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Comparison of Chemotherapy-induced Nausea and Vomiting Between Gemcitabine Plus Nab-paclitaxel Combination Chemotherapy and Gemcitabine Monotherapy in Patients With Advanced Pancreatic Cancer

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Abstract. *Background/Aim: To clarify the risk of chemotherapy-induced nausea and vomiting (CINV) with GnP therapy, gemcitabine (GEM) plus nab-paclitaxel (nab-PTX), we compared CINV between GEM and GnP therapy. Patients and Methods: Patients who had received an initial course of GEM and GnP therapy were enrolled. Primary endpoint was the incidence of nausea, and secondary endpoints were the incidence of vomiting and rescue. In addition, the association between nausea and combination therapy with GEM and nab-PTX was evaluated by multivariate logistic regression with adjustment for covariates. All patients received anti-cancer drugs under guideline-consistent, low-risk antiemetic measures. Results: Data from 105 patients were analyzed (GEM group, 44 patients; GnP group, 61 patients). The incidence of nausea, vomiting, and rescue did not significantly differ between the two groups during the acute, delayed or overall periods. The multivariate logistic regression analysis showed that combination therapy with GEM and nab-PTX was not significantly associated with nausea compared to GEM alone. Conclusion: Under guideline-consistent, low-risk antiemetic measures, GnP therapy-induced nausea and vomiting can be controlled similarly to when induced by GEM.*

Pancreatic cancer has an extremely poor prognosis and is the fourth-leading cause of cancer death in the world. In Japan, 10-year (4.6% for males and 4.8% for females) and 5-year (7.0% for males and 5.9% for females) survival rates for pancreatic cancer are the worst among various malignancies (1, 2).

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Gemcitabine (GEM) is commonly used for advanced pancreatic cancer (aPC). Burris *et al*. reported that GEM was superior to 5-fluorouracil therapy in clinical benefit response and survival duration in patients with aPC (3). Von Hoff *et al*. reported that GnP therapy, namely GEM in combination with nanoparticle albumin-bound paclitaxel (nab-PTX), exhibited clinical superiority over GEM monotherapy with respect to overall survival (OS), progression-free survival (PFS) and response rate (RR) in patients with mPC in the first-line chemotherapy setting (4). Further, Mita *et al*. reported that second-line GnP after FOLFIRINOX (5) failure for patients with aPC was more effective than GEM alone.

Chemotherapy-induced nausea and vomiting (CINV) continue to impair patient quality of life (6). Burris *et al*. reported an incidence of significant nausea and vomiting with GEM in patients with pancreatic cancer of 34.9%. In contrast, the incidence of nausea and vomiting with GnP therapy was 26.7-49.2% (3). Clinical practice guidelines for the prevention of CINV developed by the American Society of Clinical Oncology (ASCO) 2017 (7), National Comprehensive Cancer Network (NCCN) 2020 (8), Multinational Association of Supportive Care in Cancer (MASCC) 2016 (9) and the Japanese Society of Clinical Oncology (JSCO) 2015 (10) all classify GEM and nab-PTX as anticancer drugs with low emetic risk (LEC; frequency of emesis 10-30%) (7-10). To date, however, no clear consensus on emetic risk with GnP therapy has yet appeared, as the JSCO guidelines refer to it as moderate emetic risk chemotherapy (MEC; emetic frequency 30-90%) while the ASCO, MASCC and NCCN guidelines all refer to it as LEC.

To clarify the emetic risk of GnP therapy, we conducted a retrospective study to compare CINV in patients with aPC who were treated with guideline-consistent antiemetic medication for LEC between those receiving GEM or GnP.

Patients and Methods

Patients. A single-centre, retrospective cohort study was conducted at Gifu University Hospital. The study subjects were patients who received an initial course of GEM (from January 2011 to December 2014) or GnP therapy (from January 2015 to December 2018) for aPC from January 2011 to December 2018. Exclusion criteria were a reduction in the initial dose of GEM and nab-PTX of 2 or more levels (GEM 600 mg/m^2, nab-PTX 75 mg/m^2); prior chemotherapy history which included GEM, such as GEM therapy ± radiation therapy (RT), or GEM plus S-1 therapy ± RT; and deviation from guideline-consistent, antiemetic medication for LEC. Patient demographics were assessed at the time of the initiation of GEM and GnP therapy. Data were extracted from the hospital's electronic medical records and were coded under blinded conditions.

