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ORIGINAL ARTICLE

Prognostic role of chemotherapy-induced nausea and vomiting in recurrent ovarian cancer patients: results of an individual participant data meta-analysis in 1213

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Abstract

Background The aim of this study was to analyze the potential impact of chemotherapy-induced nausea and vomiting (CINV) on dose reductions, discontinuation of chemotherapy, and survival.

Patients and methods This study was designed as individual participant data meta-analysis with the original study data of three phase II/III trials that were conducted by the North-Eastern German Society of Gynecological Oncology (NOGGO) including 1213 patients with recurrent ovarian cancer. Logistic and Cox regression analyses were used to estimate odds and hazard ratios after adjusting for age, ECOG, amount of delivered cycles, amount of recurrences, and amount of comedications and study.

Results The majority of patients developed nausea (58.1%) and almost one third experienced vomiting (31.0%). CINV was not associated with FIGO stage, grading, histology, and number of recurrences. The necessity of dose reduction and discontinuation of chemotherapy did not correlate to nausea and vomiting ($p = 0.88$, $p = 0.39$ and $p = 0.25$, $p = 0.54$ respectively). Progression-free survival was shorter in patients with grade III/IV nausea and vomiting ($p = 0.02$; hazard ratio (HR) for grade III/IV nausea 1.58, 95% CI 1.14–2.20, and $p = 0.02$; HR for grade III/IV vomiting 1.67, 95% CI 1.15–2.42 respectively). CINV grade III/IV was also associated with poorer overall survival ($p < 0.001$; HR for grade III/IV nausea 2.35, 95% CI 1.64–3.37, and $p < 0.001$; HR for grade III/IV vomiting 1.67, 95% CI 1.15–2.42 respectively).

Conclusion CINV is significantly associated with poorer prognosis in recurrent ovarian cancer patients while there was no correlation found with the necessity of dose reduction and prior discontinuation of treatment. This study underlines the importance of prevention and treatment of CINV as part of early best supportive care.

Keywords Nausea · Vomiting · Recurrent ovarian cancer · Toxicity

Introduction

Chemotherapy-induced nausea and vomiting (CINV) are the most feared toxicities for cancer patients and result in deterioration of quality of life [1]. In a quality of life study with 95 recurrent ovarian cancer patients, patients were accepting a decreased progression-free survival of 6.7 months in order to minimize nausea and vomiting [2]. Although there are very comprehensive guidelines for CINV such as the MASCC guidelines (Multinational Association of Supportive Care in Cancer, www.mascc.org) and new therapeutics are evolving steadily, still many patients experience CINV. Adherence to guidelines was shown to significantly reduce CINV rates. However, adherence was only 29% in a US study for patients receiving high emetogenic chemotherapy. Even in the cohort that received guideline-consistent chemotherapy, only 53.4% of patients did not suffer from CINV showing the high incidence of CINV in cancer patients [3, 4]. CINV does not only lower quality of life but may also contribute to dose reductions or early discontinuation of chemotherapy. So far, little is known on the potential impact of chemotherapy-induced nausea and vomiting on progression-free and overall survival in ovarian cancer.

The aim of this study was to evaluate the potential influence of chemotherapy-induced nausea and vomiting in recurrent

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ovarian cancer patients on early discontinuation of chemotherapy, on dose reduction, and on progression-free and overall survival.

Patients and methods

An individual participant data meta-analysis with synthesized original data of three phase II/III trials of the North-Eastern German Society of Gynecological Oncology (NOGGO) including 1213 patients with recurrent ovarian cancer was conducted.

Data from the following three trials were available:

TOWER study—topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer [5]

This phase II trial evaluated two different topotecan regimens ((1) weekly administration of 4.0 mg/m^2/week applied on days 1, 8, and 15 of a 28-day cycle, versus (2) conventional administration of 1.25 mg/m^2/day on 5 consecutive days of a 21-day cycle) in platinum-resistant recurrent epithelial ovarian or primary peritoneal cancer after radical surgery and at least one platinum-containing chemotherapy.

