The Oncologist®

Symptom Management and Supportive Care

Personalized Symptom Goals and Patient Global Impression on Clinical Changes in Advanced Cancer Patients

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Advanced cancer • Symptom assessment • Palliative care • Personalized symptom goal • Global impression of change

Abstract

Background. The aim of this study was to assess the patients' global impression (PGI) after symptom management, as well as the achievement of personalized symptom goals (PSG). The secondary outcome was to assess related factors.

Subjects, Materials, and Methods. Advanced cancer patients admitted to palliative care units rated symptom intensity by using the Edmonton Symptom Assessment Score (ESAS) at admission and then after 1 week. For each symptom, patient-reported PGI and PSG, as well as the rate of PSG response, were evaluated.

Results. Eight hundred seventy-six patients were taken into consideration for this study. A mean of 1.71–2.16 points was necessary to perceive a bit better improvement of symptom intensity. Most patients had a PSG of $\leq$3. A statistically significant number of patients achieved their PSG after starting palliative care. Patients with high intensity of ESAS items at admission achieved a more favorable PGI response. In the multivariate analysis, symptom intensity and PSG were the most frequent factors independently associated to a best PGI, whereas high levels of Karnofsky had a lower odd ratio.

Conclusion. PSG and PGI seem to be relevant for patients' assessment and decision-making process, translating in terms of therapeutic intervention. Some factors may be implicated in determining the individual target and clinical response. ***The Oncologist*** 2019;24:239–246

Implications for Practice: Personalized symptom goals and global impression of change are relevant for patients' assessment and decision-making process, translating in terms of therapeutic intervention. Some factors may be implicated in determining the individual target and clinical response.

Introduction

Cancer patients experience a significant symptom burden along the course of disease trajectory, particularly in the advanced stage [1]. Currently, patient-reported symptom assessment is the gold standard to evaluate the clinical response and to guide decision-making. The Edmonton Symptom Assessment System is a unidimensional numeric rating scale that ranges from 0 (no symptom) to 10 (worst possible), used ubiquitously to evaluate the intensity of physical and psychological symptoms, particularly in palliative care [2, 3]. Despite its simplicity and widespread use, this tool has some important limitations because of its subjectivity. As a consequence, individual patients may interpret the scale differently and express their symptom intensity with significant variations. Furthermore, the clinical response is not easy to determine because the minimal clinically important difference (MCID), that is, the smallest amount of change required to impact the patient's feeling of improvement or deterioration, is not often established. The cutoffs for response often apply to group averages only instead of individual patients, so it is difficult to verify a reliable response. MCID has been the subject of recent research. Different methods have been proposed, including the distribution method, based on fractionations of standard deviation or standard error [4–6], as well as the use of anchors,

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for example, changes of intensity categories of well-being [7], or the magnitude of change in the patient-reported outcome, or the optimal balance between sensitivity and specificity. Patient global impression (PGI) is a validated global rating-of-change scale used to assess subjective patients' response based on the individual feeling of improvement or deterioration after receiving a treatment [8, 9]. On the other hand, to personalize cancer care, clinicians need to tailor the treatment to the individual patient. Personalized symptom goals (PSG) are recent measures that may tailor symptom management, providing a simple and individualized therapeutic "target" for each symptom [10, 11]. This approach could allow for an intra-patient determination of symptom response that is both practical and meaningful. Furthermore, the factors associated with baseline intensity of PSG and PGI have not been examined. Previous studies have variably assessed these points [7, 10–12]. However, they were performed in an outpatient setting, with variable intervals for the follow-up, or retrospectively. A better characterization of PSG, and factors associated with PSG and PGI, as perceived by patients, would help clinicians to personalize symptom management and to evaluate meaningful changes, which could be helpful. This is even more important in a palliative care unit, that is, the setting where symptom management can be more rapid and effective, because daily assessment and immediate therapeutic changes may provide symptom control in a short period. The aim of this study was to characterize the PGI after 1 week of palliative care and its relationship with PSG in advanced cancer patients admitted to a palliative care unit. The secondary aim was to find possible factors influencing these outcomes.

Subjects, Materials, and Methods

This is an international, longitudinal, observational study that examined several aspects of symptom response in advanced cancer patients. The institutional review boards at all participating centers approved the study. All participants provided written informed consent.

Participants

A consecutive sample of advanced cancer patients who were admitted to six palliative care units from Italy, Brazil, and Greece was assessed for a period of 12 months (from January 2016 to December 2016). Documentation was translated and reviewed by coordinator center.

