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SPECIAL ARTICLE

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The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients

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Abstract A multivariate analysis of the data was conducted to evaluate the effects of age, gender, and performance status on symptom profile. A comprehensive prospective analysis of symptoms was conducted in 1,000 patients on initial referral to the Palliative Medicine Program of the Cleveland Clinic. The median number of symptoms per patient was 11 (range 1–27). The ten most prevalent symptoms were pain, easy fatigue, weakness, anorexia, lack of energy, dry mouth, constipation, early satiety, dyspnea, and greater than 10% weight loss. The prevalence of these 10 symptoms ranged from 50% to 84%. Younger age was associated with 11 symptoms: blackout, vomiting, pain, nausea, headache, sedation, bloating, sleep problems, anxiety, depression, and constipation. Gender was associated with 8 symptoms. Males had more dysphagia, hoarseness, >10% weight loss and sleep problems; females, more early satiety, nausea, vomiting, and anxiety. Performance status was associated with 14 symptoms. Advanced cancer patients are polysymptomatic. Ten symptoms are highly prevalent. Symptom prevalence for 24 individual symptoms differs with age, or gender, or performance status.

Key words Symptoms · Cancer · Age · Gender · Performance status

Introduction

The incidence and mortality of cancer are increasing. The 1993 figure of 526,000 deaths due to cancer was double that in 1963 (260,000) [1], so that now each minute one person dies of cancer in the United States. Cancer care has been largely cure oriented [2], although most people who develop cancer and are not cured by surgery die of their disease. We are able to cure some uncommon cancers, but have made little or no impact on the mortality from more common diseases, with one author commenting that "intense effort focused largely on improving treatment must be judged a qualified failure" [2]. Until recently, issues related to symptomatic care of advanced cancer have been ignored [3]. Although the goal of curing cancer is laudable, the excessive emphasis on antitumor therapy has tended to obscure the real needs of patients and families dealing with a serious illness [2]. Major problems, such as pain control, have been neglected. For the patient suffering from advanced cancer the symptoms are the focus of

concern. It is inexcusable that the common problems experienced by the half million Americans who die of cancer every year should be treated as if they were of little consequence. We did this study because despite the huge morbidity and mortality, the symptomatology of cancer has been only partly described [3–9]. Our objectives were to identify common symptoms and to see whether symptoms were related to age, gender, or performance status. Symptoms are also important because they may provide information about the pathophysiology of cancer [10] and its prognosis [5], and help in directing palliative management [11, 12]. Four previous reports have been derived from the data base [3, 8–10]. We noted preliminary data suggesting that age and gender appeared to affect the prevalence and severity of certain symptoms. This report now examines all this in detail, using a multivariate analysis, and also considers the influence of performance status.

Materials and methods

Data collection

One thousand consultations carried out in the course of the Palliative Medicine Program (PMP) from 1990 to 1992 were studied. Assessments were made upon initial referral both as inpatients and outpatients. Noncancer diagnoses were excluded. The majority of patients were not receiving any antitumor treatment. Some were receiving palliative radiation therapy for symptom control. The study tool was an eight-page form on which detailed medical data are entered. It is an empirically derived clinical assessment based on conventional medical history taking, covering 38 specific symptoms affecting the cardiovascular (1), respiratory (3), gastrointestinal (15), skin (1), musculoskeletal (4), peripheral and central nervous (13) systems and a detailed pain (1) and performance status assessment (Eastern Cooperative Oncology Group; ECOG). Questions were asked as part of a traditional system review format. The review was not subjected to reliability or validity testing. The interviewer was a nurse or physician on the staff of the PMP. Data were entered via Paradox Relational Database (version 3.5 Borland International Scotts Valley, Calif.) and analyzed with SAS software (SAS Institute, Cary, N.C.).

