ORIGINAL ARTICLE

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The nature of nausea: prevalence, etiology, and treatment in patients with advanced cancer not receiving antineoplastic treatment

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Abstract

Background The prevalence of nausea/vomiting in patients with advanced cancer has a wide range. Due to a very low level of evidence regarding antiemetic treatment, current guidelines recommend an etiology-based approach. The evidence for this approach is also slim and research is urgently needed.

Objectives (Part One) to elucidate the prevalence of nausea and the possible associations with sociodemographic and clinical variables and (Part Two) to investigate possible etiologies of nausea and antiemetic treatments initiated in patients with nausea.

Methods Patients with advanced cancer and no recent antineoplastic treatment were included in a prospective two-part study. In Part One, patients completed an extended version of the EORTC QLQ-C15-PAL. Nauseated patients could then be included in Part Two in which possible etiologies and antiemetic treatment were recorded and a follow-up questionnaire was completed.

Results Eight hundred twenty-one patients were included and 46% reported any degree of nausea. Younger age and female sex were associated with a higher degree of nausea. Common etiologies included constipation, opioid use, and "other," and treatments associated with a statistically significant decrease in nausea/vomiting were olanzapine, laxatives, corticosteroids, domperidone, and metoclopramide.

Conclusion Nausea was a common symptom in this patient population and many different etiologies were suggested. Most patients reported a lower degree of nausea at follow-up. More research in treatment approaches and specific antiemetics is strongly needed.

Keywords Nausea · Advanced cancer · N/V · Etiology · Treatment

Introduction

The prevalence of nausea in patients with advanced varies in the literature between 10 and 70% [1–9]. The wide range reflects the differences in the patient populations and in the definition and assessment of nausea. In a recent Danish publication, the prevalence of nausea was 22% and was associated with patient status (in-/outpatient) and

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antineoplastic treatment [10]. Other studies have found an association between nausea and performance status, sex, and age [11].

The evidence for treatment of nausea in patients with advanced cancer is generally low. Recent reviews and guidelines have concluded that no recommendations or only recommendations with a low level of evidence can be established and recommend that treatment is based on a thorough anamnesis and examination aiming at disclosing the etiology behind nausea in the individual patient [12]. Some find this approach too time consuming in particular in patients with a limited life expectancy [13]. Hence, more research is needed concerning the use of an etiology-based antiemetic approach in patients with advanced cancer.

The objectives of this study in patients with advanced cancer were as follows: (Part One) to elucidate the prevalence of nausea and the possible associations with sociodemographic and clinical variables and (Part Two) to investigate possible etiologies of nausea and antiemetic treatments initiated in patients with nausea.

Methods

Patients

Patients were recruited from Danish Departments of Oncology and Palliative Care and included from home, hospice, or hospital wards. Criteria for inclusion were (1) advanced cancer defined as incurable metastatic solid tumor, (2) 18 years or older, (3) cognitive ability to complete questionnaires (practical help allowed), (4) life expectancy exceeding 2 weeks, (5) no antineoplastic treatment within the previous 4 weeks, (6) no major surgery within the previous 2 weeks, and (7) no general anesthesia within the previous 4 days.

Study design

This is a prospective two-part study including patients with advanced cancer.

> Part One: eligible patients were screened using an extended version of the EORTC QLQ-C15-PAL including demographic items of age, sex, and cancer diagnosis.

> Part Two: patients were eligible for inclusion in Part Two if they reported at least "a little" nausea during the past week on the screening questionnaire. After obtaining informed consent, the physician evaluated possible etiologies and treatment options for nausea. The extended EORTC QLQ-C15-PAL was completed by the patient again after 5 to 9 days.

Questionnaires

The EORTC QLQ-C15-PAL is an abbreviated version of the EORTC QLQ-C30 validated among patients in palliative care [14]. An extended version was created, by the addition of five items from the EORTC validated nausea/vomiting item bank [15]. The items were selected to measure both a higher and lower degree of nausea/vomiting than the original nausea item included in the QLQ-C15-PAL questionnaire, thereby extending measurement range and reducing "floor/ceiling-effects." One of the items (During the past week; Have you vomited?) matches the original item concerning vomiting found in the QLQ-C30, allowing estimation of the two-item nausea and vomiting (N/V) score known from the QLQ-C30. The other items selected were "During the past week; 1) Have you eaten less because of nausea or vomiting? 2) Has nausea or vomiting interfered with your physical activities like taking a walk? 3) Has nausea or vomiting interfered with your ability to enjoy life? 4) Has nausea or vomiting interfered with your sleep?"

The treating physician assessed possible etiologies of nausea using a simple questionnaire listing possible etiologies and a box to check either "yes" or "no." A total of 10 possible etiologies (bowel obstruction, increased intracranial pressure, constipation, hypercalcemia, hypomagnesemia, kidney failure, pregnancy, drugs with emetic potential, opioid treatment, and other) were listed. The list of etiologies was selected based on clinical experience in the study group and was not meant to be comprehensive, hence the box for "other." This procedure meant that more than one possible etiology could be checked as positive.

