Development of a Questionnaire for Monitoring Risk Factors for Chemotherapy-induced Nausea and Vomiting – A NOGGO Pilot Study

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Abstract. *Background:* Despite many years of clinical research and development, nausea and vomiting remain challenging toxicities related to chemotherapy. The aim of our study was to clarify the significance of non-pharmacological, patient-related risk factors for chemotherapy-induced nausea and vomiting. Furthermore, we aimed to develop a unique patient-related risk score predicting nausea and vomiting in patients with gynaecological malignancies under chemotherapy. *Materials and Methods:* Based on a literature research, 27 risk factors were identified and a preliminary questionnaire was generated. This questionnaire was assessed in 20 patients diagnosed with gynaecological malignancies. *Results:* The majority of questions were easy to understand and could be answered unambiguously. Questions regarding alcohol consumption and nutrition needed optimization due to problems with suitable answer option finding. *Conclusion:* Patient-related factors are currently not included when selecting antiemetic prophylaxis in patients under chemotherapy. After a few amendments, our questionnaire will be used in prospective study. To our knowledge, this is the first practicable questionnaire addressing these issues.

Nausea and vomiting still remain frequent side-effects of chemotherapy (1). A patient survey reported by Coates *et al.* in 1983 recognized these as the most severe adverse effects

for patients (2). Due to improved antiemetic medication, vomiting was only rated the fifth most-limiting issue when the survey was repeated in 1993, however nausea remained the most feared and severe adverse effect (3). This is still a problem nowadays as Ballatori *et al.* showed in a study in 2007, which stated that 62% of patients undergoing chemotherapy suffered from nausea and 34% experienced vomiting. Over 90% of all patients suffering from chemotherapy-induced nausea and vomiting (CINV) indicated that this had a negative impact on their daily life (1). In the Expression III study by Sehouli *et al.*, the topic of CINV still needed addressing (4). It is especially notable that CINV can be of very different severity in patients receiving the same chemotherapy despite standardized pharmacological prophylaxis (5). Consequently, the identification of further factors associated with CINV development remains of great interest. Several studies have already been conducted addressing this question, however, with contradictory results. There is a consensus that the risk factors such as female sex (6-8), young age (6, 7, 9), prior susceptibility to nausea and vomiting (10-12), and patient's expectations of nausea following chemotherapy (13, 14) are significant. The importance of other risk factors such as fear of chemotherapy (12, 15), alcohol consumption (15, 16), nausea and vomiting during pregnancy (17, 18), motion sickness (6, 19), performance status (6, 7) and the location of the tumour (20, 21) are still disputed. Moreover, neither a validated questionnaire for retrieving information regarding risk factors, nor a practicable model allowing quick and easy classification of patients into different risk classes and adaptation of the antiemetic therapy accordingly are available.

The aim of our study was the development of a questionnaire regarding patient-related CINV risk factors. A prospective, observational study will follow in which all risk factors found in literature will be re-examined in order to

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develop a risk prediction model that can be used in daily clinical practice. In order to make that possible, a validated questionnaire that reliably and globally covers all patient-related risk factors is required. Patients are supposed to complete the questionnaire on their own, therefore it needs to be easy to understand and response options need to be clear and unambiguous. This article deals with the development of such a questionnaire and the results of the validation.

Materials and Methods

A comprehensive online literature search in order to depict the current state of research on patient-related risk factors for CINV was conducted in February 2017 using PubMed as the database. Key words used in the search were “chemotherapy-induced nausea and vomiting”, “risk factors”, “prediction” and “determinants”. The identified factors were subsequently registered and included in the preliminary questionnaire. For each factor, a question was formulated. This preliminary questionnaire was assessed in a panel discussion within the Nord-Ostdeutschen Gesellschaft für Gynäkologische Onkologie (NOGGO) working group consisting of study nurses, doctors and organisational staff prior to approval for patient evaluation. The final version was presented and answered by 20 patients with gynaecological malignancies under chemotherapy. The questionnaire was handed out and answered in an interview with the examiner in order to immediately recognise problems or queries concerning the questionnaire. Patient comments, their diagnosis, prior and current therapy, number of chemotherapy cycles received and level of nausea and vomiting during chemotherapy were noted on the questionnaire. All information was given anonymously. The changes proposed by the patients were noted for further presentation to the NOGGO working group and the questionnaire was adjusted accordingly.

