

Prevalence and Management of Symptoms during the Last Month of Life

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ABSTRACT: **Background:** The prevalence and severity of the "most troublesome" symptoms in terminally ill patients are well known and have been studied in many settings. However, these symptoms change during the course of advanced disease.

Objectives: To evaluate the range and trajectory of symptoms in the final stage of life as measured a month prior to death.

Methods: Patients with an expected prognosis of less than 6 months were recruited for the study. Excluded were non-Hebrew or Russian speakers, and patients with cognitive impairment or a diagnosis of brain tumor. A structured questionnaire was used to interview patients and their caregivers at home every 2 weeks until death. We present a comparison analysis of 45 patients who completed both interviews 2 and 4 weeks before death.

Results: There were five symptoms (fatigue, pain, reduced well-being, lack of appetite, somnolence) that were reported most frequently, occurring in more than 70% of the patients. Most of the symptoms showed a worsening trend towards death.

Conclusions: Assessing the presence and severity of symptoms as a guide to start or modify treatment is recommended. Knowledge of how symptoms change in the final stage of life could better assist in the management of resources and could help patients and their families in their final preparations.

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KEY WORDS: symptoms management, end-of-life, terminally ill

In a systematic review of the prevalence of symptoms in terminal cancer patients 37 symptoms were identified (assessed in at least five studies) occurring in over 10% of the patients. Overall, fatigue, pain, lack of energy, weakness, and appetite loss were the most frequent symptoms, occurring in more than 50% of the patients. During the last weeks of life, fatigue, weight loss, weakness and loss of appetite were observed in more than 50% of patients [1]. The prevalence and severity of the "most troublesome" symptoms are well known in many settings [2]. However, little is known about the longitudinal characteristics of symptoms experienced by cancer patients near death.

Although patients suffer from different cancers, they all share a common pathway. Thus, in the last days of life, clinical evidence suggests that the prevalence and intensity of symptoms change during the course of advanced disease. Using death as the end-point and looking at these measurements within this time frame, rather than evaluating the prevalence of the symptoms at different points during the disease course, would be most informative [3]. Knowledge of symptom prevalence is important for clinical practice as it enables doctors and nurses to focus attention on the most common symptoms. In addition, this information may help to anticipate problems and plan the care for patients, educate clinical staff, direct assessments of health care needs, and plan service delivery [4].

The main aim of this study was to obtain a reliable assessment of the range and trajectory of symptoms in the final stage of life as measured a month prior to the death of the patient.

PATIENTS AND METHODS

In Israel, health care is provided under the National Insurance Law by four health maintenance organization providers – Clalit Health Services being the largest, covering 55% of the population. In the Negev District there are approximately 1200 new cancer patients per year and 400–500 die annually (personal communication, P. Shvartzman, 2009). The Clalit home palliative care service in Beer Sheva and Kiryat Gat (a town in southern Israel) cares for 28–35 patients on average at any given time, totaling about 120 patients per year. The average length of stay in the home hospice unit is 45 days [5]. Referrals are received by the Oncology Institute, primary care physicians in the community, or directly by families and patients. Services are provided only in these specific catchment areas.

STUDY POPULATION

The study group consisted of patients who met the hospice benefit criteria, were treated by the Home Palliative Care Service and had an expected prognosis of less than 6 months [6]. Patients included in the cohort were cancer patients aged 20 years and above, who spoke either Hebrew or Russian, and gave their informed consent. Patients too ill, unable to compre-

hend, did not speak Hebrew or Russian, and had a diagnosis of brain tumor or cognitive impairment were excluded.

DATA COLLECTION AND STUDY TOOLS

Data were collected during the years 2001–2003. Patients were recruited prospectively and interviewed at home every 2 weeks until death, by means of a structured questionnaire. The following tools were used:

- **Edmonton Symptom Assessment Scale Questionnaire (ESAS)** includes nine Likert scales for the following symptoms: nausea, fatigue, depression, anxiety, sleepiness, appetite, shortness of breath, general well-being, constipation, and mental clarity. The symptoms were measured on a scale of 0 to 10, with 0 indicating the absence of the symptom and 10 indicating the highest severity. This tool was validated through the Rotterdam Symptom Checklist and showed good suitability [7].
- **Brief Pain Inventory-Short Form (BPI-SF)** was used to measure and characterize pain and the influence of pain (reactive dimension) on different aspects of daily life (general activity, mood, sleep, relationships with other people, work). The BPI questionnaire includes a rating scale of 0 to 10. This tool was validated in Hebrew in a previous study [8] and has been utilized as an outcome measure in various clinical trials [9,10].

The questionnaires were translated from English to Hebrew using the double translation method [11] and were consequently culturally adapted.

STATISTICAL ANALYSIS

Patients included in the analysis were interviewed between 2 and 4 weeks before death and completed two interviews. All analyses were conducted using MS EXCEL™, MS ACCESS™ and SPSS™ 15.0. Significance between periods was tested using the Friedman Test, a one-way ANOVA test for continuous variables, and a chi-square analysis for categorical variables. *P* values ≤ 0.05 were considered statistically significant.