All institutions were tertiary care hospitals with access to comprehensive cancer treatments and supportive care. All patients underwent symptom evaluation by a specialist palliative care team. Investigators were coordinated by the principal investigator center to help the data collection process, to provide training to the local research staff, and to organize an electronic database for entering data for analysis.

Inclusion criteria were age $\geq$18 years with a diagnosis of advanced cancer. Advanced cancer was considered locally advanced, recurrent, or metastatic disease for solid cancers and relapsed or refractory disease for hematologic tumors [1, 12]. Exclusion criteria were an expected survival of $\leq$2 weeks and a value of $\geq$13 in the Memorial Delirium Assessment Scale (MDAS). MDAS is used to assess the cognitive status of patients and is a validated tool to quantify the intensity of delirium [13].

Table 1. Characteristics of patients

Characteristics	Patients, *n* (%)
Age, years	
Mean	67.2 (11.92)
Range	29–95
Gender	
Male	455 (52)
Female	421 (48)
Karnofsky Performance Status	
Mean	53.3 (13.5)
Range	30–100
Primary Tumor	
Gastrointestinal	229 (26.1)
Lung	207 (23.6)
Breast	112 (12.8)
Prostate	63 (7.2)
Urological	61 (7.0)
Gynecological	58 (6.6)
Head-neck	32 (3.6)
Hematological	28 (3.2)
Liver	25 (2.8)
Others	61 (7.0)
Education	
Illiterate	14 (1.6)
Primary	246 (28.2)
Secondary	217 (24.9)
Tertiary or undergraduate	280 (32.1)
Degree	116 (13.3); 3 missing
House situation	
Alone	122 (14.0)
Partner	399 (45.9)
Partner and sons	212 (24.4)
Sons	89 (10.2)
Nursing home	1 (0.1)
Others	46 (5.3)

Data Collection

Baseline patient characteristics, including age, sex, familiar condition, education level, cancer diagnosis, and Karnofsky performance status, were recorded.

The intensities of 10 common symptoms included in the Edmonton Symptom Assessment Score (ESAS; i.e., pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, feelings of well-being, and sleep) were assessed both at admission (T0) and after a week of palliative care (T7). ESAS is a self-reported tool assessing the intensity of most common psychological and physical symptoms and is a valid and reliable tool for assessing the overall symptom burden, sensible to changes produced by a treatment. ESAS uses a 0 (no symptom) to 10 (worst intensity) point numeric rating scale to examine the intensity of each symptom over the past 24 hours [2, 3]. A screening tool for history of alcohol dependence (CAGE: cut down, annoy, guilt, eye-opener) was also administered. A positive CAGE score

Table 2. Changes (mean and median) in intensity of ESAS symptoms from T0 to T7

ESAS		T0	T7	Δ (T7–T0)	*p* value
Pain	Mean (SD)	4.84 (3.16)	2.85 (2.34)	−2.02 (2.47)	<.001
	Median (Q1–Q3)	5 (2–7)	3 (1–3)		
Nausea	Mean (SD)	1.36 (2.40)	0.65 (1.52)	−0.70 (2.08)	<.001
	Median (Q1–Q3)	0 (0–2)	0 (0–0)		
Asthenia	Mean (SD)	5.97 (2.69)	4.36 (2.53)	−1.59 (2.43)	<.001
	Median (Q1–Q3)	6 (4–8)	5 (3–6)		
Anxiety	Mean (SD)	3.63 (3.01)	2.85 (2.63)	−0.80 (2.38)	<.001
	Median (Q1–Q3)	4 (0–6)	3 (0–5)		
Depression	Mean (SD)	3.27 (3.06)	2.59 (2.70)	−0.67 (2.42)	<.001
	Median (Q1–Q3)	3 (3–5)	2 (0–5)		
Appetite	Mean (SD)	3.91 (3.24)	2.97 (2.81)	−0.88 (2.46)	<.001
	Median (Q1–Q3)	4 (0–7)	3 (0–5)		
Dyspnea	Mean (SD)	1.63 (2.68)	1.02 (1.94)	−0.60 (1.78)	<.001
	Median (Q1–Q3)	0 (0–3)	0 (0–1)		
Drowsiness	Mean (SD)	2.84 (3.13)	2.25 (2.61)	−0.53 (2.51)	<.001
	Median (Q1–Q3)	2 (0–5)	1 (0–4)		
Insomnia	Mean (SD)	2.79 (3.05)	1.88 (2.42)	−0.90 (2.57)	<.001
	Median (Q1–Q3)	2 (0–5)	0 (0–3)		
Well-being	Mean (SD)	5.02 (2.76)	3.59 (2.31)	−1.4 (2.35)	<.001
	Median (Q1–Q3)	5 (3–7)	4 (2–5)		

Abbreviations: ESAS, Edmonton Symptom Assessment Score; Q, quartile; SD, standard deviation; T0, at admission; T7, after a week of palliative care.

of 2 has been shown to be of prognostic value in the opioid management of cancer pain [14].

