

The Emesis Trial: Depressive Patients with Brain Tumors are more Affected by Chemotherapy-induced Nausea and Vomiting

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Abstract

Purpose: Patients with malignant brain tumors face a limited life expectancy and at the same time, they suffer from afflicting symptoms and undesired effects of tumor treatment. Apart from bone marrow suppression, standard chemotherapy with temozolomide causes nausea, emesis and loss of appetite. In this pilot study, we investigated how chemotherapy-induced nausea and vomiting (CINV) affects the patients' levels of depression and their quality of life.

Methods: In this prospective observational multicentre study (n = 87), nausea, emesis and loss of appetite were evaluated with an expanded MASCC questionnaire, covering ten days during the first and the second cycle of chemotherapy. Quality of life was assessed with the EORTC QLQ-C30 and BN 20 questionnaire and levels of depression with the PHQ-9 inventory before and after the first and second cycle of chemotherapy.

Results: CINV affected a minor part of patients. If present, it reached its maximum at day 3 and decreased to baseline level not before day 8. Levels of depression increased significantly after the first cycle of chemotherapy, but decreased during the further course of treatment. Patients with higher levels of depression were more severely affected by CINV and showed a lower quality of life through all time-points.

Conclusion: We conclude that symptoms of depression should be perceived in advance and treated in order to avoid more severe side effects of tumor treatment. Additionally, in affected patients, delayed nausea was most prominent, pointing towards an activation of the NK₁ receptor. We conclude that long acting antiemetics are necessary to treat temozolomide-induced nausea.

Introduction

Brain tumors are among the most aggressive neoplasms. Glioblastoma, the malignant glioma with the worst prognosis, is associated with a median survival time of 16–18 months and a five year survival rate of 6 % for male and 9 % for female patients [1]. Standard treatment includes bulk surgery, if possible, followed by radiotherapy combined with concomitant and adjuvant chemotherapy with temozolomide (TMZ), plus tumor treating fields. TMZ is an orally available alkylating agent administered concomitantly during radiotherapy at 75 mg/m²/d followed by six adjuvant cycles at 150–200 mg/m² of body surface on day 1 to 5 of a 28 day cycle. Common side effects are bone marrow suppression and, in rare cases, liver toxicity with elevated transaminases [2], skin erythema, alopecia and others. Close monitoring of neutrophils, lymphocyte and thrombocyte count and transaminases on a weekly basis and dose reduction, if required, is crucial.

The most common non-hematological side-effects are nausea, emesis and loss of appetite. At the standard dose of 150–200mg/m², TMZ is considered to be moderately emetogenic, which means that 30–90 % of patients would experience nausea, emesis and loss of appetite during treatment without appropriate emetogenic prophylaxis.

Chemotherapy-induced nausea and vomiting (CINV) can occur as an acute or delayed reaction. Acute nausea and vomiting occur within 24 h after application of chemotherapy, usually with a peak at 5–6 h. Nausea is induced via the peripheral 5-hydroxytryptophan receptor 3 (5-HT₃) [3]. Delayed nausea occurs from 24–120 hours and is activated through a central pathway, mainly activated through the neurokinin-1 (NK₁) receptor. Anticipatory nausea is a conditioned response starting already before application of chemotherapy in expectancy of nausea, i.e. when the chemotherapy infusion comes in sight.

The most important breakthrough in antiemetic treatment took place in 1992 when ondansetron was launched as the first 5-HT₃ antagonist in the market. A second important member of this class of agents is granisetron. With a median half-life of approximately 4 h (ondansetron) and 10 h (granisetron), both substances are useful to treat acute, but not delayed nausea. Prophylactic antiemetic treatment with steroids is usually not applied in brain tumor patients since patients are often heavily pretreated with corticosteroids to reduce peritumoral edema and rapid tapering is desired. In addition, several publications suggest tumor-promoting effects of corticosteroids [4, 5].