Topotecan phase III study—nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer [6]

The aim of this phase III was the comparison of single topotecan with two different topotecan combinations ((1) topotecan 1.25 mg/m^2/day on days 1 to 5 every 3 weeks, (2) topotecan 1.0 mg/m^2/day on days 1 to 5 plus 50 mg of oral etoposide on days 6 to 12 every 3 weeks, or (3) topotecan 0.5 mg/m^2/day on days 1 to 5 plus gemcitabine 800 mg/m^2 on day 1 and 600 mg/m^2 on day 8 every 3 weeks) in recurrent epithelial ovarian cancer patients after radical surgery and first-line platinum-based chemotherapy.

Hector study—carboplatin in combination with topotecan versus standard platinum-based combinations in recurrent ovarian cancer [7]

This phase III trial analyzed the combination of topotecan and carboplatin with three standard chemotherapy regimens (topotecan 0.75 mg/m^2/day on days 1 to 3 and carboplatin AUC 5 on day 3 after topotecan, every 3 weeks versus (PC) paclitaxel 175 mg/m^2/day on day 1 and carboplatin AUC 5 on day 1, every 3 weeks; (GC) gemcitabine 1000 mg/m^2/day on days 1 and 8 and carboplatin AUC 4 on day 1, every 3 weeks; and (PLDC) pegylated doxorubicin 30 mg/m^2 on day 1 and carboplatin AUC 5 on day 1, every 4 weeks) in patients with platinum-sensitive ovarian, peritoneal, and fallopian tube carcinoma.

Exclusion criteria for all three trials were severe or uncontrolled medical conditions. Renal, hepatic, and bone marrow function had to be sufficient before enrollment and an ECOG performance status ≤ 2 was mandatory.

The NOGGO working group "Ovarian Cancer" gained access to original data. In all three trials, the National Cancer Institute Common Toxicity Criteria were applied to document toxicities (version 2.0 was used in the topotecan phase III study and version 3.0 was used in the Hector and the Tower studies).

Statistics

The statistical program PASW 23 (SPSS Inc., Chicago) was used for statistical analyses. A p value of < 0.05 was defined as significant result. Logistic regression analyses were conducted to estimate odds ratios for necessity of dose reductions and discontinuation of chemotherapy. To estimate hazard ratios for progression-free and overall survival, Cox regression analyses were performed. In all multivariate analyses, it was adjusted for the covariates age, ECOG, number of recurrences, amount of delivered chemotherapy cycles, and study and amount of comedications.

Results

This individual participant data meta-analysis includes 1213 patients with recurrent ovarian cancer. Median age at diagnosis was 59 years (range: 21–83 years). The majority was diagnosed with advanced disease (86.3%). Most patients were treated for their first recurrence (86.4%) within this study. Ascites was present in 30.6% of patients while 4.7% had gastrointestinal disease at baseline. Table 1 shows more details on patients' characteristics.

Altogether, 508 patients (41.9%) did not develop nausea at all while 661 patients (54.5%) suffered from grade I/II nausea and 44 patients (3.6%) from grade III/IV nausea. Regarding vomiting, 836 patients (68.9%) did not experience vomiting due to chemotherapy in contrast to 343 (28.3%) with grade I/II vomiting and 33 patients (2.7%) with grade III/IV vomiting. For this meta-analysis, it was not known if CINV was acute or delayed. CINV was available as CINV having occurred in any cycle not knowing the exact timepoint of onset. Regarding baseline characteristics, there were no significant differences in nausea or vomiting in relation to FIGO stage ($p = 0.07$ and $p = 0.38$), grading ($p = 0.20$ and $p = 0.60$), histology ($p = 0.80$ and $p = 0.82$), and number of recurrences ($p = 0.15$ and $p = 0.60$). Patients older than 65 years tend to have a higher risk for grade III/IV nausea compared to younger patients ($p = 0.44$, odds ratio (OR) for grade III/IV nausea 1.29, 95% confidence interval (CI) 0.68–2.46). There was no age difference regarding vomiting ($p = 0.11$). Polypharmacy was also associated with grade III/IV

