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ORIGINAL RESEARCH

Antibiotic therapy augments the efficacy of gemcitabine-containing regimens for advanced cancer: a retrospective study

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Background: The addition of antibiotics reportedly augments the efficacy of gemcitabine (GEM) in tumor-bearing mice. However, whether this phenomenon is also observed in cancer patients remains unclear. In the present study, we aimed to assess whether antibiotics for treatment or prevention of infection augments treatment efficacies of GEM-containing regimens in patients with any type of cancer.

Methods: Medical records of patients diagnosed with cancer histopathologically and treated with GEM-containing regimens (n=169) were retrospectively reviewed. Patients were assigned into two groups: antibiotics-untreated group (patients who were treated with GEM-containing regimens but without antibiotics) and antibiotics-treated group (patients who were treated with GEM-containing regimens plus antibiotics). Response rates, progression-free survival (PFS) time, and overall survival (OS) time were analyzed for each group.

Results: The response rates of the antibiotics-untreated and antibiotics-treated groups with GEM-containing regimens were 15.1% and 27.6%, respectively. The median PFS times of the antibiotics-untreated and antibiotics-treated groups were 2.5 (95% CI: 1.86–3.73) and 4.9 (95% CI: 3.47–6.0) months, respectively. The median OS times of the antibiotics-untreated and antibiotics-treated groups were 7.53 (95% CI: 5.63–9.57) months and 13.83 (95% CI: 10.83–16.43) months, respectively.

Conclusion: The addition of antibiotics augments the treatment efficacies of GEM-containing regimens, and it may be a potential therapeutic option to improve treatment efficacies of GEM-containing regimens in patients with advanced cancer.

Keywords: antibiotics, bacteria, gemcitabine, multivariate analysis, univariate analysis

Background

Gemcitabine (GEM) is one of the anticancer drugs that is often used for patients with advanced cancer.[1] GEM-containing regimens are used for patients with pancreatic cancer, biliary tract cancer, lung cancer, sarcoma, urothelial cancer, or breast cancer.[2–7] Literature is limited on the responses of GEM-containing regimens in patients with advanced cancers[5,8–10]; this necessitates the improvement of treatment efficacies of GEM-containing regimens in patients with advanced cancers.

A previous study reported that GEM (2′,2′-difluorodeoxycytidine) is metabolized into an inactive metabolite 2,2′-difluorodeoxyuridine by various microbes that express a long isoform of the bacterial enzyme cytidine deaminase (CDD_L).[11] In other previous reports, the treatment of tumor-bearing mice with antibiotics eradicates the bacteria from the tumor tissue and consequently increases the concentration of GEM in the tumor tissue.[12]

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Increased concentration of GEM in the tumor tissue resulted in robust tumor regression, whereas the mouse not treated with GEM did not exhibit tumor regression.[12] Moreover, various bacteria expressed CDD_L in human pancreatic cancer tissue, and these bacteria potently conferred the resistance of GEM in the cancer cell line in vitro.[12] Therefore, the bacteria that express CDD_L in tumor tissue may be related to the low treatment efficacies of GEM in human and that the addition of antibiotics to a regimen-containing GEM would augment its efficacy. However, no previous report had examined whether the addition of antibiotics augments the treatment efficacy of GEM in patients with advanced cancer.

In this study, we tried to assess whether antibiotics given for treatment or prevention of infection augment the treatment efficacy of GEM-containing regimens in patients with various types of advanced cancers.

Methods

Patients

Medical records of patients who were diagnosed with cancer histopathologically and were treated with GEM-containing regimens (n=169) were retrospectively reviewed at the Department of Medical Oncology, Tohoku University Hospital from 2006 to 2018. Patients with advanced stage of pancreatic cancer, biliary tract cancer, duodenal cancer, cancer of unknown primary, neuroendocrine carcinoma, sarcoma, and urinary bladder cancer were included in this study. Patients with stage III or stage IV cancers were included in the antibiotics-untreated and antibiotics-treated group. Proportions of patients with stage III or IV cancer were similar between the two groups.