The usual antiemetic treatment in patients with glioma receiving TMZ consists of a 5-HT₃ antagonist like ondansetron or granisetron, approximately one hour before chemotherapy. However, clinical experience shows that about one third of patients suffer from severe nausea and emesis despite antiemetic treatment, affecting the patients' health-related quality of life (QoL).

In addition to treatment burden, patients with gliomas develop depression during the first six months after diagnosis in about 15–20 % of cases [6] and up to 30 % of brain tumor patients suffer from clinically relevant depression (assessed at any time during the course of disease) [7]. Depression is associated with reduced physical function, cognitive impairment and QoL reduction [6, 8]. QoL is impaired in patients with high grade gliomas compared to healthy controls, and similar results were found in patients with other solid cancer, e.g. NSCLC [9]. Patients treated with TMZ experience no worsening but rather a slight improvement of QoL compared to their baseline pretreatment assessment [10]. Adding TMZ after radiotherapy has no negative implications on QoL [2, 11]. Nonetheless, treatment associated side-effects like CINV may seriously affect patients' QoL. Accordingly, one of the most common fears of patients from chemotherapy is nausea [12].

In the study presented, we investigated the level and time course of nausea, emesis and loss of appetite in patients with malignant brain tumors during their first two cycles of chemotherapy with TMZ. In addition, we asked for the patients' QoL and levels of depression prior to chemotherapy and after the first and second cycle of chemotherapy. Our aim was to determine whether there is an interaction between CINV and patients' levels of depression and QoL at any of the given time-points.

Methods

Study population

In this prospective, observational, multicentre study, we investigated patients treated in six hospitals in Germany specialised in treatment of brain cancer patients (University Hospitals Marburg, Münster, Regensburg, Würzburg as well as DIAKOVERE Henriettenstift Hannover and Hospital Barmherzige Brüder Regensburg) in between 2012 to 2016. 50 patients were planned for inclusion in the study; recruitment was extended to 87 patients as more patients could be enrolled as primarily planned. All 87 patients were included consecutively. Permission of the local ethics committee was obtained (08/13, 26.02.2013), and all patients gave informed consent to participate. Main inclusion criteria were age older than 18 years, qualification for legal acts and a brain tumor requiring chemotherapy. QoL and levels of depression were assessed prior to chemotherapy (t0) and after the first (t1) and second (t2) cycle of chemotherapy. The level and time course of nausea, emesis and loss of appetite were asked during the first two cycles of chemotherapy with TMZ (c0, c1). This study was conducted following the STROBE guidelines for observational studies.

Questionnaires

Patients' baseline characteristics (sex, age, Karnofsky Performance Score (KPS), WHO-grade, chemotherapeutic agent and dosage and concomitant antiemetic therapy) were assessed by a questionnaire designed for this study's purpose.

The validated MASCC questionnaire was used to evaluate nausea, emesis and loss of appetite. It scales nausea from 0-10 with 0 meaning no nausea at all, frequency of emesis and loss of appetite (on a dichotome scale with yes/no) on a daily basis [13]. We expanded the original MASCC questionnaire from five to ten days in order to additionally cover the five days after the last application of TMZ, which is given day 1-5 in cycles of 28 days (Supplements 2). Timepoints of evaluation were one day prior to chemotherapy as baseline, on the first day of chemotherapy (before and after application) and day 2 to 10 during c1 and c2. Patients were asked to indicate their level of nausea on a numeric rating scale to visualize the extent of nausea.

The PHQ-9 is an established tool to evaluate depression by patient self-report [14] and is validated for glioma patients [15]. PHQ-9 is sensitive for intra-patient changes [16] and consists of nine questions, ranging on a scale from 0 to 3 with a maximum of 27 points. Results can be subclassified in five groups (no symptoms: 0-4 points, minimal symptoms: 5-9 points, minor depression: 10-14 points, moderate major depression: 15-19 points, severe major depression: 20-27 points).

