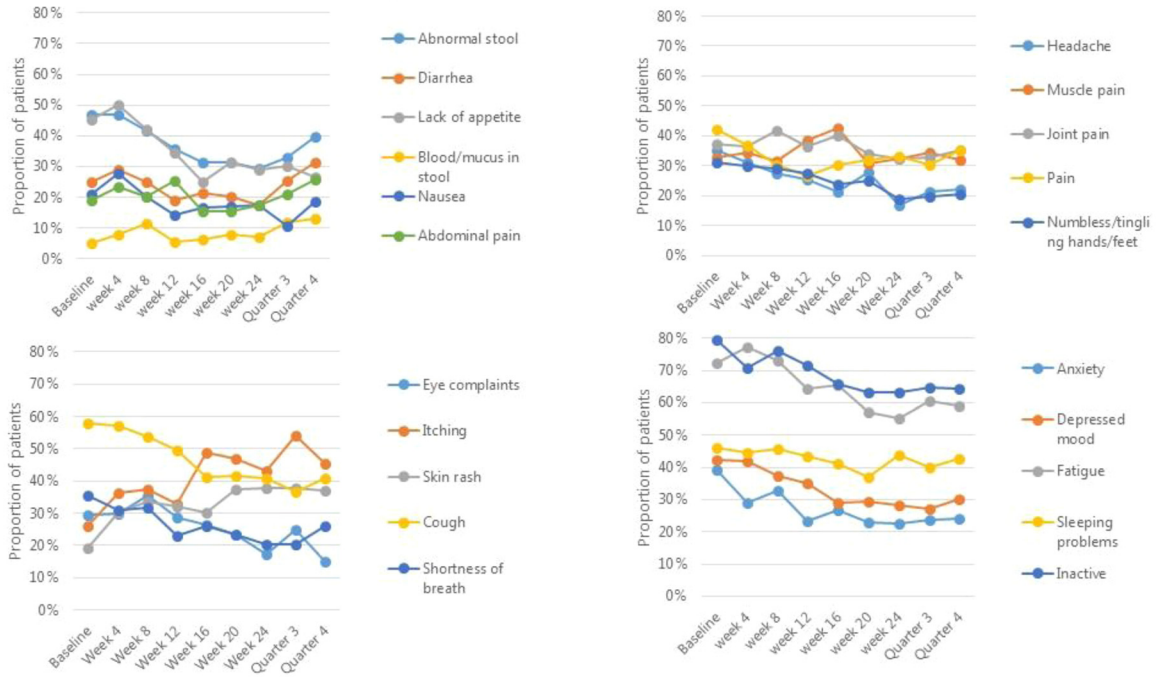
Fig. 2 shows the proportions of patients with clinically relevant USD-I scores (NRS ≥3) at the different time points. The top 5 clinically relevant symptoms at any time point were: inactivity (38-56%), fatigue (26%–57%), pain (13%–23%), cough (11%–39%) and sleeping problems (11%–29%).

When the different time points were compared to baseline, the prevalence of clinically relevant symptoms decreased for 13 out of 22 USD-I items. The largest decrease was found for cough (from week 12 to quarter 4, compared to baseline differences in proportions were between -18% to -28%; *P*-value between <0.001 and 0.006) and fatigue (from week 16 to quarter 4, compared to baseline differences in proportions were between -16% and -27%; *P*-value between 0.003 and 0.030). Contrarily, the prevalence (NRS ≥1) of skin rash and itching increased during treatment. When looking at symptoms with severe intensity (NRS ≥6), only fatigue and inactivity were reported by ≥10% of the patients at least at six out of nine time points; with