Inclusion criteria of this study included: 1) patients who had been histologically confirmed carcinoma or sarcoma; 2) patients who had unresectable cancer (or sarcoma) or metastatic lesion; 3) patients who had been treated with at least one course of GEM-containing regimen; 4) patients who had at least one measurable cancer (or sarcoma) lesion; 5) patient in whom the treatment efficacies of GEM-containing regimen in cancer (or sarcoma) had been assessed by computed tomography (CT) at least once. In all, there were 196 patients who met the inclusion criteria. Patients who did not meet inclusion criteria were all excluded from the analyses in this study.

Treatment methods

The doses and schedules of GEM treatment in this study were as follows. GEM alone (plus erlotinib): GEM 1000 mg/m^2, days 1, 8 and 15 (erlotinib 100 mg/body, days 1–28) every 4 weeks; GEM plus nanoparticle albumin binding paclitaxel (nabPTX): GEM 1000 mg/m^2, nabPTX 125 mg/m^2, days 1, 8, 15, every 4 weeks; GEM plus cisplatin (plus S-1): GEM 1000 mg/m^2, cisplatin 25 mg/m^2, days 1, 8 (S-1 80 mg/m^2, days 1–14, every 3 weeks; GEM plus docetaxel: GEM 900 mg/m^2, day 1, 8, docetaxel 70 mg/m^2 day 8, every 3 weeks.

Antibiotics were administered according to the drug attachment (e.g., levofloxacin hydrate: oral administration, 500 mg/body/day; cefdinir: oral administration, 300 mg/body/day; meropenem hydrate: intravenous administration, 0.5–1 g/body/day.) The administration period of antibiotics was determined by the chief physician of each patient.

Evaluation

Patients were assigned into two groups. The first was the antibiotics-treated group where patients had been treated with antibiotics from the start of the GEM-containing regimen to the first imaging evaluation of the efficacy of GEM-containing regimen using CT (antibiotics-treated group). The other group was the antibiotics-untreated group where patients had not been treated with antibiotics from the start of the GEM-containing regimen to the first CT evaluation of the efficacy of the GEM-containing regimen.

Responses were assessed using Response Criteria in Solid Tumor version 1.0.[13] The rates of complete response (CR; all signs of cancer disappeared by treatment with GEM-containing regimen) and partial response (PR; defined as a ≥30% reduction in the diameter of measurable lesions on CT) were combined and defined as the response rate. CR, PR, and stable disease (defined as a <30% reduction and a <20% increase in the diameter of measurable lesions as shown on CT) rates were combined, and these rates were defined as the disease control rate. In this study, the relative dose intensity of GEM was defined as the ratio of the total actual dose of GEM delivered to patients to the planned dose of GEM. All toxicities were reviewed from medical records and were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.[14]

Statistical analysis

The median progression-free survival (PFS) time and median overall survival (OS) time were calculated using the Kaplan–Meier method. *P*-values of the response rate and disease control rate were based on Fisher's exact test. All statistical analyses including univariate analysis, multivariate analysis, Pearson's chi-squared test, and Wilcoxon Mann–Whitney test were performed using JMP® 11

(SAS Institute Inc., Cary, NC, USA). All differences were regarded as statistically significant when $P<0.05$.

Results

Patient characteristics

We identified 169 patients who were treated with GEM-containing regimen (antibiotics-untreated group=93; antibiotics-treated group=76). Patient characteristics are presented in Table 1. Approximately, 80% of the subjects had pancreatic or biliary tract cancer. Relative dose intensities of GEM in the antibiotics-untreated and antibiotics-treated groups were 81.1% and 78.9%, respectively. Proportions of sex, previous surgery, types of GEM-containing regimens were similar between the two groups.

Efficacies of GEM-containing regimens

We calculated the response rate of patients to GEM-containing regimens. As shown in Table 2, the response rates in the antibiotics-untreated and antibiotics-treated groups by GEM-containing regimens were 15.1% and 27.6%, respectively. Disease control rates in the antibiotics-untreated and antibiotics-treated groups by GEM-containing regimens were 51.6% and 72.4%, respectively. The response and disease control rates were significantly higher in the antibiotics-treated group than in the antibiotics-untreated group.