In this study, depression levels were evaluated prior to the first cycle of chemotherapy (t0), after completion of the first cycle of therapy (t1) and after completion of the second cycle of therapy (t2).

In order to identify changes in patients' QoL, we asked patients to fill in the EORTC QLQ-C30 and Modul BN 20 questionnaires at t0, t1 and t2. The EORTC QLQ-C30 consists of 30 questions, which can be subclassified in 15 categories (global health, physical

functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) [17, 18]. Answers are ranging on a scale from 0 to 4 (except global health item: 0-7). The EORTC BN 20 was designed to measure QoL particularly in brain tumor patients [19]. Answers range on a scale from 0 to 4 which are subclassified in 11 brain tumor specific categories (future uncertainty, visual disorder, motor dysfunction, communication deficit, headache, seizures, fatigue, rash, alopecia, weakness of legs, and loss of bladder control).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Worldwide, Chicago, IL, USA). For patients' characteristics, descriptive statistics were performed. For EORTC QLQ-C30 and BN 20, scores for each subcategory and overall scores were calculated via linear transformation using the official EORTC QLQ-C30 Scoring Manual [20, 21]. Patients with missing data were included if more than 50 % of questions per item were completed. Missing single items, items with less than 50 % of given information and missing questionnaires were not taken into account. For PHQ-9, overall points achieved were summed up and summarized into the five given subcategories described above. Mean values for nausea, emesis and loss of appetite (MASCC) were calculated for each time point during the first two cycles of chemotherapy. Data was examined for gaussian distribution by Kolmogorov-Smirnov testing. We performed the student's t-test in equally distributed data and the Wilcoxon test in non-equally distributed data to evaluate significant effects. Effect size was calculated by Pearson's correlation coefficient r . Data were regarded as significant if $\alpha < 0.05$.

Results

Study population

In this prospective multicenter study, we included 87 patients from six different institutions (University Hospital of Marburg, $n = 33$ (37.9 %); University Hospital of Münster, $n = 4$ (4.6 %); University Hospital of Regensburg, $n = 26$ (29.9 %); University Hospital of Würzburg, $n = 15$ (17.2 %); DIAKOVERE Henriettenstift Hannover, $n = 1$ (1.1 %) and Regensburg Barmherzige Brüder, $n = 8$ (9.2 %)). The mean age was 53.78 years (25-84 years), and 39 female and 48 male patients participated. Most patients suffered from glioblastoma ($n = 50$, 57.5 %), other entities included in this study were pilocytic astrocytoma, ganglioglioma, diffuse astrocytoma, oligoastrocytoma, oligodendroglioma and anaplastic astrocytoma. Most patients received TMZ as a single chemotherapeutic agent in c1 ($n = 81$, 93.1 %) and c2 ($n = 70$, 80.5 %). Serotonine receptor antagonists were the most prevalent antiemetic prophylaxis during c1 (ondansetrone $n = 46$, 52.8 %; granisetron $n = 13$, 14.9 %; palonosetrone $n = 6$, 6.9 %) and c2 (ondansetrone $n = 39$, 44.8 %; granisetron $n = 9$, 10.3 %; palonosetrone $n = 13$, 14.9 %) (Table 1).

Table 1

Patients' characteristics, $n = 87$, chemotherapy and concomitant antiemetic therapy in cycle 1 (c1) and cycle 2 (c2), TMZ = Temozolomide, CCNU = lomustine