Table 2
Most Common and Grade 3 of 4 Reported Adverse Events

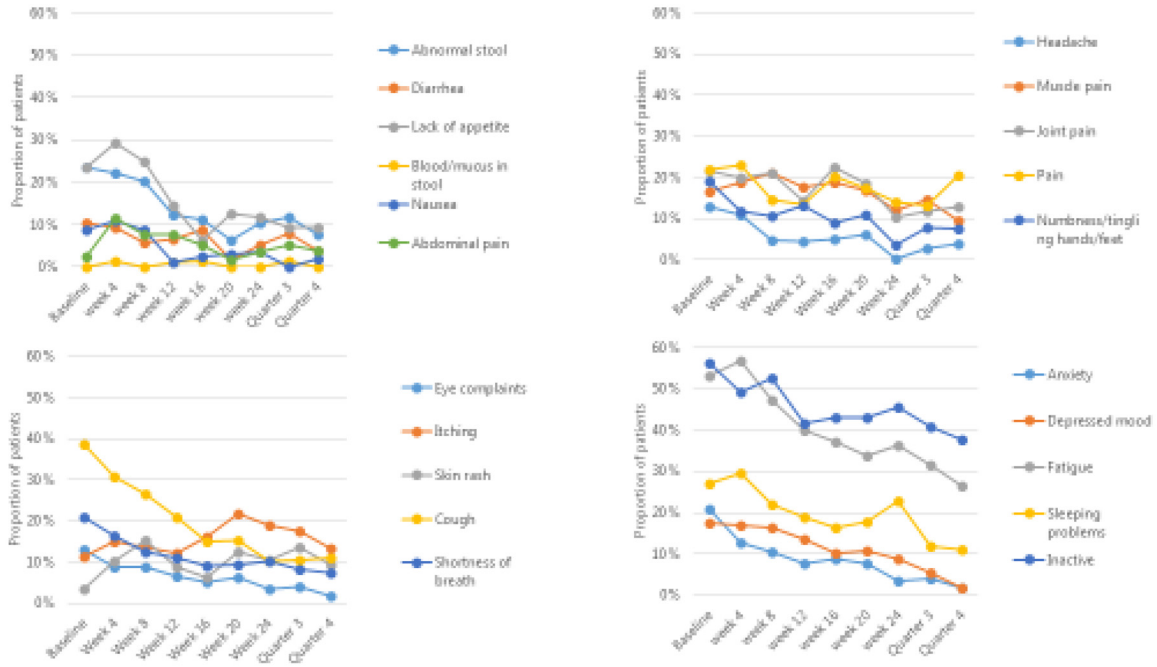
Adverse event		Any grade* *n* (%)	Grade 3/4*
Endocrinopathies	Hypophysitis	4 (2)	
	Hypothyroidism	9 (6)	
	Hyperthyroidism	7 (4)	
	Diabetes Mellitus	2 (1)	2 (1)
Gastro-intestinal	Diarrhoea and/or colitis/duodenitis	16 (10)	3 (2)
	Hepatitis	7 (4)	5 (3)
	Pancreatitis	2 (1)	1 (< 0.5)
	Pancreatic insufficiency	1 (< 0.5)	1 (< 0.5)
Skin	Dermatitis /rash	37 (23)	3 (2)
	Vitiligo	11 (7)	
Other	Pneumonitis	18 (11)	6 (4)
	Arthralgia/ bursitis/arthritis	16 (10)	
	Myalgia	10 (6)	
	Nasal or mucosal dryness/ dry eyes	7 (4)	
	Infusion related reaction	4 (2)	
	Nephritis	3 (2)	
	Vasculitis/arteritis	2 (1)	2 (1)

*Common Terminology Criteria of Adverse events v4.03



Time point	baseline	Week 4	Week 8	Week 12	Week16	Week 20	Week 24	Quarter 3	Quarter 4
I	162 (100)	159 (98)	148 (91)	118 (73)	109 (67)	95 (59)	90 (56)	87 (54)	64 (40)
II	116 (72)	140 (88)	106 (72)	91 (77)	80 (75)	65 (68)	59 (66)	76 (87)	54 (84)
III	55/61	74/66	55/51	53/38	50/30	40/25	37/22	45/31	32/22

Fig. 1. USD scores ≥1.



Time point	baseline	Week 4	Week 8	Week 12	Week16	Week 20	Week 24	Quarter 3	Quarter 4
I	162 (100)	159 (98)	148 (91)	118 (73)	109 (67)	95 (59)	90 (56)	87 (54)	64 (40)
II	116 (72)	140 (88)	106 (72)	91 (77)	80 (75)	65 (68)	59 (66)	76 (87)	54 (84)
III	55/61	74/66	55/51	53/38	50/30	40/25	37/22	45/31	32/22

Fig. 2. Clinically relevant symptoms (USD-scores ≥3).