Table 1 Patients' characteristics

Median age at diagnosis (years)		59 (range: 21–83)
		Number of patients (%)
FIGO	I	78 (6.4%)
	II	74 (6.1%)
	III	895 (73.8%)
	IV	152 (12.5%)
	Unclear	14 (1.1%)
Grading	I	46 (3.8%)
	II	380 (31.1%)
	III	694 (57.2%)
	Unclear	20 (1.6%)
Histology	Serous	910 (75.0%)
	Mucinous	45 (3.7%)
	Endometrioid	86 (7.1%)
	Other	170 (14.0%)
	Unclear	2 (0.2%)
Number of recurrences	1st	1048 (86.4%)
	2nd	164 (13.5%)
	Unclear	1 (0.1%)

nausea and vomiting ($p < 0.001$ and $p = 0.002$). Patients receiving carboplatin did less significantly have nausea and vomiting ($p = 0.031$ and $p = 0.05$ respectively) compared to patients not receiving platinum-based chemotherapy in this study suggesting a good antiemetic prophylaxis.

Dose reduction and discontinuation of chemotherapy

Dose reductions were not more often necessary due to nausea or vomiting ($p = 0.88$ and $p = 0.25$). Furthermore, there was no significant differences in early cessation/discontinuation of chemotherapy in regard to nausea and vomiting ($p = 0.39$ and $p = 0.54$).

Impact on progression-free survival

Progression-free survival (PFS) was 7 months in patients without nausea, 8 months in patients with grade I/II nausea, and 4 months in patients with grade III/IV nausea ($p = 0.01$; Fig. 1). After adjusting for covariates (age, ECOG, study, amount of delivered chemotherapy cycles, number of recurrences, and amount of comedications), the differences in PFS remained significant ($p = 0.023$, hazard ratio (HR) for grade III/IV nausea 1.58, 95% confidence interval (CI) 1.14–2.20). After stratification for platinum response, there was no relation of nausea grade III/IV with progression-free survival ($p = 0.118$; HR 1.34, 95% CI 0.93–1.94).

Median PFS was 8 months in both patients without vomiting and grade I/II vomiting in comparison to PFS of 3 months in patients with grade III/IV vomiting ($p < 0.001$; Fig. 2). Cox regression analyses confirmed the significant differences in PFS regarding vomiting ($p = 0.017$, HR for grade III/IV 1.67, 95% CI 1.15–2.42). After stratification for platinum response, there was no relation of vomiting grade III/IV with progression-free survival ($p = 0.089$, HR 1.42, 95% CI 0.95–2.14).

Impact on overall survival

Overall survival was significantly decreased in patients experiencing grade III/IV nausea. Median overall survival (OS) was 19 months in patients who did not experience nausea compared to patients with grade III/IV nausea with a median OS of 11 months and patients with grade I/II of 22 months ($p < 0.001$; Fig. 3). After adjusting for age, ECOG, study, amount of delivered chemotherapy cycles, number of recurrences, and amount of comedications, there was still a significant influence of survival ($p < 0.001$, hazard ratio (HR) for grade III/IV nausea 2.35, 95% CI 1.64–3.37). Furthermore, overall survival was also stratified for platinum response and remained significant ($p < 0.001$, HR 2.15, 95% CI 1.45–3.21). The effect on survival of grade III/IV nausea was especially high in platinum-resistant patients, $p = 0.002$ HR 2.87 (95% CI 1.47–5.61). In platinum-sensitive patients, the effect was also significant ($p = 0.02$, HR 1.82, 95% CI 1.10–3.02).