Statistical methods

Descriptive statistics are summarized as frequencies and percentages for categorical variables and as the median and range for continuous variables. Percentages are rounded to the nearest whole number. Logistic regression analysis was performed separately for each symptom to determine whether age, gender, or performance status was associated with symptom prevalence. Logistic regression analysis results are summarized as the odds ratio and 95% confidence interval for the odds ratio for each of age, gender, and performance status. The odds ratio for gender is expressed for males relative to females. Thus, for a particular symptom, an odds ratio greater than 1 indicates that male patients are more likely than female to have the symptom; similarly, an odds ratio less than 1 indicates that male patients are less likely to have the symptom than are female patients. The odds ratio for age is expressed per 10-year decrease in age. An odds ratio greater than 1 indicates that each 10-year decrease in age is associated with higher likelihood of having the symptom. ECOG score ranges from 0 to 4; a higher score on ECOG indicates poorer performance status. The odds ratio for performance status is expressed per one point increase in performance status. An odds ratio greater than 1 indicates that symptoms become more likely as performance score increases (worsens). Similar, an odds ratio less than 1 indicates that symptoms are less likely as performance status score increases. Logistic regression analyses are based on the total number of patients with complete data on age, gender, performance status and the symptom; therefore the sample size in the logistic regression analysis may be smaller than the sample size used to calculate symptom prevalence. All statistical tests were performed with a 5% level of significance.

Results

Table 1 contains patient descriptive information. The study population numbered 1,000. Over half of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4. The distribution of diagnoses (Table 2) was similar to the estimated cancer deaths in the USA for 1993 [1]. The median number of symptoms was 11 (range 1–27). The median number of gastrointestinal symptoms was 4 (range 0–11). The 11 most prevalent symptoms were pain, easy fatigue, weakness, anorexia, lack of energy, dry mouth, constipation, early satiety, dyspnea, and >10% weight loss (Table 3). The prevalence of these 10 symptoms ranged from 50% to 84%.

There were 24 symptoms that were associated with age, gender, or performance status. Eleven symptoms were more likely to occur in younger patients (Table 4). Gender was associated with 8 symptoms (Table 5). Male patients were more likely to have dysphagia, hoarseness, >10% weight loss and sleep problems. Female patients were more likely to have early satiety, nausea, vomiting, and anxiety. Performance status was associated with 14 symptoms (Table 6). The first 10

Table 1 Patient information

Variable	Total *N*	Statistic[a]
Gender (female)	999	446 (45%)
Performance status	959	
0		34 (3%)
1		150 (16%)
2		252 (26%)
3		403 (42%)
4		120 (12%)
Age (years)	997	65 (12–94)
Number of symptoms	977	11 (1–27)
Number of gastrointestinal symptoms	953	4 (0–11)
Survival from diagnosis (months)	838	14 (0–547)
Survival after referral (months)	598	2 (0.5–33)

[a] *N* (%) for categorical variables; median (range) for continuous variables

Table 2 Primary cancer sites for 1,000 patients (*CUP* carcinoma of unknown primary)

Site	%	Site	%
Lung	24	Esophagus	3
Breast	9	Bladder	3
Colorectal	8	Myeloma	2
Prostate	7	Melanoma	2
CUP	6	Cervix	2
Pancreas	6	Ovary	1
Head and neck	5	Uterus	1
Kidney	4	Leukemia	1
Lymphoma	3	Other	14

Table 3 Symptom prevalence (*N* number [of 1000] with known symptom status, % those with the symptom)

Symptom	*N*	%	Symptom	*N*	%
Pain	976	84	Confusion	974	21
Easy fatigue	971	69	Dizziness	971	19
Weakness	971	66	Dyspepsia	971	19
Anorexia	973	66	Dysphagia	971	18
Lack of energy	969	61	Belching	970	18
Dry mouth	973	57	Bloating	969	18
Constipation	972	52	Wheezing	973	13
Early satiety	972	51	Memory problems	971	12
Dyspnea	974	50	Headache	972	11
>10% weight loss	969	50	Sedation	961	10
Sleep problems	972	49	Aches	971	9
Depression	970	41	Hiccoughs	970	9
Cough	973	38	Itching	968	9
Nausea	973	36	Diarrhea	967	8
Edema	974	28	Dreams	958	7
Taste change	969	28	Hallucinations	970	6
Hoarseness	972	24	Mucositis	972	5
Anxiety	972	24	Tremors	974	5
Vomiting	973	23	Blackout	972	3