As shown in Figure 1, the median PFS times of the antibiotics-untreated and antibiotics-treated groups were 2.5 (95% CI: 1.86–3.73) days and 4.93 (95% CI: 3.47–6.0) months, respectively. The median PFS rate was significantly higher in the antibiotics-treated group than in the antibiotics-untreated group ($P<0.0001$, log-rank test). As shown in Figure 2, the median OS times of the antibiotics-untreated and antibiotics-treated groups were 7.53 (95% CI: 5.63–9.57) months and 13.83 (95% CI: 10.83–16.43) months, respectively. The median OS rate was significantly higher in the antibiotics-treated group than in the antibiotics-untreated group ($P<0.0001$, log-rank test). The median PFS and the median OS of the patients with each cancer type in antibiotics-treated group and antibiotics-untreated group were shown in Table S1. In all cancer types, both the median PFS and the median OS of antibiotics-treated group were longer than these of antibiotics-untreated group. Especially, in pancreatic cancer, both the median PFS and the median OS of the antibiotics-treated group were significantly longer than those of the antibiotics-untreated group. In sarcoma, the median OS of the antibiotics-treated group was significantly longer than that of antibiotics-untreated group. Original data of each patient were shown in Table S2.

Toxicities

Toxicities by GEM-containing regimens in the antibiotics-untreated and antibiotics-treated group are shown in Table 3. The proportions of patients with severe leukopenia and neutropenia by GEM-containing regimens in the antibiotics-treated group were higher than those in the antibiotics-untreated group. Patients with a febrile neutropenia were included only in the antibiotics-treated group. The incidence rates of anemia, thrombocytopenia, and elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level were similar between the two groups. No patients died from adverse events of GEM-containing regimens.

Univariate and multivariate analyses

We performed univariate and multivariate analyses for the relationship between the responses to GEM-containing regimens and patient background or a severe neutropenia by GEM-containing regimens. Results of univariate and multivariate analyses are shown in Table 4. We found statistically significant correlations between the response by GEM-containing regimens and antibiotic treatment (univariate analysis: $P=0.0305$, multivariate analysis: $P=0.0314$). Seven factors (age, sex, severe neutropenia, operation history, tumor stage, cancer primary site, and type of GEM-containing regimens) analyzed did not significantly correlate with the response of GEM-containing regimens.

Discussion

A previous study[12] revealed that the antitumor efficacy of GEM was augmented by the addition of antibiotics in tumor-bearing mice compared to the antitumor efficacy of GEM alone. However, no previous report has demonstrated the augmentation of antitumor efficacy of GEM by addition of antibiotics in cancer patients. In this study, we observed that the treatment efficacy of GEM-containing regimens with antibiotics was augmented compared to that of GEM-containing regimens without antibiotics in patients with various types of advanced cancer. In all cancer type in this study, there had been tendency that both the median PFS and the median OS in the antibiotics-treated group were longer than these of antibiotics-untreated group.

Table 1 Patient characteristics

	Antibiotics-untreated group	Antibiotics-treated group	*P*-value
Number	93	76	
Sex (%)			0.785
Male	56 (60.2)	46 (60.5)	
Female	37 (39.8)	30 (39.5)	
Mean age (range)	63.9 (29–80)	63.0 (31–84)	
Cancer type (%)			0.346
Pancreatic cancer	60 (64.5)	45 (59.2)	
Biliary tract cancer	16 (17.2)	18 (23.7)	
Sarcoma	9 (9.7)	9 (11.8)	
CUP	3 (3.2)	2 (2.6)	
Duodenal cancer	3 (3.2)	1 (1.3)	
Neuroendocrine carcinoma	1 (1.1)	0 (0.0)	
Breast cancer	1 (1.1)	0 (0.0)	
Ulinary bladder cancer	0 (0.0)	1 (1.3)	
Tumor stage			0.891
III	8 (8.6)	7 (9.2)	
IV	85 (91.4)	69 (90.8)	
Operation history (%)			0.755
+	23 (24.7)	23 (30.3)	
–	70 (75.3)	53 (69.7)	
GEM including regimen (%)			0.412
GEM alone	48 (52.1)	34 (44.7)	
GEM plus nabPTX	20 (22.9)	20 (26.3)	
GEM plus cisplatin	12 (12.5)	12 (15.8)	
GEM plus docetaxel	9 (9.4)	9 (11.8)	
GEM plus cisplatin plus S-1	3 (2.1)	0 (0.0)	
GEM plus elrotinib	1 (1.0)	1 (1.3)	
Relative dose intensity of GEM (%)	81.1	78.9	0.788
Treated antibiotics			
New quinolone		38 (50.0)	
Second-generation cephem		3 (3.9)	
Third-generation cephem		15 (19.7)	
Fourth-generation cephem		13 (17.1)	
Carbapenem		3 (3.9)	
β-Lactamase inhibitor		2 (2.6)	
Penicillin		1 (1.3)	
Reason of antibiotics treatment			
Because of infection		16 (21.1)	
To prevent infection		60 (78.9)	

Note: *P*-values were calculated using chi-squared test or Wilcoxon or Mann–Whitney test.
Abbreviations: CUP, cancer of unknown primary; nabPTX, nanoparticle albumin binding paclitaxel; GEM, gemcitabine.