There were also significant differences in overall survival regarding vomiting. Median OS was 22 months in patients without vomiting, compared to 20 months in patients with grade I/II vomiting and 6 months in patients with grade III/IV vomiting ($p < 0.001$; Fig. 4). In multivariate analyses adjusting for the same covariates named above, vomiting remained a prognostic factor ($p < 0.001$, HR for grade III/IV vomiting 3.4, 95% CI 2.32–5.00). The effect of vomiting grade III/IV on overall survival was also stratified for platinum response and remained significant ($p < 0.001$, HR 2.93, 95% CI 1.92–4.49).

Discussion

In this study including 1213 recurrent ovarian cancer patients, chemotherapy-induced nausea and vomiting were associated with poorer progression-free and overall survival. The necessity of dose reductions and prior discontinuation of chemotherapy were not associated with CINV. This is the first study evaluating the impact of CINV on prognosis in ovarian cancer.

Chemotherapy-induced nausea and vomiting are very common side effects of cancer treatment. Within the last years treatment guidelines for best supportive care including the prevention and management of CINV have evolved such as the MASCC guidelines (www.mascc.org). The positive effect of these guidelines could be shown in several studies [8]. Aapro et al. showed a complete response rate to antiemetic drugs in the guideline-consistent treatment group of 60% compared to 51% in the patients group that were not treated

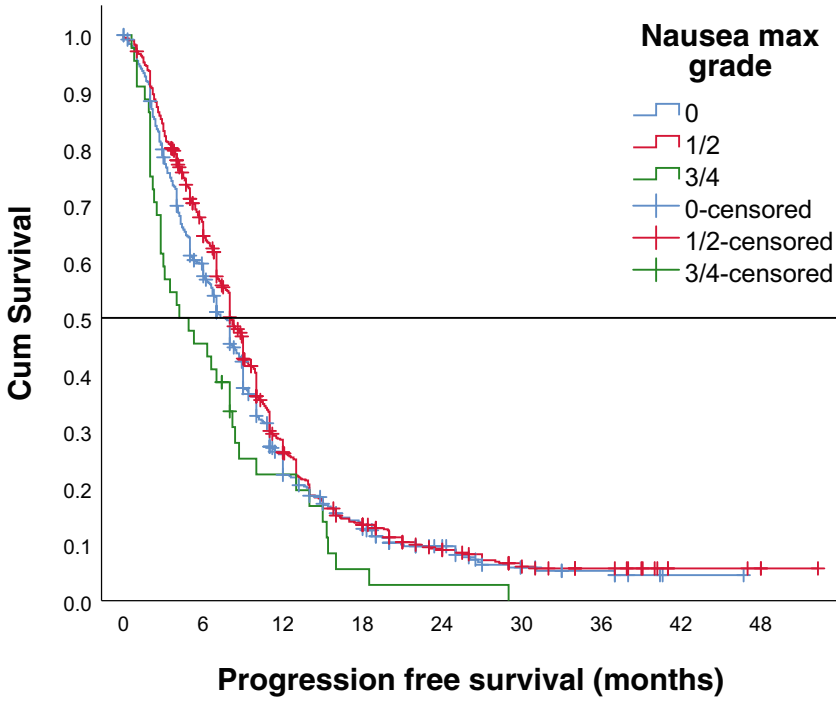

Fig. 1 Impact of nausea on progression-free survival (months)—Kaplan–Meier analysis ($p = 0.01$)

according to guidelines [9]. Despite these positive effects, adherence to guidelines is unexpectedly and disappointingly low as shown in studies from the UK, USA, and Asia Pacific countries [4, 10, 11]. As our study shows that CINV is not only deteriorating quality of life of our cancer patients but also shortens survival, the improvement of guideline adherence and hence of CINV should be one of our highest goals when treating cancer patients. Moreover, especially in incurable conditions such as diagnosis of recurrent ovarian cancer, prophylaxis and excellent treatment of side effects are a cornerstone of the best supportive care.