The treating physician also checked one of three boxes on the treatment form. The three options were as follows: (1) based on full evaluation, the patient does not meet the inclusion criteria, (2) antiemetic treatment is not initiated/changed, and (3) antiemetic treatment is initiated/changed. The first box was implemented to accommodate pre-screening primarily in the homecare teams, and boxes two and three allowed the physician to explain why no treatment was initiated or what treatment initiation/changes consisted of.

All data collected were entered into the secure database RedCap.

The study was approved by the Danish Data Protection Agency on June 10, 2015.

Statistics

Scoring of the EORTC QLQ-C15-PAL The EORTC QLQ-C15-PAL was scored using the manuals provided by the EORTC [16, 17]. This procedure yielded scores ranging from 0 to 100. A high score for the two functioning scales (physical and emotional functioning) and global QoL represents a better outcome. A high score for the symptom scales represents a worse outcome.

Scoring of the N/V items For the initial descriptive analyses, we used the QLQ-C15-PAL nausea item only.

For further analyses, we calculated the "traditional" two-item N/V score of the EORTC QLQ-C30, but not the score based on the single item in the QLQ-C15-PAL [16].

To calculate the scores for the multi-item N/V score (a so-called short-form, based on the N/V item bank), we used a customized software program developed by the EORTC [15]. Higher scores indicate worse N/V and the scores were scaled so that the European general population has a mean N/V score of 50 and a standard deviation of 10. Hence, scores on the traditional two-item N/V score and the multi-item N/V score are not directly comparable; the latter was included because it improves precision and the ability to detect change [15].

Statistical testing

Part one To compare characteristics between patients with or without nausea, we used the Wilcoxon rank sum test (age) and the chi^2 test (sex, diagnosis).

To test associations between degree of nausea (single item) and age, sex, and diagnosis, we used ordinal logistic regression.

Possible associations between the two-item N/V score and the scales in the EORTC QLQ-C15-PAL were tested using Spearman's correlation coefficient.

Part two To compare characteristics between patients included or not, we used the Wilcoxon rank sum test (age) and the chi^2 test (sex, diagnosis, degree of nausea).

Nausea (single-item score) at baseline and follow-up was tested for symmetry in a cross tabulation using an exact marginal homogeneity test.

The two-item and multi-item N/V score at baseline and follow-up were tested for mean rank differences using the Wilcoxon signed rank test for paired samples.

All analyses were done using Stata version 13 and the threshold for a significant p value was 0.05 in all analysis.

Results

Part one

Patients Between November 2015 and July 2018, we included 821 patients at four sites, (Fig. 1). For patient characteristics, see Table 1.

Prevalence Three hundred seventy-five of 821 (46.0%) patients had experienced some degree of nausea within the past week. "A little" nausea was reported in 20.2% of patients, while 13.6% and 12.1% of patients had experienced either

"quite a bit" or "very much" nausea, respectively. Mean two-item N/V score was 22 and multi-item N/V score was 63.

Associations In univariate testing, having any degree of nausea was associated with younger age ($p = 0.019$) and having a diagnosis of either gynecologic ($p = 0.024$) or stomach cancer ($p = 0.035$), whereas a not having nausea was associated with a diagnosis of either lung ($p < 0.001$), brain ($p = 0.033$), or head and neck ($p = 0.021$) cancer (Table 1). In multivariate testing, all associations between degree of nausea and diagnosis disappeared while younger age remained statistically significant ($p = 0.026$) and female sex became statistically significant ($p = 0.030$).

The multi-item N/V score was positively correlated to loss of appetite (Spearman's correlation coefficient 0.44, $p < 0.001$), constipation (0.26, $p < 0.001$), pain (0.25, $p < 0.001$), and fatigue (0.22, $p < 0.001$). A negative correlation was found to emotional functioning (-0.26, $p < 0.001$) and global QoL (-0.18, $p < 0.001$).

Part two

Patients In total, 241 of 378 nauseated patients were included in Part Two (63.8%) (Fig. 1). Possible etiologies were assessed in all patients while treatment was recorded for 231 patients (95.9%). Follow-up was completed by 160 (66.4%) patients included in Part Two. No statistically significant differences were found (age, sex, cancer diagnosis, degree of nausea) between patients included in Part Two and those not included.

Etiology of nausea The major etiologies as judged by treating physician were constipation (31.5%), "other reasons" (21.6%), and opioid related (16.6%) (Table 2). In 42.3% of patients, no etiologies were established. Cross tabulation of etiology and degree of nausea showed no correlation between degree of nausea and establishment of an etiology of nausea (Table 2).