RESULTS

In this paper we present a comparison analysis of 45 patients who completed both interviews 2 and 4 weeks before death. Table 1 shows the sociodemographic characteristics of the study population. The majority of patients were male (64.4%), with an average age of 70, married (60.5%), and born in Eastern Europe (68.2%).

Table 2 summarizes the prevalence and average severity scores of the 18 symptoms recorded at two different times. We categorized the symptoms into two groups: 11 psychological and somatic symptoms and 7 symptoms that impact

Table 1. Study population’s sociodemographic characteristics

	Interviewed 2 and 4 weeks before death (n=45)	
	n	%
Gender		
Male	29	64.4%
Female	16	35.6%
Age (yrs)		
Mean ± STD	69.8 ± 10.8	
Range	44–85	
Marital status		
Married	26	60.5%
Single/Widowed/Divorced	17	39.5%
Country of birth		
Israel	4	9.1%
East Europe	30	68.2%
West Europe	0	0.0%
Middle East	2	4.5%
North Africa/Asia	7	15.9%
Other	1	2.3%

Table 2. Prevalence and average severity scores of physical symptoms at 4 and 2 weeks before death*

Symptom	Weeks before death				N	Friedman test		
	4		2			Chi-square	df	Sig.
Worst pain	5.4	3.2	6.4	3.0	41	3.2	1	0.07
Average pain	3.8	2.3	4.7	2.5	38	4.2	1	0.04
Tiredness	7.1	2.6	8.1	2.2	44	4.5	1	0.03
General feeling	6.6	2.2	7.6	2.4	43	6.5	1	0.01
Clarity of thought	1.9	2.1	2.8	2.8	40	5.5	1	0.02
Appetite	5.8	2.7	6.6	2.7	43	0.5	1	0.48
Sleepiness	5.5	2.8	5.9	2.8	43	0.3	1	0.61
Anxiety	4.6	3.4	5.2	3.6	43	1.1	1	0.29
Depression	4.7	3.1	4.7	3.1	41	0.8	1	0.60
Constipation	4.4	3.2	4.8	3.4	40	1.7	1	0.19
Dyspnea	2.9	3.4	3.4	3.6	42	0.7	1	0.39
Nausea	3.1	2.8	2.3	2.7	44	1.7	1	0.19

*Severity measured on a scale of 0–10: 0 = no symptom, 10 = worst severity of symptom

daily activities. Five symptoms – tiredness, pain (average and worst pain), reduced general well-being, lack of appetite and sleeplessness – were the most frequent and occurred in more than 70% of patients.

For the majority of the symptoms a worsening trend towards death was observed, though these differences were not statistically significant, except for pain (for both worst and average pain), general well-being and mental clarity. Only nausea showed amelioration towards death, although this was not statistically significant.

BPI = Brief Pain Inventory

Table 3. Prevalence and average severity scores of life impact components at 4 and 2 weeks before death*

Symptom	Weeks before death				Friedman test			
	4		2		N	Chi-square	df	Sig.
	Mean	SD	Mean	SD				
Routine work	9.3	1.2	9.5	1.1	39	3	1	0.08
General activities	8.3	1.8	9.0	1.6	40	7.2	1	0.007
Walking ability	7.8	2.2	8.1	2.1	40	0.9	1	0.34
Enjoyment of life	7.3	2.3	7.9	2.3	42	1.7	1	0.19
Mood	7.2	2.2	7.8	2.1	39	0.7	1	0.38
Sleep	5.8	2.9	5.6	3.0	42	0.03	1	0.86
Relationships	4.0	3.3	4.1	3.1	42	2	1	0.66

*Severity measured on a scale of 0–10: 0 = no symptom, 10 = worst severity of symptom

Table 4. Comparison of patients with severe symptoms (above and below severity level of 5) at 2 and 4 weeks before death

Symptoms	Four weeks before death		Two weeks before death		P value
	N	%	N	%	
Average pain					
< 5	29	70.7%	18	43.9%	< 0.01
≥ 5	12	29.3%	23	56.1%	
Lightest pain					
< 5	38	88.4%	27	65.9%	< 0.01
≥ 5	5	11.6%	14	34.1%	
Clarity of thought (alertness)					
< 5	38	88.4%	29	70.7%	< 0.05
≥ 5	5	11.6%	12	29.3%	

Table 3 demonstrates the symptoms impacting daily activities. All symptoms showed a worsening trend towards death, although the difference was significant only for reduction in general activities. In Table 4, patients with symptoms rated above or below 5 in severity level are compared between the two periods. The general trend of symptoms worsening towards the time of death was observed in pain (average pain rated above 5 on the severity scale increased from 29.3% to 56.1%, $P < 0.01$, and the lightest pain endured during the week increased from 11.6% to 34.1%, $P < 0.01$) and mental clarity (severe loss of clarity increased from 11.6% to 29.3% of patients, $P < 0.05$). For all the other symptoms – worst pain, sense of well-being, lack of appetite, drowsiness, anxiety, depression, constipation, dyspnea, routine work, general activity, difficulty walking, loss of enjoyment from life, depressed mood, insomnia, and relationships – there was a notable trend of worsening as death approached, with increased severity, although none of these differences were statistically significant.