However, whether poorer survival in patients who experience grade III/IV nausea and vomiting can be counteracted by an optimized antiemetic treatment remains unclear. As all patients in this study were treated within clinical trials, we may assume that patients received an optimal antiemetic prevention and treatment, although CINV rates in our study are very similar to other trials [3, 4]. It may be possible that more factors play a role in the

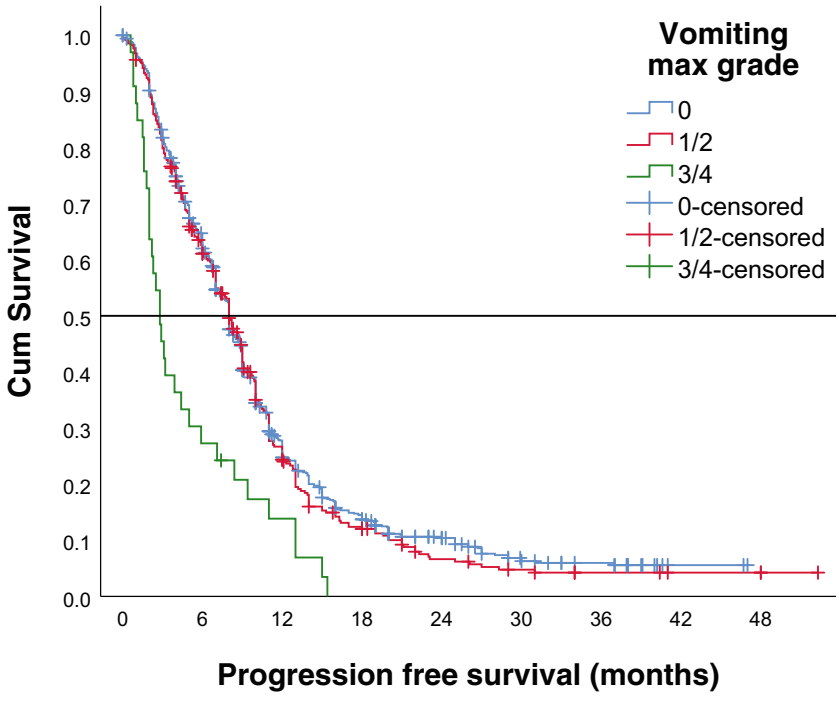

Fig. 2 Impact of vomiting on progression-free survival (months)—Kaplan–Meier analysis ($p < 0.001$)

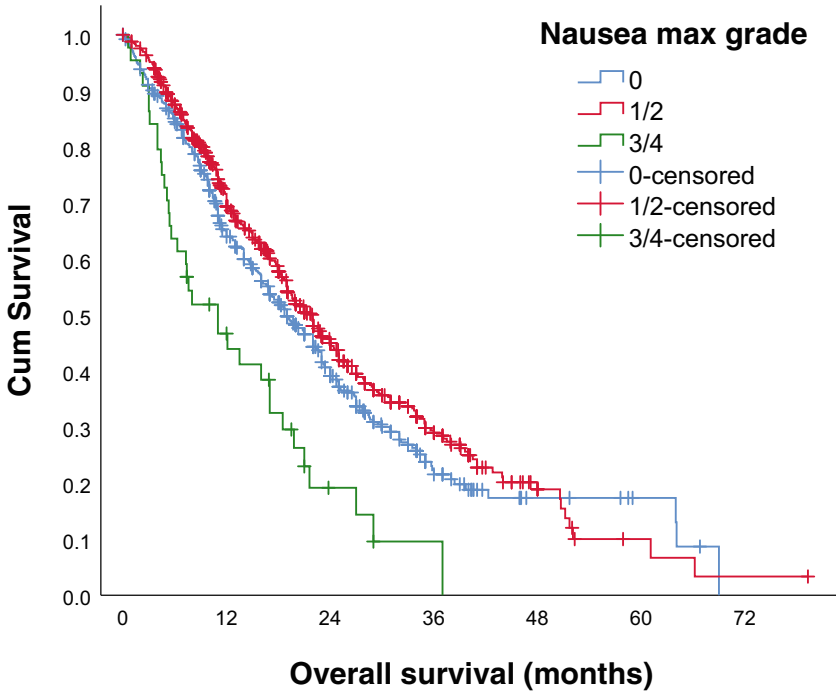

Fig. 3 Impact of nausea on overall survival (months)—Kaplan–Meier analysis ($p < 0.001$)

association of CINV and poorer survival. However, adjustments for covariates such as age, ECOG, number of recurrences, amount of delivered chemotherapy cycles, and amount of administered comedications and the entered study were conducted in order to minimize bias.