Chemotherapy and antiemetic treatments. Patients in the GnP group received dexamethasone 6.6 mg or granisetron 3 mg as a guideline-consistent, low-risk antiemetic measure (7-10), followed by nab-PTX (125 mg/m^2) and then GEM (1,000 mg/m^2). Patients in the GEM group received GEM (1,000 mg/m^2) after antiemetic measures on days 1, 8 and 15 every 4 weeks. The initial doses of GEM and nab-PTX could be reduced to those of level 1 (GEM 800 mg/m^2, nab-PTX 100 mg/m^2) at the discretion of the attending physician, based on patient condition.

Evaluation of nausea, vomiting and other adverse events. GEM and GnP therapy-induced adverse events, including nausea, vomiting, neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia, fatigue, taste disorder, peripheral neuropathy, diarrhea, fever and oral mucositis, were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (11) and the incidence of adverse events between the groups was compared. The primary endpoint was the incidence of nausea, and secondary endpoints were the incidence of vomiting, rescue, and other adverse events. Nausea was defined as a decrease in food intake to less than 80% of the pre-chemotherapy level. Further, nausea was defined as grade 2 and more. Nausea and vomiting were both assessed for severity in the acute (within 24 h after chemotherapy), delayed (during 2-5 days after chemotherapy), and overall periods (during 1-5 days after chemotherapy).

Statistical analysis. Data were analysed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). The incidence of adverse events was compared using the chi-squared test. Patient demographics were compared between the two groups by the *t*-test for parametric continuous variables, Mann-Whitney *U*-test for non-parametric continuous variables and the chi-squared test for categorical variables. Statistically significant differences were defined by a p-values <0.05. Reported risk factors for nausea include sex (female), age (younger) and CINV history (12-15). Risk factors for poor antiemetic control were examined by multivariate logistic regression analysis. The cut-off value for age was assessed by the Youden index method in receiver operating characteristic curve (ROC) analysis, in which the Youden index was calculated as the maximum value of (sensitivity + specificity − 1), according to methods described elsewhere (15).

Results

Patients. A total of 166 patients with aPC were eligible. Of these, 61 patients were excluded from the present study due to the initial dose of GEM and nab-PTX being reduced by 2 or more levels (GEM 600 mg/m^2, nab-PTX 75 mg/m^2) in 6 patients; a prior chemotherapy history which included GEM, such as GEM therapy ± radiation therapy (RT) or GS therapy ± RT in 50 patients; and deviation from guideline-consistent, antiemetic medication for LEC in 5 patients. Data for the remaining 105 patients were analysed as shown in Table I. In total, 44 patients received GEM therapy (52.3% men; median age, 70 years) and 61 received GnP therapy (54.1% men; median age, 67 years).

Control of chemotherapy-induced nausea and vomiting. The incidence of nausea and vomiting during the overall period were 29.5% and 6.8% in the GEM group versus 36.0% and 4.9% in the GnP group, respectively. The two groups did not significantly differ during any period, namely acute, delayed and overall. Further, the incidence of rescue did not significantly differ between the two groups during any period. Nevertheless, incidence of both nausea and vomiting and of rescue tended to be higher during the delayed period than in the acute period in both groups (Table II).

Risk factors for nausea. ROC analysis indicated that the cut-off value for age was 65 years. As shown in Table III, the multivariate logistic regression analyses indicated that age under 65 years (OR=2.80, 95%CI=1.02-7.67, p=0.046) was found to be significant risk factor for nausea. Further, CINV history (OR=3.86, 95%CI=0.98-15.28, p=0.054) tended to be a risk factor for nausea. In contrast, GnP therapy (OR=1.01, 95%CI=0.39-2.65, p=0.981) and female sex (OR=0.82, 95%CI=0.34-2.02, p=0.672) were not significant risk factors for nausea. On the other hand, GEM and GnP therapy as second or later line therapy were significant factors in reducing nausea (OR=0.22, 95%CI=0.07-0.73, p=0.014).