Characteristics	
	[MEAN (MIN-MAX)]
Age	53,78 (25-84)
SEX	39 (44.8)/ 48 (55.2)
	[F/M (%)]
KARNOFSKY-INDEX	83,91 (40-100)
	[N (%)]
WHO- diagnosis	
Pilozytic astrozytoma	1 (1.1)
Ganglioglioma	1 (1.1)
Diffuse astrozytoma	2 (2.3)
Oligoastrozytoma	6 (6.9)
Oligodendroglioma	11 (12.6)
Anaplastic astrozytoma	16 (18.4)
Glioblastoma	50 (57.5)
WHO-grade	
I	1 (1.1)
II	12 (13.8)
III	24 (27.6)
IV	50 (57.5)
Chemotherapy c1	
TMZ	81 (93.1)
CCNU	6 (6.9)
Chemotherapy c2	
TMZ	70 (80.5)
CCNU	5 (5.7)
lost to follow-up	12 (13.8)
Antiemetic therapy c1	
Ondansetron	46 (52.8)
Granisetron	13 (14.9)
Palonosetron	6 (6.9)
MCP	1 (1.1)
Alizaprid	20 (23)
Dronabinol	1 (1.1)
Antiemetic therapy c2	
Ondansetron	39 (44.8)

Granisetron	9 (10.3)
Palonosetron	13 (14.9)
MCP	1 (1.1)
Alizaprid	12 (13.8)
Dronabinol	1 (1.1)
lost to follow-up	12 (13.8)

Gastrointestinal symptoms

During c1, we spotted an increase of nausea directly after the application of the chemotherapeutical agent using the MASCC questionnaire (Figure 1a). Symptoms remained constantly high until day 7. The CINV associated symptoms lasted approximately two days longer than chemotherapy was applied. Similarly, emesis increased directly after application and took five days to return to baseline levels (Figure 1b). During c1, patients gradually lost their appetite with a minimum of appetite at day 5 and did not completely recover until day 10 (Figure 1c). During c2, nausea slowly increased with a maximum at day 6 (Figure 2a). In contrast to c1, emesis most often developed not before day 2 of chemotherapy and was back to baseline levels by day 4 (Figure 2b). Appetite, on the contrary, hit its minimum at day 4 during c2 and was not back to former levels at day 10 (Figure 2c).

Depression

Prior to chemotherapy, the mean baseline PHQ-9 score was 6.79 (0-22). At t1, it increased to 8.25 (0-25), but dropped to 7.13 (0-27) at t2 (Figure 3a). In total, mean PHQ-9 scores indicated minimal depressive symptoms. However, single patients with moderate or severe major depression could be identified after chemotherapy (Figure 3b). The mean PHQ-9 was significantly higher at t1 compared to the level prior to chemotherapy, with an effect size r of 0.35 ($p = 0.003$). By contrast, at t2, depression levels were not significantly different from the scores at t0 ($p = 0.341$) (Figure 3a). Patient drop-out is summarized in Supplements 1.

Patients with higher levels of depression at t0 showed a significantly higher likelihood of developing nausea ($p = 0.00$) and emesis ($p = 0.023$) during c1. Similarly, patients with higher levels of depression at t1 also had a significantly higher incidence of emesis ($p = 0.00$) and loss of appetite ($p = 0.03$) during c2. Vice versa, patients experiencing nausea ($p = 0.00$) or emesis ($p = 0.002$) during c1 showed significantly elevated levels of depression at t1. This was also found to be true for patients' depression levels at t2, if they experienced nausea ($p = 0.027$) and emesis ($p = 0.00$) during c2.

Quality of life

Patients' QoL assessment with the QLQ-C30 questionnaire showed a significant drop in the mean of the global health item with an effect size r of 0.22 ($p = 0.044$) and physical function with an effect size r of 0.22 ($p = 0.044$) at t1. Fatigue ($p = 0.002$) and nausea ($p = 0.009$) increased at t1 with effect sizes r of 0.34 and 0.29, respectively. Global health was also reduced at t2 with an effect size r of 0.24 ($p = 0.029$), as well as nausea with an effect size r of 0.28 ($p = 0.01$). The other items of the QLQ-C30 questionnaire showed no significant changes in t1 or t2. The BN20 questionnaire showed a significant increase of the weakness of legs item at t1 with an effect size r of 0.027 ($p = 0.014$). At t2 loss of hair worsened significantly with an effect size r of 0.26 ($p = 0.018$). No other items of the BN20 questionnaire showed significant effects at t1 or t2. Patient drop-out is summarized in Supplements 1.