Treatment of nausea Treatment was directed either against nausea or guided by an established etiology of nausea and was initiated or changed in a total of 183 patients (79.2%). The two most common reasons for maintaining treatment unchanged were (1) the patient did not wish to receive antiemetic treatment (mainly due to other more troublesome symptoms) (41.6%) or (2) the patient believed that the current antiemetic treatment was effective enough for them (41.6%). Most commonly initiated/changed treatments were olanzapine (initiated in 18.6% of patients), corticosteroids (18.2%), laxatives (17.7%), metoclopramide (14.3%), and domperidone (12.1%).

Cross tabulation of treatment and degree of nausea showed that 58.8% of the patients reporting "a little" nausea had an

Fig. 1 Number of patients included and followed up
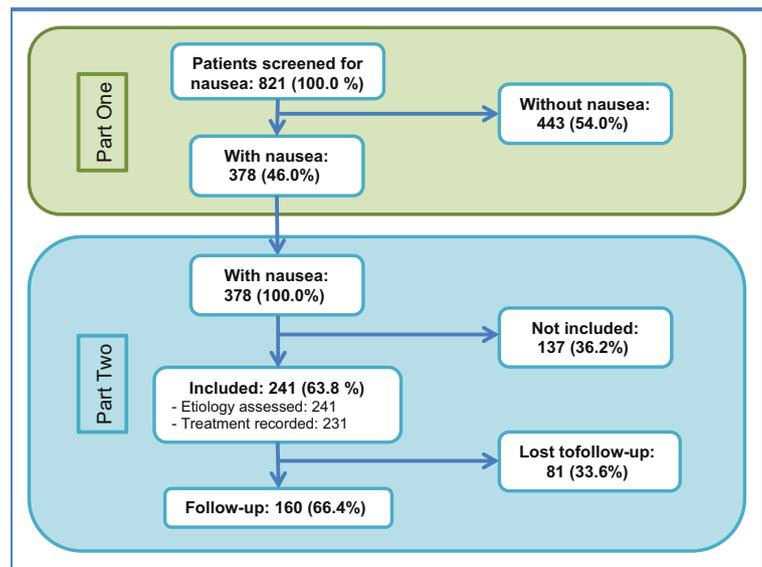
antiemetic prescribed or alternated compared to 91.7% of the patients reporting "quite a bit" or "very much" nausea (Table 2). Cross tabulation of etiology and treatment showed that the most common treatments if no etiology was established were olanzapine (30.5%), no treatment (24.2%), and corticosteroids (16.8%) (Table 3). If the etiology

Table 1 Characteristics of patients at time of screening

	With nausea* n (%)	Median	Without nausea* n (%)	Median	p value**
Total	378 (46.0)		443 (54.0)		
Female	214 (49.0)		223 (51.0)		
Male	164 (42.7)		220 (57.3)		
Age (years)		70 (range 37–93)		72 (range 28–94)	0.018
Diagnosis					
Lung	74 (19.6)		138 (31.2)		< 0.001
Gastrointestinal	55 (14.6)		63 (14.2)		
Prostatic	38 (10.1)		36 (8.1)		
Pancreatic	38 (10.1)		32 (7.2)		
Gynecologic	36 (9.6)		24 (5.4)		0.024
Breast	35 (9.3)		36 (8.1)		
Kidney	17 (4.5)		10 (2.2)		
Stomach	15 (4.0)		7 (1.6)		0.035
Hepatic	14 (3.7)		9 (2.0)		
Esophageal	10 (2.7)		14 (3.2)		
Urological	9 (2.4)		12 (2.7)		
Head and neck	7 (1.9)		20 (4.5)		0.033
Malignant melanoma	6 (1.6)		9 (2.0)		
Mesothelial	4 (1.1)		5 (1.1)		
Brain	1 (0.3)		9 (2.0)		0.021
Sarcoma	1 (0.3)		6 (1.4)		
Other/unknown	18 (4.8)		13 (2.9)		

*"Without nausea" includes patients reporting "none" nausea on the EORTC QLQ nausea item. "With nausea" includes patients reporting more than "none"

**Only statistically significant p values presented (< 0.05)

Table 2 Cross tabulations of degree of nausea at baseline and etiology and treatment of nausea