Incidence of adverse events. The incidence of grade ≥2 adverse events were 95.5% in the GEM group versus 98.4% in the GnP group. The incidence of grade ≥2 adverse events such as neutropenia (47.7% *vs*. 77.0%, p=0.0019), leukopenia (59.1% *vs*. 82.0%, p=0.0097), fatigue (18.2% *vs*. 41.0, p=0.013) and peripheral neuropathy (2.3% *vs*. 18.0%, p=0.013) was significantly higher in the GnP group than in the GEM group (Table IV).

Discussion

In this study of patients with aPC receiving GEM or GnP therapy as a guideline-consistent antiemetic medication for that of, we found that the incidence of nausea, vomiting and rescue did not significantly differ between the GEM and GnP groups. Further, multivariate logistic regression analysis showed that combination therapy with GEM and nab-PTX

Table I. *Comparison of patient demographics between the gemcitabine and nab-paclitaxel plus gemcitabine groups.*

Characteristic	Gemcitabine (n=44)		Nab-paclitaxel plus gemcitabine (n=61)	
Gender, M/F, (n)	23/21		33/28	
Age (y), median (range)	70	(53-89)	67	(49-81)
Height (cm)	157.8	(152.0-162.9)	160.6	(153.0-167.0)
Body weight (kg)	49.8	(46.8-54.4)	52.5	(47.7-59.7)
Serum albumin (g/dl)	3.5	(3.1-3.9)	3.5	(3.2-3.9)
Aspartate transaminase (U/l)	22.0	(17.8-35.3)	25.0	(19.0-34.0)
Alanine aminotransferase (U/l)	16.5	(10.8-33.3)	20.0	(16.0-36.0)
Serum creatinine (mg/dl)	0.7	(0.6-0.8)	0.6	(0.5-0.7)
Total bilirubin (mg/dl)	0.7	(0.6-1.0)	0.6	(0.4-0.8)
C-reactive protein (g/dl)	0.8	(0.1-1.9)	0.4	(0.1-2.1)
Neutrophils (/l)	3480.0	(2,255-4,431.5)	3685	(2,312.5-5,130)
White blood cells (/l)	5120	(3,942.5-6,587.5)	5700	(4,080-7,410)
Haemoglobin (g/dl)	10.8	(9.5-11.9)	10.9	(9.7-11.9)
Platelets ($\times 10^4$/l)	16.3	(15.4-21.0)	20.9	(17.8-27.2)
Carcinoembryonic antigen (ng/ml)	4.7	(2.6-12.9)	6.4	(3.2-23.3)
CA19-9 antigen (U/ml)	994.4	(128.9-3,163.2)	1832.2	(212.2-4,198.4)
With distant metastasis, n (%)	30	(68.2)	50	(82.0)
With ascites, n (%)	21	(47.7)	28	(45.9)
Disease stage, n (%)				
Advanced	43	(97.7)	55	(90.2)
Relapse	1	(2.3)	6	(9.8)
With biliary stent, n (%)	16	(36.4)	29	(47.5)
Line of therapy, n (%)				
First	23	(52.3)	26	(42.6)
Second and later	21	(47.7)	35	(57.4)
Initial dose (mg/m^2) of Gemcitabine				
First line therapy	958.2	(921.6-980.9)	804.2	(765.5-964.7)
Second and later	959.7	(933.0-977.8)	792.4	(760.1-967.6)
Initial dose (mg/m^2) of nanoparticle albumin-bound paclitaxel				
First line therapy	-	-	99.3	(96.0-122.3)
Second line therapy	-	-	99.0	(95.5-120.1)
Antiemetic measure, n (%)				
Granisetron 3 mg	8	(18.2)	7	(11.5)
Dexamethasone 6.6 mg	36	(81.8)	54	(88.5)
With diabetes mellitus, n (%)	13	(29.5)	25	(41.0)
With alcohol drinking history, n (%)	18	(40.9)	35	(57.4)
With smoking history, n (%)	17	(38.6)	25	(41.0)
With pancrelipase, n (%)	10	(22.7)	7	(11.5)