A previous study[12] demonstrated that antibiotics therapy (150 mg/kg of new quinolone) even for 2 days significantly removed bacteria from the tumor tissue in mice and consequently reduced the CDD_L from bacteria. The reduction of CDD_L resulted in the low metabolism of GEM by bacteria and the high concentration of GEM in the tumor tissue.[12] The dosage of antibiotics in that study[12] was similar to those usually used in patients in clinical

Table 2 Response rate of gemcitabine-containing regimens

	CR	PR	SD	PD	RR (%)
Antibiotics-untreated group	0	14	34	45	15.1
Antibiotics-treated group	0	21	34	21	27.6

Notes: *P*-value of response rate between two groups. Antibiotics-untreated group vs antibiotics-treated group *P*=0.0356. *P*-value of disease control rate between each group. Antibiotics-untreated group vs antibiotics-treated group *P*=0.0071.
Abbreviations: CR, complete response; DCR, disease control rate; PD, progression disease; PR, partial response; RR, response rate; SD, stable didease.

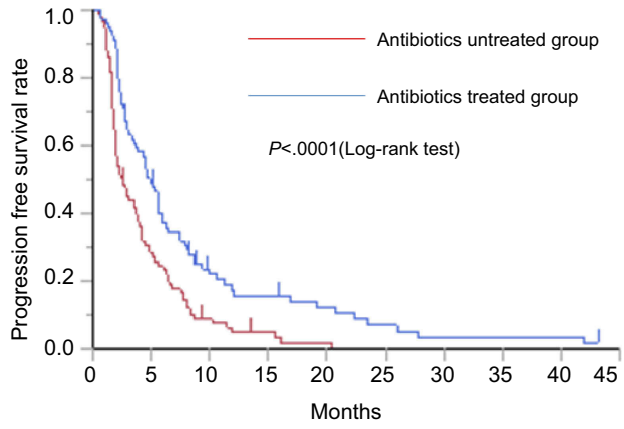

Figure 1 Kaplan–Meier curve of the PFS rate in the antibiotics-untreated group and antibiotics-treated group.
Abbreviation: PFS, progression-free survival.

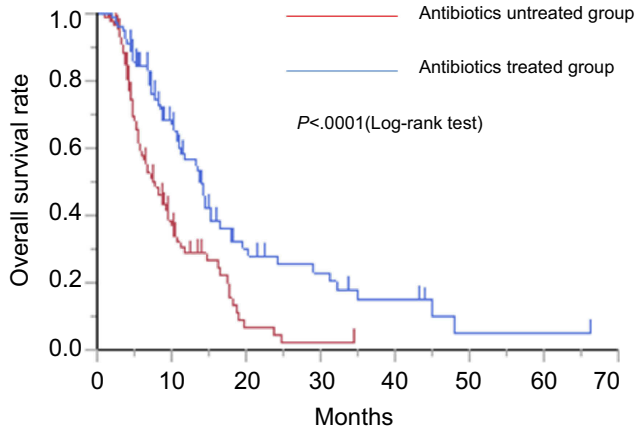

Figure 2 Kaplan–Meier curve of the OS rate with the antibiotics-untreated group and antibiotics-treated group.
Abbreviation: OS, overall survival

practice. In the present study, all antibiotics were given in doses similar to those in clinical practice. In this study, as we did not investigate the amount of bacteria in the cancer tissue from patients, it is unclear whether bacteria were sufficiently removed from the tumor tissue by the antibiotics therapy. However, based on a previous study,[12] the dosage of antibiotics used in the present study appeared to be sufficient to reduce the bacteria from the tumor tissue.