Due to a limited amount of data and the aim of this preliminary examination, only descriptive statistical methods were performed.

Results

Twenty-one studies were included in the systematic literature research in which a total of 38 risk factors were examined (Table I). Each factor was examined by a different number of studies with very different results. In our questionnaire, only factors that were examined by at least two studies and found to be significant at least once were included. These factors were: age, sex, emetogenicity of chemotherapy, antiemetic therapy, tumour location, alcohol consumption, fear of chemotherapy, expected level of nausea after chemotherapy, prior susceptibility to nausea and vomiting, motion sickness, nausea in pregnancy, educational background, ethnicity, body mass index, performance status, smoking, vertigo, comorbidities and marital status. Further factors that had not been examined before, but were considered to be important were nutrition, allergies, migraine, nausea caused by pharmaceuticals, method and date of tumour excision, postoperative nausea, co-medication, preventive measures taken by the patient to

Table I. *Risk factors for chemotherapy-induced nausea and vomiting found in the literature.*

Risk factor	Number of studies examining it (Ref)
Age	18 (6-20,22-24)
Alcohol consumption	14 (6-9,11,13,15-19,22-24)
Emetogenicity of chemotherapy	12 (6-8,10-13,15-17,22,24)
Antiemetic therapy	12 (6,10-13,15,16,19,22-25)
Gender	11 (6-8,10,12-15,19,22,23)
Motion sickness	10 (6,8,13,15,17-19,23-25)
Fear of chemotherapy	8 (8,10,12,15,17,19,24,25)
Nausea and vomiting in prior chemotherapy	6 (8,9,17,20,23,25)
Concomitant radiotherapy	5 (8,10,15,19,22)
Performance status	4 (6,7,15,22)
Nausea in the morning	4 (9,13,15,16)
Stage of cancer	4 (10,15,17,22)
Nausea in pregnancy	4 (17,18,23,24)
Prior susceptibility to nausea and vomiting	3 (11,12,15)
Expected level of nausea after chemotherapy	3 (12-14)
Smoking	2 (7,18)
Fatigue	2 (8,15)
Educational background	2 (10,15)
Comorbidities	2 (10,24)
Vertigo	2 (15,26)
Profession	2 (17,26)
Body surface area	1 (6)
Place of residence	1 (10)
Marital Status	1 (10)
Health insurance coverage	1 (10)
Ethnicity	1 (15)
Application of Traditional Chinese Medicine	1 (15)
Hypertension	1 (18)
Body Mass Index	1 (18)
Menopause	1 (18)
Digestion	1 (18)
Ascites	1 (18)
NSAIDs	1 (19)
Polymorphism in dopamine receptor	1 (19)
Location of tumour	1 (20)
Percutaneous endoscopic gastrostomy tube	1 (22)
Weight loss	1 (22)
Sleep	1 (24)

NSAIDs: Non-steroidal anti-inflammatory drugs.

avoid side-effects of chemotherapy, measures taken by patients to ease nausea, social support, company when receiving chemotherapy, distress and family members who had experienced chemotherapy. The resulting questionnaire contained 32 questions (Table II) as some factors needed to be examined using more than one question. Information concerning age, ethnicity, location and classification of tumour, chemotherapy, body mass index, performance status,

Table II. *Questionnaire used in this study.*

Table III. *Baseline patient characteristics among the study population of women (n=20) with gynaecological malignancies.*