	Degree of nausea			
	A little (n = 84) n (%)	Quite a bit (n = 82) n (%)	Very much (n = 75) n (%)	Total (n = 241) n (%)
Etiology suggested*	48 (57.1)	52 (63.4)	39 (52.0)	139 (57.7)
- Constipation	26 (30.9)	31 (31.8)	19 (25.3)	76 (31.5)
- Opioid related	14 (16.7)	17 (20.7)	9 (12.0)	40 (16.6)
- Bowel obstruction	3 (2.6)	4 (4.9)	2 (2.7)	9 (3.7)
- Drugs with emetic potential	2 (2.4)	4 (4.9)	3 (4.0)	9 (3.7)
- Hypomagnesemia	2 (2.4)	4 (4.9)	1 (1.3)	7 (2.9)
- Hypercalcemia	1 (1.2)	3 (3.7)	2 (2.7)	6 (2.5)
- Kidney failure	1 (1.2)	2 (2.4)	1 (1.3)	4 (1.7)
- Increased intracranial pressure	1 (1.2)	0	2 (2.7)	3 (1.2)
- Pregnancy	0	0	0	0
- Other *	20 (23.8)	17 (20.7)	15 (20.0)	52 (21.6)
No etiology suggested	36 (42.8)	30 (36.6)	36 (48.0)	102 (42.3)
	A little (n = 87) n (%)	Quite a bit (n = 72) n (%)	Very much (n = 72) n (%)	Total (n = 231) n (%)
Treatment initiated/changed*	51 (58.6)	66 (91.7)	66 (91.7)	183 (79.2)
- Olanzapine	1 (1.1)	16 (22.2)	26 (36.1)	43 (18.6)
- Corticosteroids	9 (10.3)	18 (25.0)	15 (20.8)	42 (18.2)
- Laxatives	14 (16.1)	16 (22.2)	11 (15.3)	41 (17.7)
- Metoclopramide	12 (13.8)	12 (16.7)	8 (11.1)	33 (14.3)
- Domperidone	9 (10.3)	11 (15.3)	8 (11.1)	28 (12.1)
- Haloperidol	3 (3.4)	5 (6.9)	9 (12.5)	17 (7.4)
- Opioid adjustment	5 (5.7)	9 (12.5)	2 (2.8)	16 (6.9)
- Serotonin antagonist	2 (2.3)	3 (4.2)	7 (9.7)	12 (5.2)
- Antibiotics	4 (4.6)	3 (4.2)	4 (5.6)	11 (4.8)
- Proton pump inhibitors	3 (3.4)	1 (1.4)	4 (5.6)	8 (3.5)
- Antifungal	3 (3.4)	2 (2.8)	2 (2.8)	7 (3.0)
- Other **	5 (5.7)	11 (15.3)	5 (6.9)	21 (9.1)
No treatment initiated/changed	36 (41.2)	6 (8.3)	6 (8.3)	48 (20.7)

*More than one etiology and/or treatment possible per patient

**Other including the following: fungal infection, bacterial infection (primarily urinary), reflux

***Other including the following: naso-gastric tube, surgery, adjustment of parenteral nutrition, acupuncture, anxiety-treatment (e.g., hospitalization, medical treatment, psychologist)

suggested was constipation, the most common treatments were corticosteroids (52.3%) and laxatives (50.8%), while the most common treatment for opioid-related nausea was an adjustment of opioid treatment (31.4%).

Change over time Nausea prevalence at follow-up after 5 to 9 days was reduced to 70% while mean two-item N/V score was reduced from 48 at baseline to 29 ($p < 0.001$) and mean multi-item N/V score was reduced from 77 to 68 ($p < 0.001$). In total, 109 of 160 patients (68.1%) reported a lower degree of nausea at follow-up than at inclusion while 19 patients (11.9%) reported worse nausea at follow-up ($p < 0.001$) (Table 4).

Etiologies with statistically significant changes in the multi-item N/V score were constipation (− 7) and "other reasons" (− 7) (Table 5). If no treatments were initiated or

changed, mean change in the two-item N/V score was 0, while any treatment initiations/changes were associated with a mean change of − 10 ($p < 0.001$). Treatments associated with significant changes in the multi-item N/V score were olanzapine (− 19), corticosteroids (− 11), metoclopramide (− 11), domperidone (− 8), and laxatives (− 7) (Table 5).

Discussion

This study aimed at assessing the real world management of nausea/vomiting in patients with advanced cancer.

The prevalence of nausea was 46% as compared to 10–71% in other studies [1–9]. This difference is primarily explained by differences in the study populations. In our

Table 3 Cross tabulations of etiology and treatment of nausea

	Etiology of nausea (four most common)*			
	No etiology (n = 95) n (%)	Constipation (n = 65) n (%)	Opioid related (n = 35) n (%)	Other ** (n = 46) n (%)
Treatments initiated/changed*	72 (75.8)	59 (90.8)	26 (74.3)	42 (91.3)
- Olanzapine	29 (30.5)	5 (7.7)	5 (14.3)	5 (10.9)
- Corticosteroids	16 (16.8)	34 (52.3)	4 (11.4)	7 (15.2)
- Laxatives	2 (2.1)	33 (50.8)	8 (22.9)	9 (19.6)
- Metoclopramide	12 (12.6)	6 (9.2)	1 (2.9)	4 (8.7)
- Domperidone	10 (10.5)	7 (10.8)	6 (17.1)	4 (8.7)
- Haloperidol	4 (4.2)	4 (6.5)	2 (5.7)	1 (2.2)
- Opioids adjustment	1 (1.1)	9 (13.8)	11 (31.4)	5 (10.9)
- Serotonin antagonist	3 (3.2)	3 (4.6)	3 (8.6)	5 (10.9)
- Antibiotics	1 (1.1)	2 (3.2)	2 (5.7)	9 (19.6)
- Proton pump inhibitors	0	3 (4.6)	0	4 (8.7)
- Antifungal	0	4 (6.5)	0	7 (15.2)
- Other ***	0	9 (13.8)	1 (2.9)	9 (19.6)
No treatment initiated/changed	23 (24.2)	9 (13.8)	9 (25.7)	4 (8.7)

