Patient- and Treatment-Related Risk Factors for Nausea and Emesis during Concurrent Chemoradiotherapy

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Purpose: To evaluate the prevalence of acute nausea and emesis during concurrent chemoradiotherapy (CRT) with emphasis on the influence of patient- and treatment-related risk factors and prophylactic antiemetic medication.
Patients and Methods: A total of 335 patients treated with different intravenous standard chemoradiotherapy protocols in the inpatient setting were included in this retrospective study. Acute nausea and emesis, scored according to the CTC (version 3.0) criteria, were evaluated during 821 chemotherapy cycles. Side effects were correlated with patient-, tumor-, and treatment-related parameters.
Results: Overall, at least one episode of acute nausea occurred in 48% of the patients and at least one episode of vomiting occurred in 25% of patients. The emetogenic level of the applied chemotherapy protocol was the most significant risk factor for developing nausea and emesis ($p < 0.0001$). The site of irradiation – namely the thorax ($p = 0.0110$) and head and neck ($p = 0.0415$) – was also confirmed as a risk factor. Patient-related parameters, e.g., female gender ($p = 0.0003$), young age (< 40 years; $p = 0.0029$), weight loss > 5% ($p = 0.0004$), and the presence of a percutaneous endoscopic gastrostomy (PEG; $p = 0.0071$), were associated with higher rates of nausea and emesis, while a history of alcohol abuse showed a protective effect ($p = 0.0553$). In high emetogenic chemotherapy protocols, prophylaxis with 5-HT3 antagonist plus dexamethasone was superior to 5-HT3 antagonist alone ($p = 0.0383$).
Conclusion: Future studies should evaluate more effective prophylaxis protocols in CRT in order to reduce the high rates of nausea and emesis.

Key Words: Nausea · Emesis · Chemoradiotherapy · Side effects · Antiemetics

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Patienten- und therapiebezogene Risikofaktoren für Übelkeit und Erbrechen unter simultaner Radiochemotherapie

Zielsetzung: Das Auftreten von akuter Übelkeit und Erbrechen unter simultaner Radiochemotherapie (CRT) sollte in Hinblick auf patienten- und therapiebezogene Parameter sowie antiemetische Prophylaxe untersucht werden.
Material und Methode: 335 Patienten, die mit unterschiedlichen intravenösen Standard-Radiochemotherapie-Protokollen stationär behandelt worden waren, konnten in diese retrospektive Studie eingeschlossen werden. Übelkeit und Erbrechen, basierend auf den CTC-Kriterien (Version 3.0), wurden während insgesamt 821 Chemotherapie-Zyklen untersucht. Die Nebenwirkungen wurden mit patienten-, tumor- und therapiebezogenen Parametern korreliert.
Ergebnisse: Mindestens eine Episode von Übelkeit trat bei 48% der Patienten auf; 25% hatten mindestens einmaliges Erbrechen. Das emetogene Potential des verwendeten Chemotherapie-Protokolls war der signifikanteste Risikofaktor für das Auftreten von Übelkeit und Erbrechen ($p < 0{,}0001$). Die Bestrahlungsregion, namentlich Thorax ($p = 0{,}0110$) und Kopf/Hals ($p = 0{,}0415$), konnte auch als Risikofaktor bestätigt werden. Patientenbezogene Parameter wie weibliches Geschlecht ($p = 0{,}0003$) und jüngeres Alter (< 40 Jahre) ($p = 0{,}0029$) sowie Gewichtsabnahme von mehr als 5% ($p = 0{,}0004$) und das Vorliegen einer PEG-Sonde ($p = 0{,}0071$) waren mit verstärkter Übelkeit und Erbrechen verbunden, während Alkoholabusus einen protektiven Effekt zeigte ($p = 0{,}0553$). Bei hoch emetogenen Chemotherapie-Protokollen war die Prophylaxe mit der Kombination aus 5-HT3-Antagonist plus Dexamethason einem 5-HT3-Antagonisten allein überlegen ($p = 0{,}0383$).
Schlussfolgerung: Künftige Studien sollten effektivere Prophylaxe-Protokolle bei simultaner Radiochemotherapie untersuchen, um die hohen Raten an Übelkeit und Erbrechen zu reduzieren.