Table 3 Severe (grade 3 or 4) toxicities by gemcitabine-containing regimens

	Antibiotics-untreated group (n=93)	Antibiotics-treated group (n=76)
Leukopenia	14 (15.1)	36 (47.4)
Neutropenia	27 (29.0)	42 (55.3)
Anemia	15 (16.1)	12 (15.8)
Thrombocytopenia	10 (10.7)	7 (9.2)
Febrile neutropenia	0 (0.0)	2 (2.6)
Elevated AST/ALT	7 (7.5)	6 (7.9)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Moreover, in the present study, the augmentation of the treatment efficacy of GEM-containing regimen by the addition of antibiotics might be attributable to the removal of bacteria from the cancer tissue, which consequently increased the concentration of GEM in cancer tissues.

In this study, the incidence rates of severe leukopenia and neutropenia by GEM-containing regimens were higher in the antibiotics-treated group than in the antibiotics-untreated group. Usually, patients who have grade 3 or 4 of leucopenia or neutropenia during chemotherapy are treated with antibiotics to prevent infections.[15] Therefore, it is inevitable that the antibiotics-treated group includes patients with severe leukopenia or neutropenia. The proportions of anemia, thrombocytopenia, or elevated AST or ALT level were similar between two groups, suggesting that the addition of antibiotics do not increase the adverse effects by GEM-containing regimens.

Alteration of gut microbiota by antibiotics influenced the efficacies and toxicities of irinotecan as irinotecan metabolism was affected by bacteria in mice gut.[16] Antibiotic treatment might change the gut microbiota in patients in the present study and might influence the metabolism of GEM by the bacteria in the gut similar to that in a previous report.[16] These changes might elevate the blood concentration of GEM, resulting in higher toxicities with GEM-containing regimen in the antibiotics-treated group. However, the incidence rates of anemia, thrombocytopenia, and elevated AST

Table 4 Univariate and multivariate analyses for the relationship between the response to the gemcitabine-containing regimens and patients' background or toxicity by gemcitabine-containing regimens

	n (%)	Univariete analysis	Multivariate analysis	
		P-value	OR (95% CI)	*P*-value
Sex				
Male	102 (60.3)	0.5621	1.39 (0.632–3.058)	0.4129
Female	67 (39.7)			
Age				
≧65	90 (53.3)	0.4144	1.733 (0.765–3.926)	0.1877
<65	79 (46.7)			
Antibiotics				
Untreated	93 (55.0)	0.0305	2.444 (1.083–5.519)	0.0314
Treated	76 (45.0)			
Severe (grade 3 or 4) neutropenia				
Negative	110 (65.1)	0.6975	0.696 (0.293–1.651)	0.4103
Positive	59 (34.9)			
Operaion history				
Negative	123 (72.8)	0.1148	0.364 (0.129–1.033)	0.0577
Positive	46 (27.2)			
Tumor stage				
III	15 (8.9)	0.4360	2.321 (0.473–11.392)	0.2995
IV	154 (91.1)			
Cancer type				
Pancreatic cancer	105 (62.1)	0.7799	0.919 (0.383–2.205)	0.8500
Other cancers	64 (37.9)			
Type of GEM-containing regimen				
GEM alone	82 (48.5)	0.0700	1.997 (0.842–4.738)	0.1165
Combination of GEM and other anticancer drug	87 (51.5)			

Note: *P*-values were analyzed using Pearson's chi-square test.
Abbreviation: GEM, gemcitabine.

or ALT level were similar between the two groups in the present study. Therefore, it is assumed that the general concentration of GEM is not elevated but elevated locally in the tumor tissue.

The univariate and multivariate analyses in the present study revealed that antibiotic treatment significantly correlated to the response of GEM-containing regimens. These results suggest that the addition of antibiotics was the cause of improvement of the treatment of efficacies of GEM-containing regimens.

This study has some limitations. First, this study has a retrospective design. Second, the number of patients is relatively small. Third, several previous studies have reported the influence of antibiotics on the activity of cytochrome P450 (CYP) or on the induction of CYP in humans.[17–20] The change in CYP activity or in CYP induction by antibiotics influences the metabolisms of other anticancer drugs.[21–24] The metabolism of GEM is possibly modified by CYP mediated by antibiotics. However, no study has reported about GEM metabolism by CYP. Therefore, it is still uncertain whether the blood concentration of GEM changes via CYP. Fourth, the timing and duration of antibiotic treatment during GEM-containing regimens varied with each patient. However, the background of the two groups was very similar, except that antibiotics were added to GEM-containing regimens only in the antibiotics-treated group. Thus, the improvement of treatment efficacy of GEM-containing regimens might be attributable to the addition of antibiotics to patients in the antibiotics-treated group. Forth, although there are several mechanisms modulating the sensitivities of GEM in cancer patients, we did not investigate the