Data indicate median values (25-75th percentiles) unless otherwise indicated.

was not significantly associated with nausea compared to GEM. This study, the first to compare the incidence of GEM and GnP therapy-induced nausea and vomiting in patients treated with guideline-consistent antiemetic medication, may suggest that antiemetic measures for GnP therapy are sufficient according to the measures for LEC, as well as GEM monotherapy.

In this study, the incidence of GnP therapy-induced nausea and vomiting was 36.0%. This is comparable with the 30.0% (grade ≥3: 3.5%) reported by Portal *et al*. in patients with aPC receiving FOLFIRINOX therapy (16). In addition, our nausea and vomiting rates for GnP therapy are consistent with those of Mita *et al*., who reported a rate of 26.7% (grade ≥3: 0.0%) following failure of first-line FX (including modified FX) therapy (17).

We showed that the incidence of nausea, vomiting and rescue did not significantly differ between the GEM and GnP groups during the acute, delayed or overall periods. Nevertheless, these rates tended to be higher during the delayed period than the acute period in both groups. Hayashi *et al*. reported that the severity of nausea gradually increased from day 1, peaking on days 4 and 5 (18).

In the present study, all patients were treated with guideline-consistent antiemetic medication for LEC consisting of a 5-HT3 receptor antagonist (day 1) or dexamethasone (days 1), but this seemed to be insufficient for the control of CINV in

Table II. *Comparison of the incidence of nausea, vomiting, and rescue during the acute, delayed and overall periods in patients with pancreatic cancer who received gemcitabine and nab-paclitaxel plus gemcitabine.*

Incidence (%)	Gemcitabine (n=44)	Nab-paclitaxel plus gemcitabine (n=61)	*p*-Value
Nausea			
Acute	13.6	9.8	0.546
Delayed	27.3	34.4	0.436
Overall	29.5	36.0	0.484
Vomiting			
Acute	2.3	1.6	1.00
Delayed	6.8	3.3	0.647
Overall	6.8	4.9	0.693
Rescue			
Acute	2.3	0.0	0.419
Delayed	9.1	3.3	0.234
Overall	9.1	3.3	0.234

Data were statistically analyzed using Fisher's exact probability test.

Table III. *Multivariate logistic regression analyses for the risk of chemotherapy-induced nausea and vomiting in patients with pancreatic cancer who received gemcitabine and nab-paclitaxel plus gemcitabine.*

Factor	Multivariate analysis		
	OR	95%CI	*p*-Value
History of chemotherapy-induced nausea and vomiting	3.86	0.98-15.28	0.054
Age under 65 years	2.80	1.02-7.67	0.046
Combination with nab-paclitaxel	1.01	0.39-2.65	0.981
Female	0.82	0.34-2.02	0.672
Second and later line therapy	0.22	0.07-0.73	0.014

Table IV. *Comparison of the incidence of hematological and non-hematological adverse events (Grade ≥2) between gemcitabine and nab-paclitaxel plus gemcitabine.*

Incidence (%)	Gemcitabine (n=44)	Nab-paclitaxel plus gemcitabine (n=61)	*p*-Value
Anemia	65.9	82.0	0.06
Leukopenia	59.1	82.0	0.0097
Neutropenia	47.7	77.0	0.0019
Thrombocytopenia	29.5	47.5	0.063
Febrile neutropenia	2.3	9.8	0.234
Fatigue	18.2	41.0	0.013
Taste disorder	15.9	31.1	0.074
Peripheral neuropathy	2.3	18.0	0.013
Diarrhea	9.1	3.3	0.234
Fever	2.3	8.2	0.397
Oral mucositis	2.3	6.6	0.396