Characteristic		Value
Age, years	Median (range)	60.1 (32-79)
Tumour, n (%)	Breast	11 (55)
	Ovary	7 (35)
	Endometrial	1 (5)
	Uterine sarcoma	1 (5)
	Primary	17 (85)
Tumour, n (%)	Relapse	3 (15)
	LEC	9 (45)
Chemotherapy, n (%)	MEC	5 (25)
	HEC	3 (15)
	Antibodies	3 (15)
	Yes	17 (85)
Surgery, n (%)	No	3 (15)
	0	7 (35)
Level of nausea (CTC), n (%)	1	5 (25)
	2	4 (20)
	3	4 (20)
	Yes	4 (20)
Vomiting, n (%)	No	16 (80)

LEC: Low emetogenic chemotherapy, MEC: moderately emetogenic chemotherapy, HEC: highly emetogenic chemotherapy, CTC: Common Toxicity Criteria (27).

method and date of surgery, pregnancies, comorbidities, co-medication and smoking were obtained from the patient's file and thus were not included in the questionnaire.

The preliminary questionnaire needed validation, which was performed on 20 patients receiving outpatient chemotherapy. Enrollment was based on three inclusion criteria (female sex, a diagnosed gynaecological tumour and current or prior chemotherapy). The youngest patient was 32 years old and the oldest 79 years old (mean=60.1 years). Relevant patient data are given in Table III. Exclusion criteria were lack of consent and therapy with antibodies only.

The emetogenicity of chemotherapy ranged from minimally emetogenic to highly emetogenic but at the same time all patients receive the same antiemetic therapy of neurokinin-1 receptor antagonist, palonosetron and dexamethasone directly before administration of chemotherapy, and metoclopramide drops if needed. Seven patients reported no nausea at all, five reported mild nausea with normal ingestion, four reported moderate nausea with restricted ingestion, and four reported severe nausea with vomiting.

All questions of the questionnaire were understandable and were answered unambiguously by patients. Only the questions asking about motion sickness in a lift or in a car were responded to negatively by all patients. Regarding the remaining 30 questions, all possible responses to all questions were ticked at least once, which shows that none of the possibilities were redundant (Table II).

The factors that were confirmed most often were motion sickness on a boat or ship (55%), vertigo (50%), subjectively sensitive stomach (45%) and nausea during pregnancy (40%). Half of the patients expected that they would suffer from at least a moderate level of nausea, whereas only one-quarter of the patients expected to be vomiting after chemotherapy. The average level of fear of nausea was only reported to be 1 out of 4 (4 being extreme fear), whereas overall fear of chemotherapy was reported to be 2 out of 4. The most frequent measures taken by patients in order to ease nausea were medication (35%) and fresh air (40%). Half of the patients did not take any preventative measures preceding chemotherapy. Four patients reported having increased their physical exercise and five had changed their nutrition in the hope of preventing side-effects of chemotherapy. Half of the patients were accompanied by a friend or relative when receiving chemotherapy, and apart from two patients, all felt they had strong social support. Overall, 17 out of the 20 patients never, or only rarely drank alcohol. The average distress level in the week preceding chemotherapy was 5.6 out of 10 (10 being extreme distress), with seven patients indicating a level of 7 or more and two even stating a level of 10. An overview of all answers is shown in Table IV.

Overall, the questionnaire was easy to understand and there were very few queries made by patients. The only problematic items were the questions concerning nutrition and alcohol consumption as eight out of 20 patients did not find suitable answer options. Therefore, we changed the answer options for alcohol consumption regarding the frequency and completely changed the question about nutrition. Regarding the question about migraine, a third possible response was inserted, "Previously yes", next to "Yes" and "No".

Discussion

The results of the validation step show that the questionnaire was well accepted and understandable, however, some weaknesses have emerged during the patient survey. The description of alcohol consumption intervals was challenging for the patients regarding the frequency and therefore objectivity. The same problem occurred when asking about nutrition as this topic seems hard to objectify.

As there were four questions asking about motion sickness (nausea in a car, in a lift, on a ship and in a roller coaster), this topic might be over-represented and one or two questions might be unnecessary, especially because none of the patients reported experiencing nausea in a car or in a lift. All four questions will be retained to determine if there are any significant results in the future.