*More than one etiology and/or treatment possible per patient

**Other including the following: fungal infection, bacterial infection (primarily urinary), reflux

***Other including the following: naso-gastric tube, surgery, adjustment of parenteral nutrition, acupuncture, anxiety-treatment (e.g., hospitalization, medical treatment, psychologist)

study, patients with advanced cancer were included from three different settings (home, hospice, and hospital wards) and patients with recent antineoplastic treatment or a very short life expectancy were excluded. The majority were either referred to a specialized palliative care unit or inpatients (hospital ward or a hospice), increasing the risk of acute symptoms. Other studies have included patients exclusively from either emergency centers/medical wards [3, 7] with a high risk of acute symptoms similar to ours and have found a prevalence of nausea of around 50%, quite comparable to our 46%. Other studies have included patients exclusively from home [10] with presumably lower probability of acute health states (nausea prevalence of 22%). Some studies

included patients from a palliative service program [9, 11, 18] only, while others included from the community or departments of oncology or surgery [1, 10, 19] indicating a wide range in patient disease trajectory and corresponding symptom scores. Some studies have focused on symptoms experienced at the very end of life [1, 6, 19] and results indicate that the prevalence of nausea may decrease during the last week(s).

Another obvious factor influencing the prevalence is the assessment tools used to measure nausea and how it is reported (e.g., which cut-off values are used). Some studies used the Edmonton Symptom Assessment Scale (ESAS) [1, 3, 5, 8], some used the EORTC instruments [4, 10], and some used the Memorial Symptom Assessment Scale (MSAS) [20], un-

Table 4 Cross tabulation of degree of nausea at baseline and at 1-week follow-up

	Degree of nausea after 7 days				
Degree of nausea at baseline	None	A little	Quite a bit	Very much	Total
None*	0	0	0	0	0
A little	25	21	11	2	59
Quite a bit	9	29	10	6	54
Very much	14	15	12	6	47
Total	48	65	33	14	160

*Only patients with follow-up are presented, hence no patients with "none" nausea at baseline

Exact marginal homogeneity test of symmetry: p value < 0.001

Table 5 Mean multi-item N/V score in relation to etiology and treatment of nausea

	Mean multi-item N/V score at baseline	Mean multi-item N/V score at follow-up	p value*	Number of observations included in the analysis
All patients	77	68	< 0.001	160
Any etiology suggested	76	70	< 0.001	85
- Constipation	76	69	0.002	50
- Opioid related	71	67		22
- Drugs with emetic potential	80	74		7
- Bowel obstruction	83	78		7
- Hypomagnesemia	72	68		6
- Hypercalcemia	72	66		4
- Kidney failure	76	84		2
- Increased intracranial pressure	58	103		1
- Other	78	71	0.005	34
No etiology suggested	78	65	< 0.001	66
Any treatment initiated/changed	78	68	< 0.001	135
- Olanzapine	82	63	< 0.001	36
- Laxatives	78	71	< 0.001	34
- Corticosteroids	81	70	< 0.001	31
- Domperidone	76	68	0.023	23
- Metoclopramide	79	68	< 0.001	22
- Antibiotics	78	68		11
- Haloperidol	84	80		10
- Opioid adjustment	73	70		10
- Serotonin antagonist	85	83		7
- Antifungal	80	72		7
- Proton pump inhibitors	89	84		6
- Other	79	72		16
No treatment initiated/changed	*68*	68		25

*Only statistically significant p values are presented (< 0.05)

specified tools [21], or tools they developed themselves [11]. This wide array of tools and methods of reporting makes comparisons difficult.

Variables associated with nausea Our results showed an association between degree of nausea and younger age as reported by others [11, 22]. An association between a high risk of nausea and the female sex has also been demonstrated, primarily in chemotherapy-induced N/V [11, 22–24]. Our results align with this finding. In univariate testing, we found an association between having any degree of nausea and gynecologic and stomach cancer similar to other studies [1, 8, 9]. This association disappeared in multivariate testing. Concerning the relationships of nausea with other symptoms and quality of life dimensions, the association between a higher degree of nausea and especially the loss of appetite item on the EORTC QLQ-C15-PAL was expected, and several previously published cluster analyses support this finding [25].