Data were statistically analyzed using Fisher's exact probability test.

a particular population of patients. It is conceivable that the control of CINV requires carefully personalized antiemetic medication which is based on risk factors for CINV among individuals. The risk factors for nausea were age under 65 years (OR=2.80, 95%CI=1.02-7.67, p=0.046) and, albeit without significance, a history of chemotherapy-induced nausea or vomiting (OR=3.86, 95%CI=0.98-15.28, p=0.054). Hayashi *et al*. also reported a history of CINV was a risk factor for delayed CINV (19). The widely accepted clinical view is that younger patients are more prone to CINV than older patients. Our data are generally consistent with those of Hayashi *et al*. (19), and the two studies therefore suggest that guideline-consistent antiemetic medication for MEC should be considered for appropriate patients.

The JSCO clinical practice guideline for antiemesis recommends that, for MEC, a combination of 5-HT3 receptor antagonist and dexamethasone be administered before chemotherapy, and dexamethasone should be additionally administered on days 2 and 3. For LEC, in contrast, dexamethasone only is administered before chemotherapy (10). Changing antiemetic measures from those for LEC to those for MEC increases exposure to dexamethasone. Jeong *et al*. reported that development rates for steroid-induced diabetes mellitus after antiemetic medication for high-emetic-risk chemotherapy (frequency of emesis >90%) or MEC consisting of dexamethasone in non-diabetic cancer patients were approximately 20% at 3 or 6 months after the first chemotherapy (20). Further, new-onset diabetes mellitus in patients with advanced pancreatic cancer is likely induced by the tumor (21, 22). In fact, approximately 35% of our present patients in both groups also had diabetes mellitus. Although antiemetic measures should be intensified for patients at risk for CINV, increased steroid exposure should be avoided because of the presence of pancreatic cancer, which may lead to the development of diabetes mellitus.

Okada *et al*. showed that regardless of known risk factors for CINV, a dexamethasone sparing regimen with palonosetron (palonosetron plus 1-day dexamethasone) was not associated with a significant decrease in overall antiemetic control in patients receiving chemotherapy, including MEC or AC (23). Hesketh *et al*. reported that palonosetron was well tolerated and effectively prevented CINV in both acute and delayed periods in patients who had incomplete control of CINV during their previous cycle of LEC (24). Therefore, antiemetic medication for MEC with steroid sparing by palonosetron should be considered for patients with diabetes mellitus. Thus, we consider that GnP therapy-induced nausea and vomiting can be

controlled with guideline-consistent antiemetic medication for LEC, and that antiemetic medication for MEC either with or without steroid sparing by palonosetron should be considered as alternative antiemetic prophylaxis for patients with factors for poor antiemetic control.

In the present study, the incidence of grade ≥2 fatigue was significantly higher in the GnP group than in the GEM group (18.2% *vs*. 41.0%). Von Hoff *et al*. reported that the incidence for grade ≥3 fatigue was higher in the GnP group than in the GEM group (7.0% *vs*. 17.0%), consistent with the present study (4). Thus, the difference in the incidence of fatigue between the two groups is considered ascribable to the nab-PTX combination.

Two limitations of the present study warrant mention. First, the study was conducted under a cohort design with a small sample size at a single centre. The results should therefore be validated against multicentre studies in larger populations. Second, the study was not a prospective, randomized or blinded study, and we could not rule out the possibility of many confounding factors, including bias in sample size between the two groups.

In conclusion, the incidence of CINV with GnP was 36.0% during the overall period, which did not significantly differ to that with GEM. GnP therapy-induced nausea and vomiting can be controlled with guideline-consistent antiemetic medication for LEC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Koichi Ohata and Hironori Fujii conceptualized this study. Shiori Sadaka, Koichi Ohata, Hiroko Kato-Hayashi, Shinya Uemura and Takuji Iwashita acquired the clinical data. Hirotoshi Iihara, Ryo Kobayashi, Masahito Shimizu and Akio Suzuki were responsible for the data interpretation. Koichi Ohata and Hironori Fujii drafted the manuscript. All Authors have read and approved the current version of the manuscript.