The fact that in this study patients were interviewed personally might be considered to invalidate some of the results as the questionnaire is designed to be answered anonymously and independently. There is the possibility that patients gave

Table IV. Frequency of responses of patients (n=20) to questions included in the questionnaire.

Factor	Response	N (%)	Factor	Response	N (%)
Nutrition	With meat	17 (85)	Preventative measures	Special food	5 (25)
	Vegetarian	2 (10)		Acupuncture	0 (0)
	Other	1 (5)		Physical exercise	4 (20)
Allergies	Yes	2 (10)	Family members with CINV	Mistletoe	1 (5)
	No	18 (90)		Vitamins	2 (10)
Alcohol intake	Never	9 (45)		Other	2 (10)
	Rarely	8 (40)		None	10 (50)
	1-3 times/week	1 (5)	Expected level of nausea	Yes	3 (15)
	4-6 times/week	1 (5)		No	17 (85)
Nausea after surgery	Daily	1 (5)	Expected vomiting	0	7 (35)
	Yes	5 (25)		1	2 (10)
	No	13 (65)		2	7 (35)
Migraine	Not applicable	2 (10)		3	2 (10)
	Yes	2 (10)		4	1 (5)
	Previously yes	2 (10)	Fear of chemotherapy	Do not know	1 (5)
Vertigo	No	16 (80)		Yes	4 (20)
	Yes	10 (50)		No	13 (65)
	No	10 (50)	Fear of CINV	Do not know	3 (15)
Nausea/vomiting after medication	Yes	5 (25)		0	3 (15)
	No	15 (75)		1	6 (30)
Sensitive stomach	Yes	9 (45)		2	2 (10)
	No	11 (55)		3	8 (40)
Nausea in pregnancy	Yes without vomiting	7 (35)	Accompanied to administration of chemotherapy	4	1 (5)
	Yes with vomiting	1 (5)		0	9 (45)
	No	8 (40)		1	5 (25)
	Never pregnant	4 (20)		2	1 (5)
Nausea in a lift	Yes	0 (0)	Sufficient social support	3	4 (20)
	No	20 (100)		4	1 (5)
Nausea in a car	Yes	0 (0)		Yes	10 (50)
	No	20 (100)		No	9 (45)
Nausea on a boat	Yes	11 (55)	Distress level	Do not know	1 (5)
	No	8 (40)		Yes	18 (90)
	Not applicable	1 (5)	CINV: Chemotherapy-induced nausea and vomiting.	No	2 (10)
Nausea in a rollercoaster	Yes	5 (25)		Median (range)	5.6 (1-10)
	No	10 (50)			
	Not applicable	5 (25)			
	Medication	7 (35)			
	Relaxation	3 (15)			
	Fresh air	8 (40)			
	Physical exercise	1 (5)			
Ways to ease nausea (multiple answers possible)	Special food	1 (5)			
	Other	3 (15)			
	Not applicable	3 (15)			

different answers in the interview than they would have written down on their own, especially regarding very personal questions concerning fear, social support and distress. For this reason, the results were not tested for correlations between the answers and the actual nausea that patients experienced. Another reason for not performing further statistical tests on the data is the small and very heterogeneous study cohort which does not represent those who might be included under our future inclusion and exclusion criteria.

In contrast to prior studies that assessed only a few risk factors at the same time, we retrieved information about all known risk factors found in literature. As far as we are aware, no questionnaire has been designed regarding patient-related risk factors for CINV that examines all risk factors as extensively as ours does.

In the next step, our questionnaire will be applied to a larger number of patients who meet the planned criteria. The patient survey showed that the questionnaire is applicable for the next step after addressing minor faults.

The aim of the survey was to examine if the questionnaire we designed was clear and understandable. This aim has definitely been reached and after implementing the proposed changes, the questionnaire is now ready for use in further studies examining risk factors for CINV.

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