Etiology Constipation and opioid-induced nausea were among the most prevalent etiologies as judged by the treating physicians. This is not surprising since pain remains one of the most common symptoms in patients with advanced cancer [26]. Opioids are administered in up to 80% of Danish cancer patients [27] and common adverse events include nausea and constipation [28]. However, constipation may also have other causes, e.g., related to having a disease in the abdomen (stomach, pancreas) or pelvis (gynecologic).

Our results reflect the very multifactorial and somewhat uncertain etiology behind nausea in patients with advanced cancer. The average number of etiologies in patients where an etiology could be established was 1.5, not taking into account that the "other" etiology often covered more than one suggestion. The "other category" was positive in 22% of patients and covered a broad spectrum of symptoms from physical symptoms like infections, reflux, and oral candidiasis to more psychological or social concerns like anxiety or fatigue leading to lack of oral intake. A more comprehensive list of

specific etiologies would probably have increased the number of patients with established etiologies and reduced the proportion of responses in the "Other" category. Other studies have found more than one possible etiology in around 25% of patients [29, 30], in line with our findings.

Treatment Five treatments were initiated/changed in more than 10% of patients (olanzapine, corticosteroids, laxatives, metoclopramide, and domperidone) but no clear relationship between the degree of nausea and choice of treatment was observed except for olanzapine which was initiated in only a single patient with "a little" nausea. Other studies have demonstrated that metoclopramide was the preferred treatment choice followed by haloperidol among Australian doctors [31] and a German study showed that antiemetics were prescribed for 27% of 1304 inpatients from palliative care units [32]. Twenty-one percent of all patients received metoclopramide while haloperidol was prescribed for 13% of patients. Metoclopramide, however, is contraindicated in complete bowel obstruction. Drug classes like proton inhibitors, corticosteroids, or laxatives were also among some of the most commonly used drugs, but no correlations between symptoms and drug prescriptions were investigated. Metoclopramide and haloperidol were listed as essential drugs for nausea and vomiting by palliative experts in a large European survey [33], but in our study, only 7.4% of patients received haloperidol while 18.6% received olanzapine; a newer drug from the same class suggested as an alternative in current guidelines for advanced cancer [12]. This might be a result of a shift in attitude towards haloperidol/olanzapine facilitated by the inclusion of olanzapine in current guidelines for chemotherapy-induced nausea and vomiting [34, 35].

There was a strong and significant reduction in nausea and vomiting after treatment with olanzapine, but the results must be viewed in light of the fact that 29 of 43 patients treated with olanzapine were followed in an open-label sub-study testing a dose of 10 mg olanzapine for 5 days. We considered removing this group of patients from our analyses, but since we included the most nauseated patients in this sub-study, this would have caused an underestimation of prevalence and overall change. While the olanzapine study was including patients, maybe physicians would more likely initiate olanzapine than other related drugs, thereby overestimating the use of olanzapine in the real world. Another possible impact is that inclusion in the olanzapine study required patients to have a relatively high degree of nausea, hence making the likelihood of large effect sizes higher than for the treatments that could be initiated for lower degrees of nausea. Therefore, the change in nausea observed following olanzapine is not directly comparable with the other treatments followed in this study. However, the possible effect seen in patients treated with olanzapine remains relevant and effect sizes are comparable when only including the 14

patients treated outside of the olanzapine study (change in mean multi-item N/V score of − 11).

Our results show a frequent use of metoclopramide in the beginning of the study period, dropping to almost none in the last part. The opposite trend was seen in the use of domperidone. The Danish Medicines Agency updated their recommendations on the use of metoclopramide recommending only 5 days of low-dose use due to neurological adverse events [36] just before initiation of this study, and a gradual implementation of this recommendation seems to have taken place. Hence, domperidone seems to have replaced metoclopramide as a first-line antiemetic in our population despite the fact that high doses and long duration of therapy should be avoided, particularly in older patients, due to cardiac adverse events [37].

Strengths and limitations The major strength of this study is the prospective evaluation of etiology and treatment of nausea in this very under-researched patient group. The inclusion of patients from home, hospice, and hospital wards represents all settings from where patients with unmet palliative needs are encountered. The evaluation of possible etiologies and treatments was done by the treating physicians, and not biased by the involvement of the investigators.

In the beginning of the study, we tried to implement a 7-day diary in Part Two including registration of adverse events. This setup was sadly not doable leading to very few records on patient compliance or treatment changes within the study period. In retrospect, we would also have liked to include data on previous antiemetic treatment at screening as well as time to death.

Difficulties in the implementation of the study and the nature of the patient within palliative care with a high number of deaths and patients being too ill to complete the follow-up questionnaire affected our analyses. Difficulties in inclusion and follow-up are common in research within palliative care [38–40] and combined with a very heterogeneous patient group often limit the possibility of making firm conclusions.