Schlüsselwörter: Übelkeit · Erbrechen · Radiochemotherapie · Nebenwirkungen · Antiemetika

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Introduction

Nausea and emesis are major side effects of oncologic treatment, which weaken the physical condition, impair quality of life, and cause treatment modification or interruption, which occasionally has a negative impact on treatment outcome [3, 23]. Even in the era of 5-HT_3 antagonists, nausea and vomiting were rated by patients as the most distressing side effects of chemotherapy [8]. For radiotherapy, where these acute reactions are considered to be less frequent and severe, the problem tends to be underestimated: according to a recent survey, one-third of patients with radiotherapy-induced nausea considered their antiemetic treatment insufficient [5].

Many studies have evaluated the incidence and severity as well as the prophylaxis and treatment of nausea and emesis caused by chemotherapy and – although having received less attention – by radiotherapy [8, 9, 12]. Thus, patient- and treatment-related risk factors could be established. For chemotherapy, the emetogenic risk is mainly defined by the substance, dosis, and route of administration. For radiotherapy, the emetogenic risk is, apart from fractionation schedule and the irradiated volume (e.g., total body irradiation), mostly defined by the anatomic site of irradiation. Treatment- and patient-related risk profiles were elaborated and guidelines for prophylaxis and treatment could be established separately for both modalities [6, 7, 9, 14, 15, 22]. (For combined regimen, emesis prevention according to the chemotherapy-related risk level (based on the drug with the highest emetic risk as well as patient specific risk factors) is recommended [20]). Concurrent chemoradiotherapy (CRT) is increasingly becoming standard treatment in the management of solid tumors [4, 21, 25, 26]. It is reported to lead to a significantly higher incidence of acute toxicity, including severe treatment-associated nausea and emesis [12]. However, there are only a few studies focusing on the prevention of these side effects during CRT [1, 13].

In this study, the prevalence of nausea and emesis and the impact of patient- and treatment-related factors during CRT with or without 5-HT_3 antagonist-based antiemetic prophylaxis were retrospectively evaluated.

Patients and Methods

Patient and Tumor Characteristics

A total of 335 adult patients treated with standard CRT protocols, in whom intravenous chemotherapy was administered in the inpatient setting and for whom acute side effects were sufficiently documented, were included in this retrospective study. There were 218 men (65%) and 117 women (35%) with a median age of 58 years (range, 19–78 years; Table 1). At the beginning of CRT, the median WHO performance status was 1 (range, 0–2). Most patients had normal weight (56%) or were overweight (30%) according to their body mass index. The most frequent diagnoses were head and neck cancer (47%) and rectal cancer (17%), followed by esophageal cancer (15%), cervical cancer (12%), anal cancer (7%), or other tumors (2%). Most patients suffered from advanced tumor disease (UICC stage III or IV in 70% of cases).

Concurrent Chemoradiotherapy

Three-dimensional (3D) conformal RT was performed using either a 6 or 25 MV photon beam accelerator with individual field arrangement. In general, the target volume

Table 1. Acute nausea and emesis according to patient related risk factors. CRT: chemoradiotherapy; PEG: percutaneous endoscopic gastroenterostomy.

Tabelle 1. Akute Übelkeit und Erbrechen in Hinblick auf patientenassoziierte Parameter. CRT: Radiochemotherapie; PEG: perkutane endoskopische Gastroenterostomie.

	Patients	Nausea		Emesis		Nausea (grade 2/3) ± emesis	
	n (%)	%,	p value	%,	p value	%,	p value
Sex							
Male	218 (65)	41	**0.0003**	23	0.09	34	**0.002**
Female	117 (35)	62		31		50	
Age							
≤ 40 years	25 (8)	72	**0.0128**	44	**0.0261**	60	**0.0029**
41–60 years	175 (52)	45		23		37	
> 60 years	135 (40)	48		25		39	
Performance status (WHO)							
0	87 (26)	48		26		38	
1	226 (68)	48		24		39	
2	22 (7)	46	0.5675	36	0.2204	55	0.1534
Alcohol anamnesis							
Yes	25 (8)	31	0.0553	24	0.6383	31	0.3354
No	310 (92)	50		26		40	
Weight during CRT							
No change (± 5%)	243 (73)	42	**0.0051**	20	**0.0016**	33	**0.0004**
Weight loss > 5%	81 (24)	64		41		57	
Weight gain > 5%	11 (3)	64		36		55	
PEG							
Yes	118 (35)	56	**0.0334**	33	**0.0173**	49	**0.0071**
No	217 (65)	44		21		34	
Tumor stage (n = 314)							
I	21 (6)	43		29		38	
II	60 (18)	47	0.6912	15	0.5439	35	0.7193
III	98 (29)	46		30		43	
IV	135 (40)	50		24		38	

included the primary tumor and the locoregional lymph nodes. The site of irradiation was the head and neck (47%), pelvis (33%), thorax (16%), and abdomen (±pelvis) (4%). The patients were treated with a median total dose of 52.4 Gy (range, 19.8–70.6 Gy) with daily fractions of 1.9 Gy (range, 1.8–2 Gy) (ICRU Report 50).