Patients, whose PHQ-9 levels reached a score above 15, were defined as moderately or severely depressed and analysed in a separate QoL subanalysis. In contrast to patients with a PHQ-9 score lower than 15 during all time-points of observation (t0, t1, t2), patients with signs of major depression showed a significant impairment in their QoL concerning global health, physical function, role function, social function, future uncertainty and fatigue during all time points of measurement (Table 2).

Chemotherapy-induced nausea was not significantly different between the two groups, whereas loss of appetite was significantly more frequent in patients with higher levels of depression at t1 and t2 (Table 2).

Table 2

Comparison of the mean of the items of the EORTC QLQ-C30 and BN 20 questionnaire at t0 prior to chemotherapy and after the first (t1) and second cycle of chemotherapy (t2) in patients with a PHQ-9 score of < 15 and ≥ 15 . P-values are provided for each time-point and each item; significant p-values are highlighted.

Questionnaire/ Item	t0 PHQ- 9 < 15	t0 PHQ- 9 ≥ 15	t0 p	t1 PHQ-9 < 15	t1 PHQ-9 ≥ 15	t1 p	t2 PHQ-9 < 15	t2 PHQ-9 ≥ 15	t2 p
QLQ-C30									
Global health	57,82	42,19	0.013	54,27	28,65	0.012	57,85	41,67	0.026
Physical functioning	73,52	38,65	0.001	71,49	33,33	0.005	71	41,33	0.006
Role functioning	59,58	22,92	0.00	56	12,22	0.001	58,22	27,38	0.03
Emotional functioning	67,9	46,88	0.239	62,2	38,02	0.084	62,78	45	0.026
Cognitive functioning	67,9	47,92	0.011	65,45	37,5	0.060	65,28	45,56	0.033
Social functioning	59,26	33,33	0.002	57,52	24	0.004	58,33	31,11	0.007
Fatigue	44,86	80,56	0.011	50,47	85,42	0.000	46,88	80,74	0.001
Nausea	8,85	18,75	0.111	16,06	29,17	0.164	11,81	16,67	0.218
Pain	14,2	35,42	0.139	14,63	35,56	0.181	11,87	26,67	0.438
Dyspnea	15,23	33,33	0.385	15,64	35,56	0.029	16,44	31,11	0.096
Insomnia	26,34	50	0.033	33,33	43,75	0.143	21,46	42,22	0.046
Appetite loss	20,16	33,33	0.140	26,75	52,08	0.002	21,3	37,78	0.02
Constipation	20,16	31,25	0.013	25,2	31,25	0.081	27,31	28,89	0.395
Diarrhoea	8,64	14,58	0.755	11	31,25	0.468	8,33	20	0.901
Financial difficulties	24,17	33,33	0.170	24,4	20,83	0.023	26,85	40	0.039
BN 20									
Future uncertainty	47,81	62,5	0.074	46,44	66,84	0.017	44,95	60,56	0.024
Visual disorder	12,92	22,92	0.052	13,14	23,61	0.175	12,21	18,52	0.381
Motor dysfunction	19,9	39,58	0.126	20	39,24	0.235	18,94	28,15	0.204
Communication deficit	21,46	25,69	0.509	18,1	21,53	0.233	18,31	22,96	0.438
Headache	21,67	39,58	0.222	22	39,58	0.127	22	40	0.052
Seizures	8,33	2,08	0.733	6,91	12,5	0.205	3,76	0	0.353
Fatigue	47,26	79,17	0.003	52,03	85,42	0.003	44,6	75,56	0.005
Rash	24,05	41,67	0.357	24,4	35,42	0.803	25,35	31,11	0.960
Alopecia	30	29,17	0.733	28,8	20,83	0.362	18,31	11,11	0.644
Weakness of legs	23,75	56,25	0.038	8,94	58,33	0.745	27,7	40	0.370

Loss of bladder control	7,5	16,67	0.950	29,67	16,67	0.571	7,98	0	0.527
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Discussion

To our knowledge, this is the first prospective multicenter study assessing patients with malignant brain tumors over a defined period during and after application of chemotherapy and its effects on QoL and levels of depression.