Conclusion

This study found that 46% of patients with advanced cancer and no recent antineoplastic treatment had experienced some degree of nausea within the past week. Younger age and female sex were associated with a higher degree of nausea. One or more etiologies of nausea could be established in around six out of ten patients and the most common etiologies were constipation, opioid use, and "other" covering a broad spectrum of causes. More than two-thirds of patients reported a lower degree of nausea at follow-up than at baseline with statistically significant improvements among patients receiving olanzapine, laxatives, corticosteroids, domperidone, and metoclopramide.

The study elucidates the multifactorial nature of nausea in patients with advanced cancer. Future research should focus on establishing additional evidence for the antiemetic treatment modalities. Furthermore, it would be relevant to compare the currently accepted etiology-based approach to other strategies like the single-drug approach.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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References

1. Seow H, Barbera L, Sutradhar R, Howell D, Dudgeon D, Atzema C, Liu Y, Husain A, Sussman J, Earle C (2011) Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. J Clin Oncol 29(9):1151–1158

2. Kirkova J, Rybicki L, Walsh D, Aktas A (2012) Symptom prevalence in advanced cancer: age, gender, and performance status interactions. Am J Hosp Palliat Care 29(2):139–145

3. Gupta M, Sahi MS, Bhargava A, Talwar V (2016) A prospective evaluation of symptom prevalence and overall symptom burden among cohort of critically ill cancer patients. Indian J Palliat Care 22(2):118–124

4. Laugsand EA, Sprangers MA, Bjordal K, Skorpen F, Kaasa S, Klepstad P (2010) Health care providers underestimate symptom intensities of cancer patients: a multicenter European study. Health Qual Life Outcomes 8:104

5. Sigurdardottir KR, Haugen DF (2008) Prevalence of distressing symptoms in hospitalised patients on medical wards: a cross-sectional study. BMC Palliat Care 7:16

6. Fainsinger R, Miller MJ, Bruera E, Hanson J, Maceachern T (1991) Symptom control during the last week of life on a palliative care unit. J Palliat Care 7(1):5–11

7. Delgado-Guay MO, Rodriguez-Nunez A, Shin SH, Chisholm G, Williams J, Frisbee-Hume S, Bruera E (2016) Characteristics and outcomes of patients with advanced cancer evaluated by a palliative care team at an emergency center. A retrospective study. Support Care Cancer 24(5):2287–2295

8. Jimenez A, Madero R, Alonso A, Martinez-Marin V, Vilches Y, Martinez B et al (2011) Symptom clusters in advanced cancer. J Pain Symptom Manag 42(1):24–31

9. Vainio A, Auvinen A (1996) Prevalence of symptoms among patients with advanced cancer: an international collaborative study. Symptom Prevalence Group. J Pain Symptom Manag 12(1):3–10

10. Harder SL, Groenvold M, Herrstedt J, Johnsen AT (2019) Nausea in advanced cancer: relationships between intensity, burden, and the need for help. Support Care Cancer 27(1):265–273

11. Walsh D, Donnelly S, Rybicki L (2000) The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. Support Care Cancer 8(3):175–179

12. Walsh D, Davis M, Ripamonti C, Bruera E, Davies A, Molassiotis A (2017) 2016 updated MASCC/ESMO consensus recommendations: management of nausea and vomiting in advanced cancer. Support Care Cancer 25(1):333–340

13. Glare P, Miller J, Nikolova T, Tickoo R (2011) Treating nausea and vomiting in palliative care: a review. Clin Interv Aging 6:243–259

14. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, Fayers PM, de Graeff A, Hammerlid E, Kaasa S, Sprangers MA, Bjorner JB, EORTC Quality of Life Group (2006) The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. Eur J Cancer 42(1):55–64

15. Petersen MA, Aaronson NK, Arraras JI, Chie WC, Conroy T, Costantini A, Dirven L, Fayers P, Gamper EM, Giesinger JM, Habets EJJ, Hammerlid E, Helbostad J, Hjermstad MJ, Holzner B, Johnson C, Kemmler G, King MT, Kaasa S, Loge JH, Reijneveld JC, Singer S, Taphoorn MJB, Thamsborg LH, Tomaszewski KA, Velikova G, Verdonck-de Leeuw IM, Young T, Groenvold M, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group (2018) The EORTC CAT Core-the computer adaptive version of the EORTC QLQ-C30 questionnaire. Eur J Cancer 100:8–16

16. Fayers PM, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A (2001) The EORTC QLQ-C30 scoring manual, 3rd edn. European organisation for research and treatment of cancer, Brussels

17. Groenvold M, Petersen MA (2006) Addendum to the EORTC QLQ-C30 scoring manual: scoring of the EORTC QLQ-C15-PAL. European organisation for research and treatment of cancer, Brussels