We evaluated 821 cycles of chemotherapy in 335 patients which were administered by intravenous infusion concomitantly to radiotherapy. The agents and regimens used were as follows: 5-FU (rectal cancer: 1000 mg/m^2, days 1–5 and 29–33), cisplatin (cervical cancer: 40 mg/m^2, days 1, 8, 15, 22, 29), docetaxel (head and neck cancer: 20 mg/m^2, days 1, 8, 15, 22, 29), 5-FU plus cisplatin (head and neck cancer, cancer of the esophagus: 800 mg/m^2 plus 20 mg/m^2, days 1–5 and 29–33), or 5-FU plus mitomycin C (anal cancer: 5-FU: 1000 mg/m^2, days 1–4 and 29–32; mitomycin C: 10 mg/m^2, days 1 and 29). The emetogenic level of the mono- or poly-chemotherapy protocols was graded according to the classification described by Hesketh et al. [10]: cisplatin ≥ 50 mg/m^2 = level V; cisplatin < 50 mg/m^2 = level IV; 5-FU = level II; mitomycin = level II; docetaxel = level II. The algorithm for defining the emetogenicity of combined regimens was adopted: adding one or more level II agents increases the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination, thus, e.g., cisplatin < 50 mg/m^2 plus 5-FU = level V and 5-FU plus mitomycin C = level III.

Table 2. Acute nausea and emesis according to treatment related risk factors. Cis: cisplatin; 5-FU: 5-fluorouracil; Mito: mitomycin C; Doc: docetaxel. [a]Emetogenity of chemotherapy according to Hesketh et al. [10].

Tabelle 2. Akute Übelkeit und Erbrechen in Hinblick auf therapieassoziierte Parameter. Cis: Cisplatin; 5-FU: 5-Fluorouracil; Mito: Mitomycin C; Doc: Docetaxel.

	Patients	Nausea		Emesis		Nausea (grade 2/3) ± emesis	
	n (%)	%,	p value	%,	p value	%,	p value
Emetogenic level of chemotherapy[a]							
V (Mono Cis 100 mg/m^2 or Cis + 5-FU)	148 (44)	68	**0.0015**	37	**0.0123**	56	**0.0001**
IV (Mono Cis 20–40 mg/m^2)	44 (13)	52		30		52	
III (Mito + 5-FU)	38 (11)	40	**<0.0001**	16	**<0.0001**	21	**<0.0001**
II (Mono 5-FU or Doc)	105 (31)	22		11		17	
Time (n = 295)							
First chemotherapy cycle	295 (100)	33	0.9579	17	0.8954	26	0.6275
Last chemotherapy cycle	295 (100)	34		16		23	
Irradiation site							
Pelvis	112 (33)	38	**0.0110**	18	**0.0179**	30	**0.0151**
Thorax	52 (16)	60		35		50	
Head and neck	157 (47)	51	**0.0415**	26	0.1109	42	0.0507
Abdomen	14 (4)	50		43		43	
Irradiation single dose							
1.8 Gy	161 (48)	46	0.4732	25	0.1911	40	0.7743
1.9 Gy	143 (43)	50		24		40	
2.0 Gy	31 (9)	52		36		36	
Prophylaxis in level IV/V[a] (n = 192)							
5-HT$_3$ Antagonist	70 (36)	61	**0.0383**	27	0.8187	49	0.1749
5-HT$_3$ Antagonist + dexamethasone	122 (64)	46		29		38	
Prophylaxis in level II/III[a] (n = 143)							
Dexamethasone	44 (31)	2		0		2	
5-HT$_3$ Antagonist	38 (27)	37		16		21	
5-HT$_3$ Antagonist + dexamethasone	12 (8)	8	0.1445	0	0.2486	0	0.2973
None	49 (34)	10		6		10	

All patients with high emetogenic chemotherapy (level V or IV: cisplatin monotherapy or cisplatin + 5-FU) had an antiemetic prophylaxis, consisting of a 5-HT$_3$ antagonist plus dexamethasone in 64% or a 5-HT$_3$ antagonist alone in 36% (Table 2). In chemotherapy with low emetogenic potential (level III or II: 5-FU monotherapy, 5-FU + mitomycin or docetaxel), dexamethasone (31%), a 5-HT$_3$ antagonist (27%), the combination of both (8%) or no prophylaxis (34%) was administered.