Table 4 Symptoms associated with age, with adjustment for gender and performance status Odds ratio (*OR*) is expressed per 10-year decrease in age. (*G*, *P*) Also associated with gender and performance status, (*G*) also associated with gender, *CI* confidence interval

Symptom		*N*	OR	95% CI	% with symptom	
					<65	>65
Blackout	(P)	942	1.7	1.3–2.3	5	2
Vomiting	(G)	942	1.4	1.2–1.5	26	18
Pain	(P)	941	1.3	1.1–1.5	88	80
Nausea	(G)	942	1.2	1.1–1.4	40	32
Headache	–	942	1.2	1.1–1.4	15	8
Sedation	(P)	931	1.2	1.0–1.4	11	9
Bloating	–	940	1.2	1.0–1.3	19	16
Sleep problems	(G)	942	1.2	1.1–1.3	54	43
Anxiety	(G, P)	942	1.2	1.0–1.3	29	19
Depression	–	940	1.2	1.1–1.3	46	36
Constipation	(P)	942	1.1	1.0–1.2	53	50

Table 5 Symptoms associated with gender, with adjustment for age and performance status. Odds ratio (*OR*) is expressed for males relative to females. (*A*, *P*) Associated with age and performance status, (*A*) associated with age

Symptom		*N*	OR	95% CI	% with symptom	
					Male	Female
Dysphagia	–	942	1.8	1.3–2.6	22	14
Hoarseness	–	942	1.7	1.2–2.2	29	20
>10% weight loss	–	938	1.3	1.0–1.7	53	46
Sleep problems	(A)	942	1.3	1.0–1.7	52	45
Early satiety	–	941	0.7	0.5–0.9	46	56
Nausea	(A)	942	0.6	0.5–0.8	31	42
Vomiting	(A)	942	0.6	0.4–0.8	18	28
Anxiety	(A, P)	942	0.6	0.5–0.8	20	29

symptoms in Table 6 were more likely in patients with higher (worse) performance status score, while the last 4 were less likely in patients with good performance status.

As we were concerned that the observed gender differences might be explained by cancer primary site, we repeated the logistic regression analysis after excluding gender-specific primary sites (cancer of the breast, prostate, ovary, uterus, and cervix). There were 769 patients whose data were complete for this analysis. Six results changed: three gender results and three performance status results. Male patients now also had more coughing and headaches than female patients, while gender differences in sleep problems disappeared. Performance status differences in pain, anxiety, and memory problems also resolved.

Discussion

The primary site distribution and age of patients in the study were typical of cancer mortality in the USA [3], and we therefore believe our findings are representative for the advanced cancer population. The most important results clinically are that persons with advanced cancer are polysymptomatic, and that symptom prevalence is affected independently by age, gender, and performance status. The effect of age is undirectional, unlike gender or performance status. Younger patients perhaps have more psychosocial distress, so that it may not be surprising that they had more anxiety, depression and sleep problems. The greater prevalence of pain, headache, nausea, constipation and vomiting is more difficult to explain. The fact that the symptom analysis did not change significantly when gender-specific sites are removed suggests that gender- or age-related differences in symptomatology are not explained by differences in primary site distribution.

Table 6 Symptoms associated with performance status, adjusting for age and gender. OR is expressed per one point increase in performance status score. (*A*, *G*) Associated with age and gender, (*A*) associated with age

Symptom		*N*	OR	95% CI	ECOG score: % with symptom				
					0	1	2	3	4
Confusion	–	942	2.2	1.8–2.7	3	9	14	24	47
Sedation	(A)	931	2.0	1.6–2.7	3	3	7	11	23
Blackout	(A)	942	1.8	1.2–2.7	0	1	4	3	6
Hallucinations	–	941	1.7	1.2–2.3	3	1	4	8	6
Weakness	–	942	1.6	1.4–1.8	21	47	68	75	67
Mucositis	–	942	1.5	1.1–2.0	0	1	5	7	5
Anorexia	–	943	1.3	1.1–1.5	36	55	67	69	70
Memory problems	–	940	1.3	1.0–1.6	9	9	9	14	17
Dry mouth	–	942	1.3	1.1–1.4	39	49	54	63	60
Constipation	(A)	942	1.2	1.1–1.4	27	46	53	55	52
Anxiety	(A, G)	942	0.9	0.7–1.0	21	31	26	22	19
Wheezing	–	942	0.8	0.7–1.0	9	19	17	11	9
Pain	(A)	941	0.8	0.6–0.9	77	91	87	84	70
Itching	–	939	0.6	0.5–0.8	21	15	9	7	4

However, it appears there are symptoms common to all primary sites when cancer is advanced.