In order to measure nausea, emesis and loss of appetite, we applied the expanded MASCC questionnaire, modified with a numeric rating scale and assessed nausea, emesis and loss of appetite for ten consecutive days, during the c1 and c2 of chemotherapy. Overall, the burden of CINV symptoms was moderate. Interestingly, nausea, emesis and loss of appetite appeared to develop with delay after the application of TMZ during day 1-5 in both c1 and c2. In view of the prominent delayed nausea and emesis observed in this study, it is tempting to speculate that a relevant activation of the NK1 pathway takes place supported by several clinical trials improving nausea by combining a NK1 receptor antagonist to a setron [22-24]. Shorter acting antiemetics should therefore be substituted by longer acting substances like palonosetron or through addition of a NK1 receptor antagonist like aprepitant, rolaprepitant or the fix combination of netupitant and palonosetron [25, 26]. We also observed a tendential decrease of emesis in c2 possibly as a consequence of an adjustment in antiemetic prophylaxis after c1, e.g. increase in palonosetron intake (Table 1). In view of the fact that higher levels of nausea and emesis exhibit significant intercorrelations with depressive symptoms and QoL, constant monitoring and treatment of gastrointestinal side effects seems to be crucial.

While the PHQ-9 score prior to chemotherapy indicated only minimal symptoms of depression in most patients, PHQ-9 scores of 15 or higher in single patients pointed towards moderate to severe pre-existing symptoms of depression in a specific subpopulation. After completion of c1, levels of depression increased significantly. The occurrence of undesired effects of chemotherapy like nausea and emesis or myelosuppression and infections, but also the fear of these symptoms may enhance the psychosocial burden of patients and lead to a higher level of psychological stress [27, 28]. After completion of c2, however, levels of depression decreased. This may point towards a reduced level of stress if patients acquire a certain routine when receiving treatment.

Interestingly, we observed that not only the extent of gastrointestinal symptoms was associated with a significantly higher level of depression after the respective cycle of chemotherapy, but vice versa, patients with higher baseline levels of depression experienced significantly more severe nausea, emesis or loss of appetite. It can be presumed that treatment-resistant or anticipatory nausea during chemotherapy might have psychosomatic causes to a relevant extent [29, 30].

The QLQ-C30 and BN20 questionnaire assessed prior to and after the first and second cycle of chemotherapy indicated fatigue and loss of hair, which may not necessarily have been caused by chemotherapy, but possibly was secondary to previous radiotherapy [31-33]. Interestingly, the QLQ-C30 questionnaire showed a significant increase of nausea at t1 and t2, respectively, and by such underlined the results obtained by the MASCC questionnaire. Global health significantly dropped at t1 and t2. Patients with signs of depressive mood, as indicated by a PHQ-9 score of 15 or higher, were more severely affected by decreased QoL than non-depressed patients. Global health, physical function, role function, social function, future uncertainty and fatigue were significantly impaired already prior to chemotherapy in depressed patients. In the further course of disease, these executing aspects of the patients' lives deteriorated more markedly than in non-depressed patients. By contrast, emotional functioning, dyspnea, appetite loss, financial difficulties and headache were significantly impaired only during chemotherapy at either t1 or t2.