A limitation of this study is that all patients were treated within randomized phase II/III trials. An ECOG performance status of ≤ 2 was mandatory to be included in the study. The treatment within trials is prone to not reflecting everyday clinical routine with many frail and comorbid patients. Patients with recurrent ovarian cancer have a high burden of symptoms [12]. Data on nausea and vomiting at baseline was not available for this meta-analysis. However, pre-existing cancer-related nausea and vomiting in women with recurrent ovarian cancer may have been worsened by chemotherapy which reflects on the survival outcomes. Furthermore, our study was retrospective. The original study data derived from studies that were not powered for the evaluation of CINV but

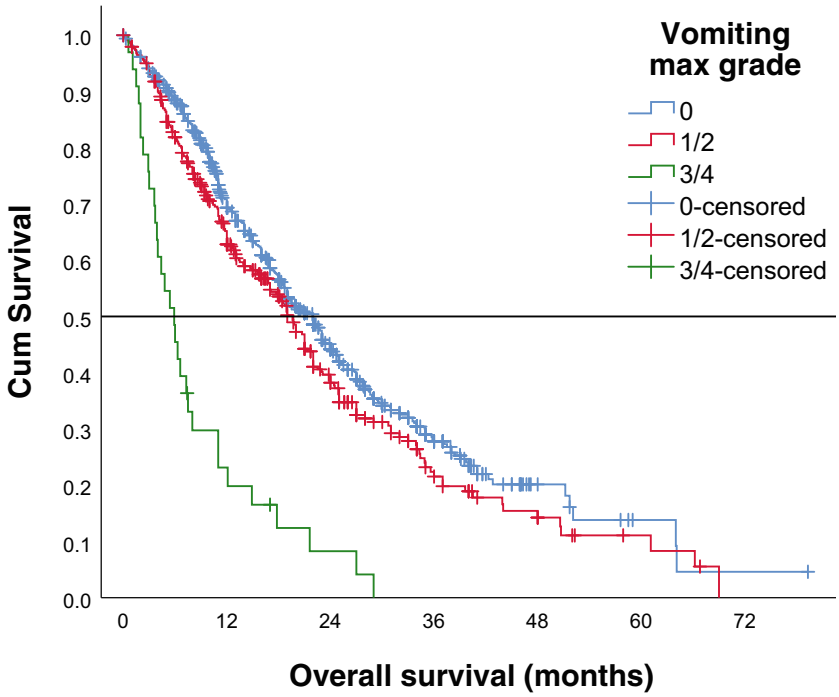

Fig. 4 Impact of vomiting on overall survival (months)—Kaplan–Meier analysis ($p < 0.001$)

for different chemotherapy regimens. The timepoint of onset of CINV and details of acute or delayed CINV and the occurrence of bowel obstruction during the trial were not available for this meta-analysis. However, individual participant data meta-analyses are very important in order to gain more patient data that would be available for just one trial. Additionally, due to the fact that our study data derived from large phase II/III trials, toxicities were very well documented and completely available for this study.

Chemotherapy-induced nausea and vomiting is associated with worse survival in patients with recurrent ovarian cancer. Whether an optimized antiemetic treatment can compensate the inferior outcome should be confirmed in further trials.

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Compliance with ethical standards

Conflict of interest Prof. Sehouli has received research funding from GlaxoSmithKline. Dr. Hannah Woopen, MSc was a participant in the Charité Clinical Scientist Program funded by the Charité Universitätsmedizin Berlin and the Berlin Institute of Health.

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