At admission, for each of the 10 symptoms, patients were asked about their PSG. The question was as follows: "At what level would you feel comfortable with this symptom?" The same 0–10 numeric rating scale used for ESAS was used [12]. Palliative treatment was started according to patients' needs and local policy. One week after (T7), ESAS and PSG were measured to detect changes after a palliative care intervention. Patients were considered to have achieved a PSG response if their follow-up symptom intensity (measured T7) was equal or less than their PSG. PGI of changes after symptom management was measured after a week (T7) according to the following scale: 3 = much better, 2 = better, 1 = a bit better, 0 = the same, −1 = a little worse, −2 = worse, −3 = much worse. The PGI has been used as an anchor for a clinically significant change of a symptom [12]. MCIDs were calculated by PGI of improvement or deterioration at T7 (bit better or a little worse, respectively). The data collection was performed by a palliative care specialist.

Statistical Analysis

The sample size of 800 patients was based on previous studies performed with similar designs and aims, which included 777 patients [10–12]. The analysis performed an explorative data analysis of the symptoms' scales, ESAS, PSG, and PGI using their distributions, means and standard deviations, medians, and interquartile range. We checked symptoms' changes carrying out paired *t* tests estimating mean symptoms' changes and their corresponding standard deviation (SD) with 95% confidence intervals, with I type error set at 5%. Likewise, we tested PSG variations, estimating them according to each symptom. PGI was categorized into three classes: deterioration (PGI ≤ -1), no change (PGI = 0), improvement (PGI ≥ 1). We assessed the minimal symptoms' variation impacting patients' well-being. Furthermore, we calculated the minimal changes associated to PGI grades ranging from −3 up to +3. An analysis of variance (ANOVA) test has been applied to compare PSG and PGI response proportions graphing the pattern detected. ANOVA analysis has been carried out stratifying symptoms' intensity (Mild = 1–3; Moderate = 4–6; Severe = 7–10). The factors associated with PGI scores have been analysed setting a multivariate polytomous logistic regression, setting the reference category at PGI = 0 (no PGI changes). Model fitting has been assessed using a likelihood ratio test. The statistical analysis has been carried out using the statistical software STATA (Release 14; StataCorp, College Station, TX).

Results

Of 1,437 patients screened in the period taken into consideration, 561 patients were excluded, because of refusal (20; 3.6%), age <18 years (4; 0.7%), non-cancer diagnosis (117; 20.8%), an MDAS ≥13 (150; 26.7%), unable to perform the interview due to poor condition (266; 47.4%), and language disturbances (15; 2.7%). Eight hundred seventy-six patients met the inclusion criteria and were taken into consideration for this study.

The mean MDAS value at admission was 4.2 (SD = 3.34); 231 patients (26.4%) had MDAS values ≥7 at T0. Only 30 patients (3.45%) were CAGE positive. The demographics recorded at admission are shown in Table 1.

The mean intensities of ESAS items at T0 and T7 are presented in Table 2. A statistical decrease in symptom intensity for all items was observed after 1 week of palliative care.

At T0, a high percentage of patients reported severe symptom intensity (≥7/10); in a rank order: asthenia (49.6%), pain