18. Potter J, Hami F, Bryan T, Quigley C (2003) Symptoms in 400 patients referred to palliative care services: prevalence and patterns. Palliat Med 17(4):310–314

19. Addington-Hall J, McCarthy M (1995) Dying from cancer: results of a national population-based investigation. Palliat Med 9(4):295–305

20. Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Kiyasu E, Sobel K, Coyle N, Kemeny N, Norton L (1994) The memorial symptom assessment scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer 30a(9):1326–1336

21. Conill C, Verger E, Henriquez I, Saiz N, Espier M, Lugo F et al (1997) Symptom prevalence in the last week of life. J Pain Symptom Manag 14(6):328–331

22. Cheung WY, Le LW, Gagliese L, Zimmermann C (2011) Age and gender differences in symptom intensity and symptom clusters among patients with metastatic cancer. Support Care Cancer 19(3):417–423

23. Sekine I, Segawa Y, Kubota K, Saeki T (2013) Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. Cancer Sci 104(6):711–717

24. Jordhoy MS, Fayers P, Loge JH, Saltnes T, Ahlner-Elmqvist M, Kaasa S (2001) Quality of life in advanced cancer patients: the impact of sociodemographic and medical characteristics. Br J Cancer 85(10):1478–1485

25. Dong ST, Butow PN, Costa DS, Lovell MR, Agar M (2014) Symptom clusters in patients with advanced cancer: a systematic review of observational studies. J Pain Symptom Manag 48(3):411–450

26. Johnsen AT, Petersen MA, Pedersen L, Groenvold M (2009) Symptoms and problems in a nationally representative sample of advanced cancer patients. Palliat Med 23(6):491–501

27. Jarlbaek L, Hansen DG, Bruera E, Andersen M (2010) Frequency of opioid use in a population of cancer patients during the trajectory of the disease. Clin Oncol (R Coll Radiol) 22(3):199–207

28. Kane-Gill SL, Rubin EC, Smithburger PL, Buckley MS, Dasta JF (2014) The cost of opioid-related adverse drug events. J Pain Palliat Care Pharmacother 28(3):282–293

29. Stephenson J, Davies A (2006) An assessment of aetiology-based guidelines for the management of nausea and vomiting in patients with advanced cancer. Support Care Cancer 14(4):348–353

30. Bentley A, Boyd K (2001) Use of clinical pictures in the management of nausea and vomiting: a prospective audit. Palliat Med 15(3):247–253

31. To TH, Agar M, Yates P, Currow DC (2014) Prescribing for nausea in palliative care: a cross-sectional national survey of Australian palliative medicine doctors. J Palliat Med 17(9):1032–1036

32. Nauck F, Ostgathe C, Klaschik E, Bausewein C, Fuchs M, Lindena G, Neuwöhner K, Schulenberg D, Radbruch L, Working Group on the Core Documentation for Palliative Care Units in Germany (2004) Drugs in palliative care: results from a representative survey in Germany. Palliat Med 18(2):100–107

33. Lindqvist O, Lundquist G, Dickman A, Bukki J, Lunder U, Hagelin CL et al (2013) Four essential drugs needed for quality care of the dying: a Delphi-study based international expert consensus opinion. J Palliat Med 16(1):38–43

34. Berger MJ, Ettinger DS, Aston J, Barbour S, Bergsbaken J, Bierman PJ, Brandt D, Dolan DE, Ellis G, Kim EJ, Kirkegaard S, Kloth DD, Lagman R, Lim D, Loprinzi C, Ma CX, Maurer V, Michaud LB, Nabell LM, Noonan K, Roeland E, Rugo HS, Schwartzberg LS, Scullion B, Timoney J, Todaro B, Urba SG, Shead DA, Hughes M (2017) NCCN guidelines insights: antiemesis, version 2.2017. J Natl Compr Cancer Netw 15(7): 883–893

35. Herrstedt J, Roila F, Warr D, Celio L, Navari RM, Hesketh PJ, Chan A, Aapro MS (2017) 2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following high emetic risk chemotherapy. Support Care Cancer 25(1):277–288

36. Available from: http://pro.medicin.dk/Generelt/Nyheder/222. Accessed Sep 2018

37. Leelakanok N, Holcombe A, Schweizer ML (2016) Domperidone and risk of ventricular arrhythmia and cardiac death: a systematic review and meta-analysis. Clin Drug Investig 36(2):97–107

38. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E (2013) Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer 119(5):1098–1105

39. Hardy JR, O'Shea A, White C, Gilshenan K, Welch L, Douglas C (2010) The efficacy of haloperidol in the management of nausea and vomiting in patients with cancer. J Pain Symptom Manag 40(1): 111–116

40. Sinnott C (2002) Problems recruiting cancer patients to a comparative clinical trial of drug treatments for neuropathic pain in palliative care. J Pain Symptom Manag 23(4):270–272