DISCUSSION

The aim of this study was to assess the range and trajectory of symptoms in the final stages of life. As a prospective study,

the time of death was unknown at the point of recruitment. The underlying assumption was that interviewing patients every 2 weeks would cover any anticipated changes in their symptom management and daily functioning. Our findings showed a general trend of increased symptom severity as death approached.

A review of the literature demonstrated a lack of studies tracking the prevalence and severity of symptoms over time until the moment of death. Most of the studies are limited in scope, addressing symptom prevalence only in advanced cancer patients and in specific settings. The first systematic review on symptom prevalence in patients with incurable cancer analyzed results across 5 studies and identified 37 symptoms occurring in more than 10% of patients [1]. Fatigue, pain, lack of energy, weakness and appetite loss were the most frequent symptoms, occurring in over 50% of patients. During the last 2 weeks of life, fatigue, weight loss, weakness and appetite loss occurred in more than 50% of patients [1]. This coincides with the findings of our study; however, that systematic review [1] did not measure changes in symptoms leading up to the time of death.

This survey emphasizes the importance of the current lack of a standardized comprehensive assessment for symptoms seen in palliative care settings. Some symptoms are freely mentioned by patients or are explicitly and routinely addressed by doctors and nurses. For other symptoms, studies using a questionnaire showed a higher prevalence of reported symptoms than in studies using a standardized interview [1]. In our study, reported pain worsened close to death, although nausea symptoms subsided. All of the most prevalent 18 symptoms were observed in more than 50% of patients. In our study, only standardized interviews were used.

Previous papers describing the intensity of symptoms as death approached also found an increase in symptom intensity before death [12]. A comparison of initial symptom severity scores with those 1 week after admission and 2 days before death suggested six common symptom changes observed across the patient cohort. These symptom patterns can be divided into two categories according to the relative symptom severity measured 1 week after admission and 2 days before death. The first category includes symptom patterns that showed improvement with palliative care, or a continuous static pattern (pain, depression, anxiety, aggression, restlessness, abdominal fullness, constipation, dizziness, insomnia) [12]. The second category of symptoms, which included anorexia-cachexia syndrome and dyspnea, as well as fatigue, nausea/vomiting, taste alteration, diarrhea, dry mouth, and night sweats, did not show any amelioration and worsened over time. In our study, there was a worsening in all major symptoms 2 weeks before death, although the increase in intensity was too small to be statistically significant. This may be due to the fact that the study sample size was too small to

demonstrate these differences, or it can be attributed to the nature of palliative care with patients treated intensively as death approaches.

We did not evaluate performance status but noted some deterioration in several parameters, such as routine work, general activity, and difficulty in walking in the 2 weeks before death. Similarly, performance scores have been found to be inversely related to the survival time [13], with low performance scores associated with shortened survival. Mercadante et al. [3] showed that changes in the prevalence and intensity of symptoms according to the Karnofsky performance score may yield more meaningful results than assessment of individual symptoms.

There are a number of limitations to our study:

- The study population was quite small. Since this was a prospective study, the date of death was unknown and many patients were thus excluded in the comparative longitudinal analysis
- There was no true control population for comparison
- It was difficult to compare our study with others as the assessment scales used and the models of care were different.

CONCLUSIONS

As noted in previous studies, the intensity of physical symptoms increases as death approaches. However, the results from this investigation suggest that this increase can be reduced with intensive palliative care. As a result of our study we recommend that physicians and researchers not only use the presence and severity of symptoms as a guide when starting or modifying treatment regimens, but that they be aware of the way in which symptoms evolve in the final stage of life. Ultimately this knowledge will lead to improved resource management, with clinicians delivering higher quality care and with patients and their families more fully informed as they make their end-of-life preparations.

Capsule

Development of therapies to treat lung pathologies

Although few organisms are able to fully regenerate new tissue after injury, tissue can often be repaired. The specific mechanisms that drive such repair, however, are not fully elucidated. Two studies used different models of lung injury in mice to uncover mechanisms that drive lung repair and regeneration. Kumar et al. (*Cell* 2011; 147: 525) infected mice with influenza A virus, severe cases of which can cause extensive, life-threatening lung pathology in humans. Despite early damage to lungs after infection, they had essentially returned to normal 3 months later. Repair was initiated by stem cells that proliferated in the bronchiolar epithelium

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and migrated to sites of damage, where they formed clusters around bronchioles and differentiated into alveolar structures destroyed by the infection. Taking a different approach, Ding et al. (*Cell* 2011; 147: 539) surgically removed the left lung of mice, which is known to drive the formation of more alveoli in the remaining lung. Pulmonary capillary endothelial cells initiated this regeneration by producing angiocrine factors, which promoted the proliferation of epithelial progenitor cells. Studies such as these may aid in the development of therapies to treat lung pathologies.

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