Nausea and Emesis

Data on nausea and emesis, which were collected from charts, were scored according to the CTC criteria (version 3.0). The reaction grade represented was the highest grade that occurred in a particular patient during the complete (radio)chemotherapy. As oral intake, which is a main parameter for the scoring of nausea, is often reduced in head and neck cancer patients by tumor and/or mucositis, the need of antiemetic drugs was also considered for scoring in these patients. Nausea and emesis were correlated with patient-, tumor- and treatment-related parameters.

Statistical Analysis

Mean values are indicated with standard deviation. Differences between groups on continuous variables were tested using the Mann–Whitney test. For categorical variables, Fisher's exact test was applied. The McNemar test was used to test differences between paired groups on categorical variables. Statistical analyses were computed on a significance level of 5%.

Results

Overall, 161 patients (48%) developed at least one episode of acute nausea during CRT. It was mild (grade 1) in 26%, moderate (grade 2) in 53%, and severe (grade 3) in 21%. No patient suffered from excessive grade 4 nausea. At least one episode of acute emesis developed in 85 patients (25%). It was mild (grade 1) in 48%, moderate (grade 2) in 34%, and severe (grade 3) in 18%. No patient suffered from excessive grade 4 emesis. Thus, overall 132 patients (39%) had grade 2/3 nausea and/or emesis.

Nausea and Emesis vs. Patient and Tumor Characteristics

Female patients (nausea: 62% vs. 41%, $p = 0.0003$) and patients younger than 40 years (nausea: 72% vs. 46%, $p = 0.0128$; emesis: 44% vs. 24%, $p = 0.0261$) suffered significantly more from nausea and emesis compared with men and patients over 40, respectively (Table 1). Patients with a percutaneous endoscopic gastroenterostomy (PEG) for additional or sole nutrition developed emesis/nausea grade 2/3 more often. Nausea and emesis was also significantly correlated with weight loss of more than 5% during CRT. There was a strong trend for less nausea and emesis when a history of alcohol abuse was present. No significant correlations were noted regarding tumor stage and performance status.

Nausea and Emesis vs. Treatment

The emetogenic level of the applied chemotherapy protocol, as graded according to Hesketh et al. [10], had a significant influence on nausea and emesis which was most pronounced between the highest and lowest level ($p < 0.001$; Table 2). The emetogenic risk of radiotherapy, as established according to the site of irradiation, also showed an influence during CRT: irradiation of the thorax was associated with the highest rates of grade 2/3 nausea ± emesis, which was also significant when compared with irradiation of the pelvis. Regarding the 295 patients with more than one cycle of chemotherapy, there was no difference when comparing acute nausea and emesis during the first and the last cycles.

Nausea and Emesis vs. Antiemetic Prophylaxis

Patients with high (level IV/V) emetogenic chemotherapy suffered significantly less from acute nausea when they received a combination of 5-HT3 antagonist and dexamethasone for prophylaxis compared with 5-HT3 antagonist alone. In low (level II/III) emetogenic chemotherapy, no significant differences were observed between the prophylaxis groups.

Discussion

During CRT almost half of the patients (48%) had at least one episode of nausea and one-fourth (25%) suffered from emesis, despite most patients having received an antiemetic prophylaxis based on the guideline recommendations at that time. These data are in line with a recently published prospective observational trial on emesis in radiotherapy from Italy: nausea occurred in 51.7% and emesis in 22.5% of the 125 patients receiving CRT compared with 23.7% and 9.2%, respectively, of the 879 patients treated with radiotherapy alone [16]. In a study on head and neck cancer patients treated with intensity modulated radiation therapy, 65% of the 23 patients with concurrent chemotherapy suffered from nausea (grade 1: 35%; grade 2: 30%) compared with 50% (grade 1) of the 20 patients with radiotherapy alone [17]. Higher grade (grade 2) nausea was significantly associated with concurrent chemotherapy. In our study, the emetogenic level of the chemotherapy was the strongest risk factor for nausea and emesis. We found that adopting the algorithm of Hesketh et al. [10], which considers each agent in combined regimens, results in a more accurate gradation than considering only the most-emetic chemotherapy agent which is actually recommended [20].