GEM resistant mechanisms in patients in this study. It has been reported that the dysregulation of proteins participating in GEM metabolism pathway or the high expression of GEM efflux pump is the mechanisms responsible for GEM resistance.[25–27] Moreover, it was also reported that *BRCA1 associated protein 1 gene (BAP1)* mutation is responsible for the sensitivity of GEM in patients with malignant mesothelioma.[28] To investigate whether these resistant mechanisms influence on efficacies of the antibiotics and GEM-containing regimen combination therapy or not is needed.

Conclusion

The addition of antibiotics to GEM-containing regimens might be a potential therapeutic option to improve treatment efficacies of GEM-containing regimens in patients with advanced cancer.

Ethics approval and consent to participate

This study protocol was approved by the ethics committee of Tohoku University Hospital. The ethics committee of Tohoku University Hospital has permitted to conduct retrospective studies without consent statements by patients (opt-out system). All data in the current study had no personal identifiers and were kept confidential.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDD_L, long isoform of the bacterial enzyme cytidine deaminase; CR, complete response; CT, computed tomography; CYP, cytochrome P450; OS, overall survival; PFS, progression-free survival; PR, partial response.

Author contributions

Hiroo Imai designed the study and wrote the initial draft of the manuscript. Chikashi Ishioka is the corresponding author and contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

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Supplementary materials

Table S1 The median progression free survival time (PFS) or the median OS of the patients with biliary tract cancer, pancreatic cancer, sarcoma and other cancers in antibiotics-untreated group and antibiotics-treated group

Primary site	Median PFS (months)		*P*-value	Median OS (months)		*P*-value
	Antibiotics-untreated gourp	Antibiotics-treated group		Antibiotics-untreated gourp	Antibiotics-treated group	
Biliary tract	3.4	5.4	0.1580	10.6	14.3	0.4305
Pancreas	2.5	4.2	0.0035	6.6	13.8	0.0020
Sarcoma	1.9	5.1	0.2642	4.0	10.9	0.0400
Other cancers	4.0	7.9	0.1445	9.9	10.8	0.5997

Notes: Other cancer: CUP, NEC, duodenal cancer, breast cancer, urinary bladder cancer. *P*-value was calculated using log-rank test.