Due to its design, the results obtained in this pilot study should be interpreted with some caution. At first, the study is not adequately powered for the quantity of QoL parameters assessed with the EORTC QLQ-C30 and BN 20. Second, we investigated a patient series treated at different hospitals with inhomogeneous chemotherapy and antiemetic medication. While most patients received TMZ alone, some patients were treated additionally with lomustine. In addition, we cannot provide information about the consecutive development of depression, CINV or QoL beyond the first two courses of chemotherapy. Although these factors may have influenced the severity of nausea, emesis and loss of appetite, the mode of evaluation established in this study appears to be adequate and the observations on duration of gastrointestinal side effects, intercorrelation with depressive symptoms and effect on QoL seems to be robust enough to draw first conclusions.

Taken together, we observed a relevant interaction between gastrointestinal side effects of chemotherapy and depressive symptoms. CINV may be underestimated in patients with brain tumors, last longer than anticipated, and appears to be aggravated by pre-existing depressive symptoms, severely affecting the QoL of the affected patients. During treatment, CINV should be asked for thoroughly and treated with effective, long-lasting antiemetics not only to reduce gastrointestinal symptoms, but also to prevent depressive mood and impairment of quality of life.

Moreover, quality of life was impaired after initiation of chemotherapy, especially in patients suffering from pre-existing depressive mood. We therefore consider a regular screening of the extent of psychosocial burden and depressive symptoms during the course of disease, as it has become standard within German certified oncological centres, which is of major importance. Early detection and treatment of depression may not only stabilize the patient's mood, but also prevent deterioration of gastrointestinal symptoms and of QoL.

Declarations

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Conflicts of interest:

The authors declare that they have no conflict of interest.

Availability of data and material:

The data that support the findings of this study are available from the corresponding author upon reasonable request

Authors' contributions:

Study conception and design were prepared by Herwig Strik, Larissa Just and Karin Jordan, and consented with all co-authors. Material preparation was performed by Almuth Kessler, Peter Hau, Hendrik Pels, Oliver Grauer, Bettina Wiese, Mario Löhner, Karin Jordan and Herwig Strik. Data collection was coordinated by Herwig Strik and Larissa Just. Statistical analysis was performed by Vera Dufner. The manuscript was prepared by Vera Dufner, Herwig Strik and Almuth Keßler and commented by all authors. All authors read and approved the final manuscript.

Ethics approval:

The local medical ethical committees gave permission for the study (08/13, 26.02.2013). All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate:

Informed consent was obtained from all patients included in the study.

Consent for publication:

Informed consent was obtained from all patients included in the study.

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Figures

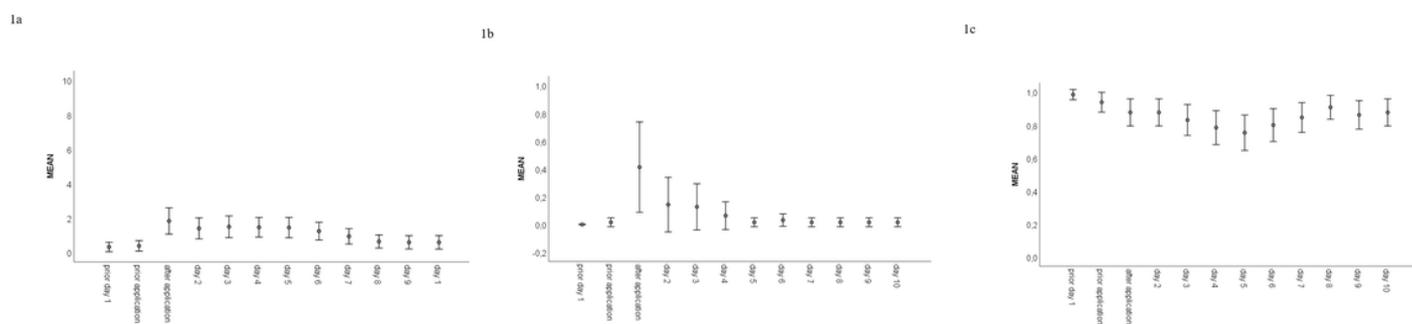


Figure 1

a-c: Mean of nausea (1a), emesis (1b) and loss of appetite (1c) during the first ten days of the first cycle of chemotherapy is represented by circles, standard deviation by brackets