Table 3. Minimal clinical differences according to PGI

ESAS change score		PGI						
		Much better	Better	A bit better	The same	A little worse	Worse	Much worse
Pain	*n*	147	167	228	278	18	6	1
	Mean (SD)	−4.60 (2.01)	−3.18 (2.23)	−2.01 (1.50)	−0.32 (1.58)	1.34 (1.68)	4.5 (2.58)	—
Nausea	*n*	65	71	69	614	14	10	3
	Mean (SD)	−3.06 (2.98)	−2.98 (2.43)	−2.11 (2.09)	−0.20 (1.15)	2.5 (2.10)	3.4 (2.80)	3.34 (5.29)
Asthenia	*n*	56	132	284	290	50	26	8
	Mean (SD)	−4.07 (2.49)	−3.38 (2.05)	−2.16 (1.56)	−0.54 (1.78)	0.34 (1.96)	1.61 (2.92)	5.12 (3.75)
Anxiety	*n*	35	68	149	517	53	18	6
	Mean (SD)	−2.74 (3.65)	−2.86 (2.94)	−1.75 (2.26)	−0.52 (1.59)	1.15 (2.19)	2.28 (2.32)	6.17 (3.43)
Depression	*n*	35	46	137	567	40	12	7
	Mean (SD)	−3.14 (3.71)	−3.04 (3.36)	−1.71 (2.53)	−0.40 (1.68)	0.34 (2.13)	3.25 (1.60)	3.43 (2.64)
Appetite	*n*	46	82	153	491	49	20	4
	Mean (SD)	−4.28 (3.60)	−2.82 (2.88)	−2.05 (1.79)	−0.24 (1.63)	1.04 (1.89)	2.70 (2.18)	3.50 (3.00)
Dyspnea	*n*	36	51	97	636	15	7	2
	Mean (SD)	−2.64 (3.25)	−2.64 (2.43)	−1.80 (1.87)	−0.21 (1.17)	1.40 (2.23)	2.57 (3.55)	
Drowsiness	*n*	34	56	111	534	68	35	8
	Mean (SD)	−3.00 (3.66)	−3.09 (3.25)	−2.02 (2.45)	−0.34 (1.43)	1.32 (2.49)	3.28 (3.09)	3.62 (3.70)
Insomnia	*n*	31	72	155	547	31	5	5
	Mean (SD)	−3.58 (4.29)	−3.51 (2.99)	−1.92 (2.26)	−0.37 (1.72)	1.87 (3.14)	3.80 (1.30)	3.00 (6.00)
Well-being	*n*	58	103	264	365	38	13	1
	Mean (SD)	−4.33 (3.56)	−2.79 (2.63)	−1.80 (1.46)	−0.68 (1.64)	1.26 (2.00)	1.80 (3.03)	

Abbreviations: —, none; ESAS, Edmonton Symptom Assessment Score; PGI, patient global impression; SD, standard deviation.

Table 4. Symptom intensity distribution of PSG recorded at T0

Symptom	PSG at T0, *n* (%)										
	0	1	2	3	4	5	6	7	8	9	10
Pain	485 (55.7)	70 (8.0)	137 (15.7)	93 (10.7)	59 (6.8)	16 (1.8)	8 (0.9)	3 (0.3)	0	0	0
Nausea	714 (82.1)	25 (2.9)	65 (7.5)	36 (4.1)	21 (2.4)	7 (0.8)	2 (0.2)	0	0	0	0
Asthenia	327 (37.5)	84 (9.64)	150 (17.2)	114 (13.1)	124 (14.2)	56 (6.4)	11 (1.3)	4 (0.5)	1 (0.1)	0	0
Anxiety	525 (60.4)	100 (11.5)	111 (12.8)	65 (7.5)	45 (5.2)	15 (1.7)	4 (0.5)	1 (0.1)	3 (0.3	0	0
Depression	562 (64.6)	72 (8.3)	104 (11.9)	68 (7.8)	42 (4.8)	14 (1.6)	6 (0.7)	2 (0.2)	0	0	0
Appetite	442 (50.9)	70 (8.1)	137 (15.8)	95 (10.9)	76 (8.8)	37 (4.3)	4 (0.5)	2 (0.2)	3 (0.3)	1 (0.1)	1 (0.1)
Dyspnea	709 (81.6)	50 (5.7)	65 (7.5)	26 (3.0)	11 (1.3)	6 (0.7)	2 (0.2)	0	0	0	0
Drowsiness	552 (63.4)	56 (6.4)	100 (11.5)	73 (8.4)	52 (6.0)	27 (3.1)	6 (0.7)	3 (0.3)	1 (0.1)	0	0
Insomnia	607 (69.8)	69 (7.9)	73 (8.4)	69 (7.9)	37 (4.3)	11 (1.3)	1 (0.1)	2 (0.2)	0	0	0
Well-being	416 (47.9)	77 (8.9)	163 (8.9)	93 (10.7)	72 (8.3)	38 (4.4)	6 (0.7)	3 (0.3)	0	0	0

Abbreviations: PSG, personalized symptom goals; T0, at admission.

intensity (35.9%), well-being (31.5%), appetite (25.1%), anxiety (19.4%), depression (17.7), drowsiness (17.0%), insomnia (15.4%), dyspnea (9.6%), and nausea (5.5%). At T7, a lower percentage of patients had symptoms of severe intensity ($\geq$7/10); in a rank order: asthenia 19%, appetite 11.8%, poor bell being 9.2%, depression 8.7%, drowsiness 8.1%, pain 7.2%, anxiety 6.4%, insomnia 5.2%, dyspnea 2.7%, and nausea 0.9%. These differences were highly significant ($p < .0001$, chi-square test).