Female gender and young age – known as important patient-related risk factors for developing nausea and emesis during chemotherapy and during radiotherapy – as well as the protective effect of alcohol abuse have also proven to be relevant factors for CRT [12, 19]. Abdomen as the site of irradiation, which is the most evaluated parameter for nausea and emesis in radiotherapy, was not confirmed, probably because this site was underrepresented (4%) in our study. In the Italian trial, the irradiated site, i.e., upper abdomen and a field size > 400 cm^2, were the only radiotherapy-related risk factors for nausea and emesis [16]. Instead, irradiation of the thorax and head and neck, i.e., in patients with esophagus or head and neck cancer, was associated with significant nausea and emesis. In the head and neck IMRT trial already mentioned (with nausea in 50% of the patients even during radiotherapy alone), the dose to the dorsal vagal complex of the mid-medulla and the use of a low neck field (besides younger age) were identified as significant factors for nausea [17]. In our study, weight loss, as a potential consequence of these side effects, and the presence of a PEG, which is used to prevent weight loss, was significantly associated with nausea and emesis during CRT. It could be shown in former studies that weight loss during chemotherapy correlates with impaired tumor response, disease-free survival, and overall survival [25]. Thus, the importance of effective antiemetic prophylaxis in CRT is evident, especially in predisposing conditions, such as cisplatin-based CRT in younger women (cervix cancer), in head and neck cancer patients, and in CRT of the upper abdomen/lower thorax.

All patients with high emetogenic chemotherapy had an antiemetic prophylaxis, more or less in line with the guidelines at that time [7, 15]. In this group, we could confirm the superiority of the combination of a 5-HT3 antagonist with dexamethasone against a 5-HT3 antagonist alone which is also the basis for more recent clinical recommendations [19]. There were no differences between the efficacy of the 5-HT3 antagonists used, namely ondansetron and granisetron, which are thought to have an equivalent effect at prescribed doses [15]. In the Italian trial, an antiemetic drug was given to a minority (prophylactic in 12.4%, symptomatic in 4.6%), thus, confirming the radiation

oncologists' attitude in underestimating radiotherapy-induced emesis and underprescribing antiemetics [16]. Novel substances, such as the neurokinin-1 receptor antagonist aprepitant, have been established as potent prophylactic antiemetics in chemotherapy [2, 11, 27, 29,] but have not been evaluated in CRT. Only a few studies have focused on the prevention of nausea and emesis in CRT: based on promising data in hyperthermo-chemo-radiotherapy for esophageal cancer [18], the 5HT3 antagonist ramosetron was evaluated in CRT for pancreaticobiliary cancer. In 10 patients who were refractory to prophylactic metoclopramide and rescue ondansetron, prophylactic ramosetron could reduce the symptoms in 60% (5-FU 500 mg/m^2 day 1–3; 40 Gy; split of 2 weeks) [13]. In a feasibility study, the prophylactic use of aprepitant (plus 5HT3 plus dexamethasone) resulted in a reduction of nausea and emesis when compared to historical controls (19 patients with pancreatic cancer, gemcitabine plus 5-FU/capecitabine-based CRT with 50.4 Gy: grade 3 nausea and grade 4 vomiting in one patient) [1].

Our study has several limitations, including those associated with collection of any retrospective data, especially when assessing subjective symptoms such as nausea and emesis. Furthermore, we did not evaluate potential causes other than chemoradiotherapy (e.g., opioid comedication, gastroparesis, and bowel obstruction). However, to the best of our knowledge, this is the only study investigating acute nausea and emesis with the use of different standard protocols of CRT in clinical practice.

Conclusion

We conclude that, despite the use of 5-HT3 antagonist plus dexamethasone-based prophylaxis in the majority of patients, acute nausea and emesis are still major adverse effects of CRT affecting half of the patients. Potent novel antiemetics which are already established as prevention of chemotherapy-induced nausea and emesis should also be evaluated for CRT protocols.

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