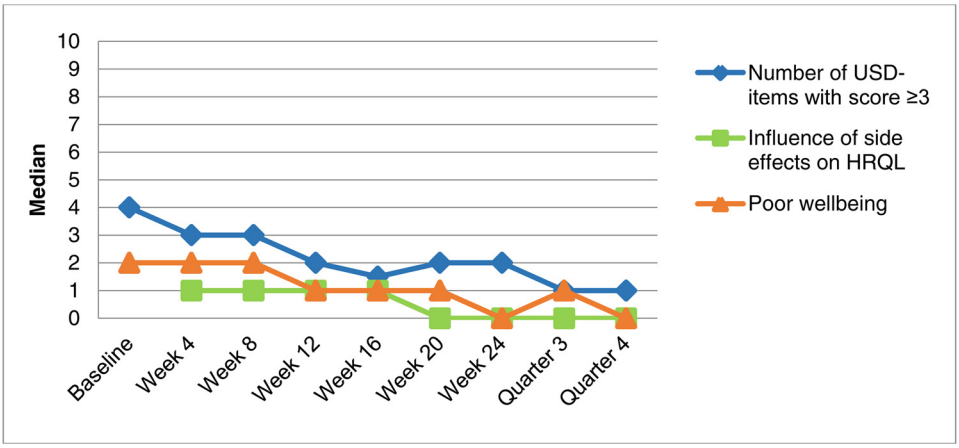


Fig. 3. Number of clinically relevant symptoms, influence of side effects on health-related quality of life and wellbeing (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

highest prevalence at week 4 (21% and 24% respectively).

When looking at clinically significant symptoms (NRS ≥3) at baseline per tumour type (Appendix B), NSCLC patients more often reported cough (63% vs. 11%; *P*=<0.001), shortness of breath (37% vs 4% vs.; *P*=<0.001) and fatigue (67% vs. 38%; *P*=0.002) than melanoma patients.

Total Symptom Distress Score and Number of Clinically Relevant Symptoms

The median total symptom distress score at baseline was 26 (IQR 10−43), which at week 12 decreased to 18 (IQR 6−32); *P*=0.007. At time of grade ≥3 irAE occurrence, the median total symptom distress score in the 13 of 23 patients (57%) who completed a USD-I (range -2 to 3 weeks) was 31 (IQR 16−58). At baseline, patients with NSCLC had a higher score than patients with melanoma; 36 (IQR 22−52) vs. 17 (IQR 6-28); *P*<0.001.

At baseline, patients reported a median of four (IQR 1-7) clinically relevant symptoms (NRS ≥3), which decreased to one (IQR 0-4) at quarter 3 (*P*=0.011) (Fig. 3). At time of grade ≥3 irAE occurrence, the 13 of 23 patients (57%) who completed a USD-I (range -2−3 weeks) reported a median of five (IQR 2-9) clinically relevant symptoms. At baseline patients with NSCLC had a higher number of clinically relevant symptoms than patients with melanoma; median 5 (IQR 3−8) vs median 2 (IQR 1-4); *P*<0.001).

Wellbeing and Influence of Side Effects on HRQL

At baseline, patients reported a relatively good wellbeing; NRS 2;IQR 1-4). During treatment wellbeing scores decreased to 1 or lower after 12 weeks (IQR 0-2 to 0-4), suggesting a slight improvement in wellbeing. Over time, there was a moderate to strong correlation between the number of symptoms NRS ≥3 and a poor wellbeing with correlation coefficients (ρ) ranging from 0.622 to 0.835.

The item influence of side effects on HRQL was the only USD-I item which was missing in ≥10% of cases from week 20 through quarter 3. During treatment patients consistently reported a low influence of side effects on HRQL, median 0 or 1 (IQR 0-1 or 0-2) (Fig. 3). During treatment, we found moderate positive correlations of influence of side effects on HRQL and total symptom distress score (ρ varying from 0.713 at week 4 to 0.559 at quarter 4).

Added USD-I Items and Symptoms Given Priority for Support

From week 4 to quarter 4 oral complaints such as taste alteration, dry mouth, painful tongue, increased dental plaques were added by one to three patients per time point. Patients most often assigned priority to pain (baseline: *n*=5); fatigue (week 4: *n*=5) and muscle pain and/or joint pain (week 16: *n*=4).

Discussion

Our study is one of the first describing patient-reported symptoms during treatment with PD(L)1-inhibitors by using a brief, ICI-tailored PROM in daily clinical oncology practice. The top 5 clinically relevant symptoms reported by patients were: inactivity, fatigue, pain, cough and sleeping problems. When compared to baseline the prevalence and number of clinically significant symptoms decreased, wellbeing slightly increased and patients generally reported a low influence of side effects on HRQL.