References

1 Ito Y, Miyashiro I, Ito H, Hosono S, Chihara D, Nakata-Yamada K, Nakayama M, Matsuzaka M, Hattori M, Sugiyama H, Oze I, Tanaka R, Nomura E, Nishino Y, Matsuda T, Ioka A, Tsukuma H, Nakayama T and J-CANSIS Research Group: Long-term survival and conditional survival of cancer patients in Japan using population-based cancer registry data. Cancer Sci *105(11)*: 1480-1486, 2014. PMID: 25183551. DOI: 10.1111/cas.12525

2 Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T and Research Group of Population-Based Cancer Registries of Japan: Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. Jpn J Clin Oncol *41(1)*: 40-51, 2011. PMID: 20819833. DOI: 10.1093/jjco/hyq167

3 Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD and Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol *15(6)*: 2403-2413, 1997. PMID: 9196156. DOI: 10.1200/JCO.1997.15.6.2403

4 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J and Renschler MF: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med *369(18)*: 1691-1703, 2013. PMID: 24131140. DOI: 10.1056/NEJMoa1304369

5 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M, Groupe Tumeurs Digestives of Unicancer and PRODIGE Intergroup: FOLFIRINOX *versus* gemcitabine for metastatic pancreatic cancer. N Engl J Med *364(19)*: 1817-1825, 2011. PMID: 21561347. DOI: 10.1056/NEJMoa1011923

6 de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G and Verweij J: Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer *76(8)*: 1055-1061, 1997. PMID: 9376266. DOI: 10.1038/bjc.1997.507

7 Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacio D and Lyman GH: Antiemetics: ASCO Guideline Update. J Clin Oncol *38(24)*: 2782-2797, 2020. PMID: 32658626. DOI: 10.1200/JCO.20.01296

8 National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology Antiemetics. Verson2; 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf [Last accessed on March 23, 2021]

9 Multinational Association of Supportive Care in Cancer. Clinical Practice Guidelines in Antiemetics. 2016. Available at: https://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_v.1.5SEPT29.2019.pdf [Last accessed on March 23, 2021]

10 Aogi K, Takeuchi H, Saeki T, Aiba K, Tamura K, Iino K, Imamura CK, Okita K, Kagami Y, Tanaka R, Nakagawa K, Fujii H, Boku N, Wada M, Akechi T, Iihara H, Ohtani S, Okuyama A, Ozawa K, Kim YI, Sasaki H, Shima Y, Takeda M, Nagasaki E, Nishidate T, Higashi T and Hirata K: Optimizing antiemetic treatment for chemotherapy-induced nausea and vomiting in Japan: Update summary of the 2015 Japan Society of Clinical Oncology Clinical Practice Guidelines for Antiemesis. Int J Clin Oncol *26(1)*: 1-17, 2021. PMID: 33161452. DOI: 10.1007/s10147-020-01818-3

11 U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. Available at: https://www.eortc.be/services/doc/ctc/ [Last accessed on September 1, 2018]

12 Sekine I, Segawa Y, Kubota K and Saeki T: Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. Cancer Sci *104(6)*: 711-717, 2013. PMID: 23480814. DOI: 10.1111/cas.12146

13 Tamura K, Aiba K, Saeki T, Nakanishi Y, Kamura T, Baba H, Yoshida K, Yamamoto N, Kitagawa Y, Maehara Y, Shimokawa M, Hirata K, Kitajima M and CINV Study Group of Japan: Testing the effectiveness of antiemetic guidelines: results of a prospective registry by the CINV Study Group of Japan. Int J Clin Oncol *20(5)*: 855-865, 2015. PMID: 25681876. DOI: 10.1007/s10147-015-0786-7

14 Andrykowski MA, Jacobsen PB, Marks E, Gorfinkle K, Hakes TB, Kaufman RJ, Currie VE, Holland JC and Redd WH: Prevalence, predictors, and course of anticipatory nausea in women receiving adjuvant chemotherapy for breast cancer. Cancer *62(12)*: 2607-2613, 1988. PMID: 3191461. DOI: 10.1002/1097-0142(19881215)62:12<2607::aid-cncr2820621226>3.0.co;2-s