Table S2 Patient's original data in the present study

Age	Sex	Primary site	Operation history	GEM-containing regimen	GEM containing regimen		Date of death	Antibiotics treatment
					Date of start	Date of discontinuation		
69	Female	Pancreas	No	GC	11-05-2017	31-08-2018	31-08-2018	Carbapenem
63	Female	Biliary tract	No	GC	14-11-2008	01-05-2009	29-07-2009	Carbapenem
67	Female	Pancreas	No	GEM	27-06-2008	24-09-2008	14-11-2008	Carbapenem
54	Male	Biliary tract	No	GC	05-07-2017	12-10-2017	31-08-2018	Cephem
67	Male	Biliary tract	No	GC	15-10-2015	17-12-2015	08-04-2017	Cephem
62	Male	Biliary tract	No	GC	17-10-2013	02-07-2015	20-08-2015	Cephem
69	Male	Pancreas	No	GC	25-07-2016	26-09-2016	23-05-2017	Cephem
75	Female	Pancreas	No	GC	16-06-2015	29-04-2016	24-08-2016	Cephem
25	Male	Sarcoma	No	GD	16-12-2013	25-05-2017	25-11-2017	Cephem
32	Female	Sarcoma	No	GD	30-10-2017	16-11-2017	12-01-2018	Cephem
68	Male	Biliary tract	No	GEM	24-11-2015	20-06-2017	31-08-2018	Cephem
57	Male	CUP	No	GEM	18-08-2017	10-11-2017	02-01-2018	Cephem
74	Female	Pancreas	No	GEM	05-04-2010	02-06-2010	04-06-2010	Cephem
76	Female	Pancreas	No	GEM	11-12-2006	10-10-2008	11-12-2008	Cephem
70	Female	Pancreas	No	GEM	24-08-2006	04-12-2008	12-01-2009	Cephem
49	Male	Pancreas	No	GEM	24-07-2014	05-12-2014	21-02-2015	Cephem
67	Male	Pancreas	No	GEM	06-02-2018	27-02-2018	29-04-2018	Cephem
66	Male	Pancreas	No	GEM	23-03-2017	24-05-2017	26-06-2018	Cephem
66	Female	Pancreas	No	GEM	11-12-2017	31-08-2018	31-08-2018	Cephem
68	Female	Pancreas	No	GEM	12-05-2017	19-07-2017	24-09-2017	Cephem
50	Male	Pancreas	No	GEM	30-09-2016	09-12-2016	23-04-2017	Cephem
72	Male	Pancreas	No	GEM	04-08-2016	15-09-2016	17-11-2016	Cephem
84	Female	Biliary tract	No	GnP	27-12-2017	31-08-2018	31-08-2018	Cephem
42	Female	Biliary tract	No	GnP	16-03-2016	12-09-2016	01-02-2017	Cephem
62	Female	Biliary tract	No	GC	31-05-2016	01-11-2016	01-11-2016	New quinolone
58	Male	CUP	No	GC	26-03-2010	18-11-2010	14-02-2011	New quinolone
70	Male	Pancreas	No	GC	31-10-2015	12-01-2016	25-03-2016	New quinolone
66	Male	Pancreas	No	GC	22-08-2014	29-01-2015	19-03-2015	New quinolone
68	Female	Ulinary bladder	No	GC	12-09-2011	05-12-2011	16-04-2012	New quinolone
36	Male	Sarcoma	No	GD	19-06-2015	07-04-2016	07-04-2016	Ne w quinolone
59	Male	Biliary tract	No	GEM	30-08-2016	11-04-2017	31-07-2017	New quinolone
61	Male	Biliary tract	No	GEM	04-06-2012	23-08-2012	25-10-2012	New quinolone
58	Male	Biliary tract	No	GEM	01-11-2012	31-01-2013	03-01-2014	New quinolone

(*Continued*)

Table S2 (Continued).