Although at baseline most patients had an ECOG PS 0-1, they reported a median of four symptoms that caused relevant symptom burden. The number of symptoms with a NRS ≥3 correlated with a decreased

wellbeing and relevant influence of side effects on HRQL. During the first three months of treatment, the prevalence of clinically relevant abnormal stool, cough, shortness of breath, anxiety, inactivity and fatigue decreased with at least 10%. From week 20 the prevalence of itching and skin rash increased with at least 10%. These data suggest that during ICI treatment patient experienced symptom burden changes from more cancer-related to treatment-related. Although this change could be explained by response to treatment, it is likely also partially explained by the gradual selection of patients with a favourable disease course.[6,26] Since a USD-I is offered before treatment administration, only symptom burden in patients remaining on treatment is shown, excluding patients with progressive disease or treatment discontinuation due to severe irAEs. The decrease of symptom prevalence and symptom intensity as well as increase of wellbeing within three months of treatment are in contrast with findings in our previous studies on patient-reported symptoms during targeted therapy. In these studies, symptom prevalence increased and wellbeing decreased during treatment.[27,28] The increase in wellbeing during treatment in our current study might be explained by the less frequent and relatively late occurrence of irAEs as a result of immunotherapy compared to targeted therapy as well as by more durable responses. Our data endorse the findings of Tykodi et al and Nishijima et al who showed that ICI treated patients across tumour types maintained HRQL or even experienced HRQL-improvement, which is in contrast with the HRQL deterioration observed in other anticancer therapies.[6,26]

In this analysis we focused on anti-PD(L)1 monotherapy treated patients. In the last few years combination treatments of anti-PD1 plus anti-CTLA4 and anti-PD1 plus chemotherapy have progressively been applied in melanoma and NSCLC.[29–31] Since treatment-related symptoms more often occur during these combinational treatments, separate analysis in patients receiving these treatments are of interest.

This study shows the potential value of a tailored PROM during ICI treatment. Since the ICI-specific items - except blood/mucus in stool - occur in a relevant number of patients, we consider the addition of these items as relevant, making the USD-I a tailored PROM for assessing and monitoring treatment and cancer-related symptoms during ICI. Since oral complaints (e.g., dry mouth) were spontaneously reported by patients and dry mouth has shown very good validity in the USD validation study[17] we will add this item to the USD-I.

The use of the brief USD-I in clinical practice can contribute to shared decision making by early detection and monitoring of symptoms and their impact over time. As shown by others, the standard use of patient-reported outcomes in clinical practice increases the frequency and depth of discussion of symptoms and is associated with improved symptom control as well as increased patient satisfaction.[32] Discussing the USD-I scores with the patient may have increased insight into the subjective intensity from the patients' perspective, adding valuable information to healthcare professional-assessed AE grading only.[26]

One of the strengths of our study is the good completion rate of 66% to 88% USD-Is per time point in this real world study. The incompleteness of PROM data has been identified as a challenge by others.[6,26] In comparison, questionnaire completion rates in controlled clinical trials with ICI, ranged from 50% to 87%.[6] Compliance could potentially be further increased by an improved electronic data collection instead of using paper questionnaires as suggested by Tykodi et al.[6] Moreover, training patients and healthcare professionals about the (e) PROM could optimize usage.[33,34]

Our study has some limitations. First of all, we are aware that the differences we observe should be interpreted with some caution because of the number of statistical tests in relation to our group size. Little is known about patient-reported symptoms and their burden during treatment with ICI in daily clinical practice. Therefore we chose a hypothesis-generating approach and to not correct for multiple testing. Secondly, USD-I outcomes were only collected from patients who were on treatment and may primarily be a representation of a 'middle' group of patients, because most common reasons not to complete a USD-I, were no or unchanged symptom burden and clinical deterioration. Furthermore, although the USD is a validated PROM,[17] a validation study for the extra items related to immunotherapy on the USD-I still needs to be performed. The same accounts for the time frame since the USD asks about symptom intensity at that moment ('now') whilst the treatment specific USD-I interrogates symptom burden over the last (treatment) period of time (since the last time the patient visited the outpatient clinic).

In conclusion, these data illustrate that immunotherapy is generally well tolerated. Although patients consistently report a low influence of side effects on HRQL, healthcare professionals should be aware that the number of symptoms with a NRS ≥3 experienced at the same time can decrease patients wellbeing. Using an ICI-tailored PROM in daily clinical practice could create a window to discuss symptoms and their impact in a structured way and improve personalized care during treatment.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jpainsymman.2022.02.013.

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