15 Morrow GR and Morrell C: Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. N Engl J Med *307(24)*: 1476-1480, 1982. PMID: 6128673. DOI: 10.1056/NEJM198212093072402

16 Portal A, Pernot S, Tougeron D, Arbaud C, Bidault AT, de la Fouchardière C, Hammel P, Lecomte T, Dréanic J, Coriat R, Bachet JB, Dubreuil O, Marthey L, Dahan L, Tchoundjeu B, Locher C, Lepère C, Bonnetain F and Taieb J: Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort. Br J Cancer *113(7)*: 989-995, 2015. PMID: 26372701. DOI: 10.1038/bjc.2015.328

17 Mita N, Iwashita T, Uemura S, Yoshida K, Iwasa Y, Ando N, Iwata K, Okuno M, Mukai T and Shimizu M: Second-line gemcitabine plus nab-paclitaxel for patients with unresectable advanced pancreatic cancer after first-line FOLFIRINOX failure. J Clin Med *8(6)*: 761, 2019. PMID: 31146420. DOI: 10.3390/jcm8060761

18 Hayashi T, Shimokawa M, Miyoshi T, Toriyama Y, Yokota C, Taniguchi J, Hanada K, Tsumagari K, Okubo N, Koutake Y, Sakata K, Kawamata Y, Goto T, Tsurusaki Y and Koyabu M: A prospective, observational, multicenter study on risk factors and prophylaxis for low emetic risk chemotherapy-induced nausea and vomiting. Support Care Cancer *25(9)*: 2707-2714, 2017. PMID: 28341971. DOI: 10.1007/s00520-017-3679-7

19 Hayashi T, Shimokawa M, Matsuo K, Miyoshi T, Toriyama Y, Yokota C, Taniguchi J, Hanada K, Tsumagari K, Okubo N, Koutake Y, Sakata K, Kawamata Y, Goto T, Tsurusaki Y and Koyabu M: Risk factors for delayed chemotherapy-induced nausea and vomiting with low-emetic-risk chemotherapy: a prospective, observational, multicenter study. Cancer Manag Res *10*: 4249-4255, 2018. PMID: 30323680. DOI: 10.2147/CMAR.S176574

20 Jeong Y, Han HS, Lee HD, Yang J, Jeong J, Choi MK, Kwon J, Jeon HJ, Oh TK, Lee KH and Kim ST: A pilot study evaluating steroid-induced diabetes after antiemetic dexamethasone therapy in chemotherapy-treated cancer patients. Cancer Res Treat *48(4)*: 1429-1437, 2016. PMID: 26987397. DOI: 10.4143/crt.2015.464

21 Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M and Petersen GM: Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology *134(1)*: 95-101, 2008. PMID: 18061176. DOI: 10.1053/j.gastro.2007.10.040

22 Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM and Chari ST: Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology *134(4)*: 981-987, 2008. PMID: 18395079. DOI: 10.1053/j.gastro.2008.01.039

23 Okada Y, Oba K, Furukawa N, Kosaka Y, Okita K, Yuki S, Komatsu Y, Celio L and Aapro M: One-day *versus* three-day dexamethasone in combination with palonosetron for the prevention of chemotherapy-induced nausea and vomiting: A systematic review and individual patient data-based meta-analysis. Oncologist *24(12)*: 1593-1600, 2019. PMID: 31217343. DOI: 10.1634/theoncologist.2019-0133

24 Hesketh PJ, Morrow G, Komorowski AW, Ahmed R and Cox D: Efficacy and safety of palonosetron as salvage treatment in the prevention of chemotherapy-induced nausea and vomiting in patients receiving low emetogenic chemotherapy (LEC). Support Care Cancer *20(10)*: 2633-2637, 2012. PMID: 22733373. DOI: 10.1007/s00520-012-1527-3

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