There is clustering of some neuropsychological and gastrointestinal symptoms, perhaps due to lack of definition of individual symptoms. This may also be explained by common pathophysiological mechanisms, e.g. gastroparesis. The 10 most common symptoms were similar to those in previous retrospective studies [5, 7], but lack of energy, easy fatigue and weakness ranked higher in our study. As our patients were all referred to the PCS, their symptoms may have been subject to referral bias, although the primary site distribution, age, and performance status data all suggest they represent the reality of patients with advanced cancer. The assessment form was a crude instrument; symptoms may have overlapped (e.g. easy fatigue and weakness) or have been ill-defined (e.g. dyspepsia, early satiety). Not all statistically significant differences in symptoms are clinically important.

We previously described the frequency and severity of presenting symptoms in 100 patients on referral to our Program [3, 10]. The advantages of this current study were that it was prospective, involved 1,000 consecutive patients and analyzed 38 symptoms and performance status using a standard format. Previous studies in patients with advanced cancer from other centers were retrospective [4, 6, 7], limited symptom number [4, 5], involved few patients [3, 4, 6, 7], or did not have direct clinical assessment [4]. Comparison of the present results with those recorded in our earlier study reveals a similar rank order [3], but it is noteworthy that easy fatigue and lack of energy, while much more prevalent in the larger data base, were seemingly unaffected by performance status. Secondly, where there was a difference in prevalence, most symptoms were more frequent, suggesting that large data sets provide information that is not accessible from small studies. Given the multiplicity of problems, patients with advanced cancer need comprehensive individualized care with detailed attention to symptom management. Improved education of caregivers and more research in symptom definition, pathophysiology and control are essential.

Conclusions

The study population was representative of patients with advanced cancer, who are multisymptomatic. Gastrointestinal symptoms are common. Weakness is related to poor performance status, but easy fatigue and lack of energy are not. Specific symptoms were affected by age, or gender, or performance status. All symptoms affected by age are more common in younger patients. Age and gender analysis should be considered along with performance status in all cancer treatment and symptom control studies, as independently of each other and of primary site they appear to be important predictors of morbidity in advanced cancer.

References

1. American Cancer Society (1993) Cancer facts and figures. ACS, Atlanta, Ga
2. Smith BJ (1986) Progress against cancer? N Engl J Med 314:1226-1232
3. Curtis E, Krech R, Walsh TD (1991) Common symptoms in patients with advanced cancer. J Palliat Care 7:25–29
4. Brescia F, Adler D, Gray G, et al (1990) Hospitalized advanced cancer patients: a profile. J Pain Symptom Manage 5:221–227
5. Reuben DB, Mor V, Hiris J (1988) Clinical symptoms and length of survival in patients with terminal cancer. Arch Intern Med 148:1586–1591
6. Hoskins PJ, Hanks GW (1988) Management of symptoms in advanced cancer: experience in a hospital based continuing care unit. J R Soc Med 81:341–344
7. Coyle N, Adelhardt J, Foley KM, et al (1990) Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last 4 weeks of life. J Pain Symptom Manage 5:83–93
8. Krech R, Davis J, Walsh D, Curtis E (1992) Symptoms of lung cancer. Palliat Med 6:309–315
9. Krech R, Walsh D (1991) Symptoms of pancreatic cancer. J Pain Symptom Manage 6:360–367
10. Donnelly SM, Walsh TD, Rybicki L (1995) The symptoms of advanced cancer: identification of clinical and research priorities by assessment of prevalence and severity. J Palliat Care 11:27–32
11. Donnelly SM, Walsh D (1995) Symptoms in advanced cancer. Semin Oncol 22:67–72
12. Walsh D (1994) Palliative care: management of the patient with advanced cancer. Symptoms Adv Cancer 21 [Suppl 7]:100–106