PGI

Data regarding PGI are presented in Table 3. Patients perceived an MCID (a bit better) with an improvement of symptom intensity ranging from 1.71 to 2.16 points, with some differences among symptoms. A better improvement ranged from 2.64 to 3.51 points, and a much better improvement ranged from 2.64 to 4.60 points. In 278 patients (31.7%), the clinical condition was the same. A minority of patients deteriorated. A little worse ranged from −0.34 to −2.5 points, with some differences among symptoms, with nausea having the highest value (−2.5). Worse ranged from −1.61 to −3.8 points, and much worse ranged from −3 to −7.17 points.

PSG

The distribution of PSG for the different ESAS items recorded at T0 and changes at T7 are shown in Tables 4 and 5. PSG ranged between 0.40 (for dyspnea) and 1.84 (asthenia). Most patients

Table 5. Mean and median PSG recorded at T0 and T7

PSG		T0	T7	Δ (T7–T0)	*p* value
Pain	Mean (SD)	1.16 (1.54)	0.83 (1.22)	−0.32 (1.28)	<.001
	Median (Q1–Q3)	0 (0–2)	0 (0–2)		
Nausea	Mean (SD)	0.45 (1.08)	0.37 (0.94)	−0.09 (0.76)	<.001
	Median (Q1–Q3)	0 (0–0)	0 (0–0)		
Asthenia	Mean (SD)	1.84 (1.79)	1.42 (1.63)	−0.41 (1.58)	<.001
	Median (Q1–Q3)	2 (0–3)	1 (0–3)		
Anxiety	Mean (SD)	0.95 (1.45)	0.76 (1.28)	−0.20 (1.30)	<.001
	Median (Q1–Q3)	0 (0–2)	0 (0–2)		
Depression	Mean (SD)	0.89 (1.42)	0.79 (1.37)	−0.10 (1.28)	.013
	Median (Q1–Q3)	0 (0–2)	0 (0–1)		
Anorexia	Mean (SD)	1.38 (1.72)	1.25 (1.63)	−0.11 (1.34)	.007
	Median (Q1–Q3)	0 (0–3)	0 (0–2)		
Dyspnea	Mean (SD)	0.40 (0.30)	0.30 (1.35)	−0.08 (1.26)	.036
	Median (Q1–Q3)	0 (0–0)	0 (0–0)		
Drowsiness	Mean (SD)	1.01 (1.52)	0.89 (1.42)	−0.10 (1.25)	.007
	Median (Q1–Q3)	0 (0–5)	0 (0–2)		
Insomnia	Mean (SD)	0.74 (1.32)	0.64 (1.18)	−0.11 (1.08)	.002
	Median (Q1–Q3)	0 (0–1)	0 (0–1)		
Well-being	Mean (SD)	1.40 (1.12)	1.12 (1.47)	−0.28 (1.41)	<.001
	Median (Q1–Q3)	1 (0–2)	0 (0–2)		

Abbreviations: PSG, personalized symptom goals; Q, quartile; SD, standard deviation; T0, at admission; T7, after a week of palliative care.

Table 6. PSG (symptom intensity ≤ PSG) and PGI, according to different categories of symptom intensity, recorded at T0