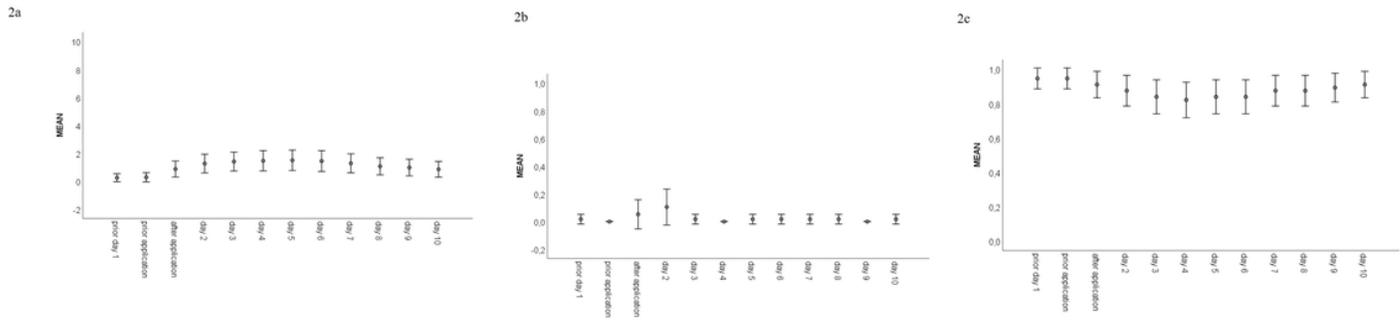
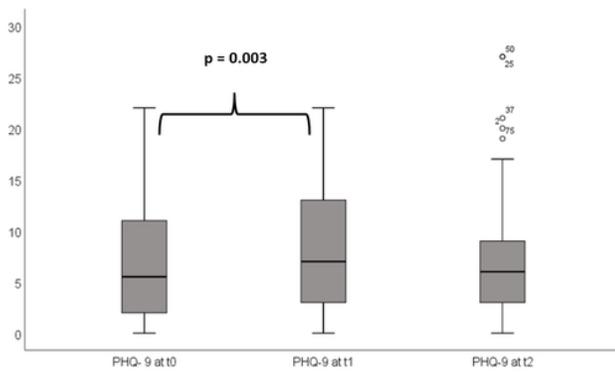


Figure 2

a-c: Mean of nausea (2a), emesis (2b) and loss of appetite (2c) during the first ten days of the second cycle of chemotherapy is represented by circles, standard deviation by brackets

3a



3b

		T0, N = 73	T1, N = 77	T2, N = 67
		[N (%)]	[N (%)]	[N (%)]
NO SYMPTOMS	0-4	0	29 (39.7)	26 (33.8)
MINIMAL SYMPTOMS	5-9	1	24 (32.9)	22 (32.8)
MINOR DEPRESSION	10-14	2	13 (17.8)	8 (11.9)
MODERATE MAJOR DEPRESSION	15-19	3	5 (6.8)	4 (6.0)
SEVERE MAJOR DEPRESSION	20-27	4	2 (2.7)	4 (6.0)

Figure 3

a, b: PHQ-9 prior to (t0) and after the first (t1) and second (t2) cycle of chemotherapy: The mean PHQ-9 at t1 is significantly ($p = 0.003$) higher than mean PHQ-9 at t0 indicating a higher burden of depression at t1. No significant difference was found in PHQ-9 at t1 and t2 (3a). 3b shows the classification of PHQ-9 symptoms, the number of patients and the severity of their symptoms respectively at t0, t1 and t2.

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