	Mild at T0, *n* (%)		Moderate at T0, *n* (%)		Severe at T0, *n* (%)		Total, *n* (%)	
Symptom	PSG response	PGI	PSG response	PGI	PSG response	PGI	PSG response	PGI
Pain	169 (56.5)	77 (25.5)	77 (29.4)	220 (84.0)	85 (27.0)	276 (87.6)	331 (37.8)	573 (65.4)
Nausea	611 (85.8)	114 (16.0)	61 (53.0)	82 (71.3)	26 (53.1)	39 (79.6)	698 (79.7)	235 (26.8
Asthenia	69 (44.2)	54 (34.6)	64 (22.5)	155 (54.4)	80 (18.4)	293 (67.4)	213 (24.3)	502 (57.3)
Anxiety	247 (58.5)	83 (19.7)	59 (20.8)	109 (38.5)	36 (21.0)	90 (52.6)	342 (39.0)	282 (32.2)
Depression	298 (64.6)	76 (16.5)	53 (20.5)	90 (34.7)	44 (28.2)	84 (53.8)	395 (45.1)	250 (28.5)
Anorexia	265 (68.3)	61 (15.7)	59 (22.1)	125 (46.8)	50 (22.6)	126 (57.0)	374 (42.7)	312 (35.6)
Dyspnea	573 (84.5)	82 (12.1)	38 (33.7)	71 (62.8)	21 (24.7)	63 (74.1)	632 (72.1)	216 (24.7)
Drowsiness	373 (71.6)	54 (10.4)	55 (26.8)	86 (41.9)	35 (23.3)	91 (60.7)	463 (52.8)	231 (26.4)
Insomnia	387 (71.8)	88 (16.3)	65 (32.3)	107 (53.2)	35 (25.7)	93 (68.4)	487 (55.6)	288 (32.9)
Well-being	118 (50.0)	70 (29.7)	68 (18.8)	189 (52.2)	64 (23.0)	199 (71.6)	250 (28.5)	458 (52.3)

Abbreviations: PGI, patient global impression; PSG, personalized symptom goals; T0, at admission; T7, after a week of palliative care

had a PSG of ≤3 for all ESAS items as a target at T0. In a rank order: pain 90.1%; asthenia 77.5%; nausea 96.5%; depression 92.6%; anxiety 92.2%; drowsiness 89.8%; dyspnea 97.8%; insomnia 94.1%; appetite 85.7%; and well-being 86.3%. About 5% of patients targeted their symptoms at ≥4, being >10% for asthenia, appetite, and well-being.

At T7, a statistically significant increase in the proportion of patients who achieved their PSG was observed (pain, $n = 331$ [37.8%]; nausea, $n = 698$ [79.7%]; asthenia, $n = 213$ [24.3%]; anxiety = 342 [39%]; depression, $n = 395$ [45.1%]; appetite, $n = 374$ [42.7%]; dyspnea, $n = 632$ [72.1%]; drowsiness, $n = 463$ [52.8%]; insomnia, $n = 487$ [55.6%]; well-being, $n = 250$ [28.5%]; $p = .00001$). All PSG targets significantly changed after 1 week of palliative care, according to a correspondent decrease in all ESAS items (Pearson's correlation $p = .00001$).

PSG Response and PGI

Data regarding the PSG response and PGI, according to the different levels of intensity recorded at baseline (T0), are represented in Table 6. PGI response ranged between 18.4% and 85.8%. Patients with high intensity of ESAS items at T0 achieved a favorable PGI response even when the target, based on PSG response, was not achieved.

Table 7. Multivariate analysis of factors influencing PGI

PGI	Factor	OR	*p* value	95% CI
Pain	Karnofsky	0.97	<.001	0.96–0.98
	MDAS	0.98	.65	0.93–1.10
	Education	0.78	.01	0.65–0.93
	Intensity at T0	1.58	.00	1.50–1.70
	PSG at T0	1.29	.00	1.11–1.52
Asthenia	Karnofsky	1.00	.89	0.99–1.10
	Education	0.78	<.001	0.66–0.90
	Intensity at T0	1.26	<.001	1.20–1.35
	PSG at T0	1.02	.64	0.93–1.14
Nausea	MDAS	0.99	.92	0.94–1.10
	Lung cancer	1.21	.83	0.92–1.12
	Gastrointestinal cancer	1.35	.64	0.94–1.27
	Intensity at T0	1.93	<.001	1.75–2.14
	PSG at T0	0.85	.15	0.67–1.10
Depression	Karnofsky	0.97	<.001	0.95–0.98
	Education	0.76	<.001	0.64–0.90
	Intensity at T0	1.27	<.001	1.20–1.35
	PSG at T0	1.15	.06	1.01–1.30
Anxiety	Age	0.98	.06	0.97–1.00
	Gender	1.22	.23	0.88–1.69
	Lung cancer	1.31	.11	0.87–1.02
	Gastrointestinal cancer	1.45	.16	0.91–1.14
	Karnofsky	0.96	<.001	0.94–0.97
	MDAS	0.91	<.001	0.85–0.96
	Intensity at T0	1.20	<.001	1.13–1.28
	PSG at T0	1.31	<.001	1.16–1.50
Drowsiness	Karnofsky	0.98	<.001	0.96–0.99
	MDAS	0.95	.14	0.89–1.00
	Intensity at T0	1.50	<.001	1.40–1.61
	PSG at T0	1.04	.54	0.91–1.19
Dyspnea	Karnofsky	0.97	.00	0.96–0.98
	Lung cancer	1.78	.02	1.11–2.87
	Gastrointestinal cancer	0.18	.03	0.04–0.81
	Intensity at T0	1.54	<.001	1.41–1.68
	PSG at T0	1.68	<.001	1.28–2.22
Appetite	Karnofsky	1.00	.81	0.99–1.01
	Lung cancer	1.24	.07	0.98–1.11
	Gastrointestinal cancer	1.38	.09	0.89–1.13
	Breast Cancer	1.11	.12	0.97–1.08
	Intensity at T0	1.41	<.001	1.32–1.51
	PSG at T0	0.98	.69	0.87–1.09
Insomnia	Karnofsky	0.98	.01	0.96–0.99
	MDAS	0.98	.45	0.92–1.04
	Intensity at T0	1.53	<.001	1.43–1.65
Well-being	Karnofsky	0.99	.23	0.98–1.00
	MDAS	1.01	.59	0.96–1.06
	Intensity at T0	1.31	<.001	1.23–1.40
	PSG at T0	1.13	.02	1.01–1.26

Abbreviations: CI, confidence interval; MDAS, Memorial Delirium Assessment Scale; OR, odds ratio; PGI, patient global impression; PSG, personalized symptom goals; T0, at admission.

Factors Associated with PGI

After performing univariate analysis to examine factors related to the outcomes, several factors were found independently associated with PGI for each symptom in the multivariate analysis. In particular, symptom intensity, as well as PSG recorded at T0, were the most frequent factors independently associated with a best PGI for ESAS items, whereas high levels of Karnofsky had a lower odd ratio for PGI improvement for pain, depression, drowsiness, dyspnea, and insomnia. The other factors are explicated in Table 7.

Discussion

This international, multicenter study performed in different palliative care units, recruiting a large number of patients, provided interesting data that could help physicians in personalizing treatment, focusing on what and how much patients would improve their condition, in terms of symptom intensity. Symptom intensities significantly improved after 1 week of palliative care treatment. Specifically, to make patients able to perceive a minimal improvement, a change of about two points was required for most symptoms. Values were more variable with deterioration. PSG response was also achieved in many patients, and this was remarkable in patients who had higher symptom intensity at admission. Baseline symptom intensity and PSG were the most important factors determining an improvement in PGI. Indeed, a high Karnofsky level less likely provided an improvement in PGI.

PGI

As expected, symptom intensity significantly improved after 1 week of palliative care. One week has been invariably reported to be an acceptable period to stabilize patients admitted to a palliative care unit, where symptom management can be more intensive and effective [1]. PGI improved, particularly for pain, possibly as a consequence of a decrease in intensity of all ESAS items. Only a minority of patients felt that their pain had worsened, and in about 30% of patients, the clinical condition did not change. For many symptoms, including nausea, anxiety, depression, dyspnea, appetite, drowsiness, and insomnia, no significant changes were found in the majority of patients. In a previous study, based on PGI scale, globally half of patients had a clinically significant improvement, 32% no significant changes, and 21% a deterioration [12].

The finding of the MCID, evaluated by PGI, suggested that patients require at least two points of a numerical scale from 0 to 10 to be able to distinguish a minimal improvement, more than two points to feel better, and more than three points to

stay much better, on average. This in contrast with previous data in which values ranging from 0.1 to 1.2 and 0.1 to 1.8 of MCID for improvement and deterioration, respectively, were found among the different ESAS items [7]. This can be explained by the retrospective design of the study, the use of categories anchored to well-being rather than raw numbers, the outpatient setting of radiotherapy, and the longer intervals among observations (4–12 weeks). Indeed, different outcomes can be achieved when moving from one category to another of well-being, that is a multidimensional construct, unable to detect the weight of each symptom [15]. In a previous study, an MCID between 1 and 2 was found for the majority of symptoms. In the sensitivity-specificity analysis, however, that was less than 80%, the universal cutoff for both improvement and deterioration was ≥1 [12]. As opposed to the present study, in which patients were admitted to a palliative care unit and followed up for a week, this study was performed in an outpatient setting with a 3-week follow-up interval. One could wonder if an optimal management requires different magnitude of effect, for example, that patients feel better rather than only a bit better. In this case, a significant PGI would require 2–3 points of differences with baseline data. Of interest, for acute pain, ≥2 points or 33% decrease are considered to be the cutoff for MCID [9, 16], resembling data found in this study.

The factors principally related to PGI improvement have never been explored. The level of symptom intensity and PSG at admission seem to have a role. The higher the symptom intensity, the better the PGI, despite not all patients having achieved their target, as expressed by PSG. This observation can be explained by the best possibilities to improve a symptom when this has an elevated level of intensity, for example, for pain, that was the typical example of a manageable symptom because, different from other symptoms, there are many efficacious therapeutic options. Similarly, higher PSG were also independently associated with a better PGI. This can be explained by the fact that patients experiencing even a high level of symptom intensity are more likely to achieve a better satisfaction. In this study, 5%–10% of patients had higher values of PSG and admission and possibly required only minimal changes of symptom intensity to improve their condition in terms of PGI.

PSG

Most patients admitted to the palliative care unit had as a target a PSG of ≤3 for all ESAS items, as reported in previous trials [10, 11]. Although a relevant percentage of patients achieved the target after 1 week of treatment, a gap between response rates evaluated by achieving PSG and PGI has been found. It was expected that patients' expectations would be superior to the real personal outcome achieved after a palliative care intervention. This is confirmed by another finding of this study with PSG changing after a week of treatment, accordingly to the improvement in intensity of ESAS items, lowering the targeted intensity, as patients would achieve something more once an improvement has been achieved.

In a previous retrospective study, PSG remained unchanged in outpatients at a follow-up visit performed 1–6 weeks after the initial consultation [10]. This dynamic aspect underlines the utility of PSG rating the individual improvement rather than an average change. The finding that the higher the symptom intensity at admission, the larger the number of patients having a favorable PSG response is in contrast with previous studies in which patients with a lower baseline symptom intensity were more likely to achieve the PSG response [10, 11]. As mentioned before, differences may rely on the different setting and evaluation times.

Important information was gathered from the multivariate analysis, in which some factors were independently associated with PGI for each symptom examined. The symptom intensity and PSG recorded at T0 were independently associated with a positive PGI for many ESAS items. As mentioned above, PGI may be perceived to be positive much more often in patients starting from high levels of symptom intensity. The clinical response has been reported to be higher among patients with baseline severe intensity [10]. Similarly, patients with higher PSG (that means modest requests or limited expectations) may experience a better impression of improvement. Of interest, about 5%–10% of patients, depending on the symptom examined, have these characteristics.

In contrast, patients with higher Karnofsky level had fewer chances for PGI improvement, particularly for some symptoms like pain, depression, drowsiness, dyspnea, and insomnia. One could argue that patients with a lower Karnofsky status may be more positively impressed after a palliative care treatment or have fewer expectations. This aspect deserves specific studies.

This study has some limitations. In comparison with previous trials examining issues regarding the clinical changes as perceived by patients and PSG, data were gathered from a large number of patients recruited in palliative care units where symptom assessment and therapeutic changes are more frequently performed to achieve an improvement in the clinical condition. Therefore, data are not extendable to outpatients or home-care settings. In this study, a PGI scale was used to test MCID, that is, the patients' feeling to perceive a clinical change. This proved to be easy for patients, although other external criteria could be useful and require further investigation.

Conclusion

PSG and PGI seem to be relevant for patients' assessment and decision-making process, translating in terms of therapeutic intervention. This study also suggests that some factors may be implicated in determining the individual target and clinical response. Further investigation should eventually confirm these preliminary data in other palliative care settings.

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Disclosures

The authors indicated no financial relationships.

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For Further Reading:
Stuart L. Goldberg, Dhakshila Paramanathan, Raya Khoury et al. A Patient-Reported Outcome Instrument to Assess Symptom Burden and Predict Survival in Patients with Advanced Cancer: Flipping the Paradigm to Improve Timing of Palliative and End-of-Life Discussions and Reduce Unwanted Health Care Costs. ***The Oncologist*** 2019;24:76–85; first published on September 28, 2018.

Implications for Practice:
A seven-item patient-reported outcome (PRO) instrument was administered to 1,191 patients with advanced cancers. Patients self-reporting higher levels of physical and psychological symptom burden had inferior overall survival rates. High individual item symptom PRO responses should serve as a useful trigger to initiate supportive interventions, but when scores indicate global problems, discussions regarding end-of-life care might be appropriate.