Age	Sex	Primary site	Operation history	GEM-containing regimen	GEM containing regimen		Date of death	Antibiotics treatment
					Date of start	Date of discontinuation		
80	Female	Biliary tract	No	GEM	28-02-2011	16-05-2011	21-10-2011	New quinolone
59	Female	Biliary tract	No	GEM	31-07-2009	12-11-2009	01-04-2011	New quinolone
78	Male	Biliary tract	No	GEM	18-09-2007	06-11-2009	10-05-2010	New quinolone
54	Male	Pancreas	No	GEM	26-03-2015	28-05-2015	16-07-2015	New quinolone
72	Male	Pancreas	No	GEM	13-02-2015	31-08-2018	31-08-2018	New quinolone
64	Male	Pancreas	No	GEM	21-02-2011	08-08-2011	29-03-2012	New quinolone
66	Male	Pancreas	No	GEM	24-09-2010	11-03-2011	28-05-2011	New quinolone
74	Male	Pancreas	No	GEM	26-05-2010	05-01-2011	03-08-2011	New quinolone
48	Male	Pancreas	No	GEM	06-04-2009	21-08-2009	08-05-2010	New quinolone
71	Male	Pancreas	No	GEM	06-09-2007	16-11-2007	18-01-2008	New quinolone
70	Male	Pancreas	No	GEM	26-05-2006	23-05-2007	05-02-2010	New quinolone
69	Female	Pancreas	No	GEM	05-10-2006	21-02-2007	23-11-2007	New quinolone
73	Male	Biliary tract	No	GnP	18-05-2015	16-07-2015	11-09-2015	New quinolone
77	Male	Pancreas	No	GnP	02-07-2015	26-10-2015	18-06-2016	New quinolone
58	Male	Pancreas	No	GnP	12-12-2011	20-01-2012	10-02-2012	New quinolone
87	Female	Pancreas	No	GnP	16-02-2018	23-04-2018	19-06-2018	New quinolone
70	Male	Pancreas	No	GnP	04-09-2017	24-05-2018	05-07-2018	New quinolone
80	Male	Pancreas	No	GnP	30-08-2017	18-12-2017	19-02-2018	New quinolone
63	Male	Pancreas	No	GEM	28-06-2017	21-08-2017	31-08-2018	Penicilline
66	Male	Pancreas	No	GEM	25-11-2014	01-09-2015	01-04-2016	β-lactamase inhibitor
61	Female	Biliary tract	No	GC	25-08-2014	18-09-2014	25-09-2014	None
70	Male	Biliary tract	No	GC	24-03-2014	30-05-2014	29-07-2014	None
78	Female	Biliary tract	No	GC	16-02-2016	13-06-2016	31-07-2016	None
71	Male	Biliary tract	No	GC	12-08-2016	07-10-2016	05-05-2017	None
68	Female	Biliary tract	No	GC	14-07-2014	07-10-2014	15-05-2015	None
75	Female	Biliary tract	No	GC	29-01-2013	12-09-2013	17-08-2014	None
58	Male	Biliary tract	No	GC	21-01-2013	21-09-2013	06-12-2013	None
69	Female	Biliary tract	No	GC	10-05-2010	29-06-2010	21-02-2011	None
79	Female	CUP	No	GC	31-05-2012	24-05-2013	30-09-2013	None
50	Male	NEC	No	GC	06-10-2014	20-04-2015	27-09-2015	None
64	Female	Biliary tract	No	GCS	09-10-2015	16-06-2016	06-04-2017	None
74	Male	Biliary tract	No	GCS	06-01-2016	15-07-2016	12-10-2016	None
32	Male	Sarcoma	No	GD	06-03-2017	21-03-2017	04-04-2017	None
52	Female	Sarcoma	No	GD	31-10-2016	26-12-2016	28-02-2017	None
70	Male	Biliary tract	No	GEM	10-02-2011	12-04-2011	28-06-2011	None
72	Female	Biliary tract	No	GEM	04-09-2008	28-10-2008	17-04-2009	None
78	Male	CUP	No	GEM	27-06-2017	25-07-2017	05-10-2017	None
70	Male	CUP	No	GEM	14-04-2008	18-08-2008	28-08-2008	None
46	Female	Breast	No	GEM	10-04-2008	22-05-2008	18-02-2009	None
76	Male	Pancreas	No	GEM	20-09-2016	05-01-2017	13-05-2017	None
29	Male	Pancreas	No	GEM	06-01-2014	28-02-2014	20-06-2014	None
80	Female	Pancreas	No	GEM	04-09-2014	30-10-2014	14-02-2015	None
42	Male	Pancreas	No	GEM	22-08-2013	15-12-2013	15-12-2013	None
61	Female	Pancreas	No	GEM	17-01-2014	17-09-2014	14-11-2014	None
65	Male	Pancreas	No	GEM	16-05-2013	08-10-2013	02-10-2013	None
45	Female	Pancreas	No	GEM	23-04-2013	06-06-2013	12-07-2013	None
61	Male	Pancreas	No	GEM	05-10-2012	06-11-2012	21-11-2012	None

(*Continued*)

Table S2 (Continued).

Age	Sex	Primary site	Operation history	GEM-containing regimen	GEM containing regimen		Date of death	Antibiotics treatment
					Date of start	Date of discontinuation		
55	female	Pancreas	no	GEM	19-04-2013	18-06-2013	23-09-2013	none
69	male	Pancreas	no	GEM	15-01-2013	25-06-2013	05-07-2014	none
63	female	Pancreas	no	GEM	26-04-2012	01-06-2012	01-09-2012	none
56	male	Pancreas	no	GEM	22-09-2011	31-10-2011	17-11-2011	none
52	male	Pancreas	no	GEM	13-12-2010	11-04-2011	11-04-2011	none
69	male	Pancreas	no	GEM	12-08-2010	14-10-2010	02-11-2010	none
62	female	Pancreas	no	GEM	14-01-2010	18-02-2010	15-03-2010	none
66	female	Pancreas	no	GEM	14-12-2009	08-02-2010	01-06-2010	none
68	male	Pancreas	no	GEM	06-10-2009	10-02-2010	30-11-2010	none
73	male	Pancreas	no	GEM	14-07-2009	13-08-2009	21-11-2009	none
69	male	Pancreas	no	GEM	07-07-2009	27-08-2009	17-10-2009	none
74	female	Pancreas	no	GEM	02-02-2009	23-03-2009	23-03-2009	none
64	male	Pancreas	no	GEM	27-11-2008	21-01-2009	24-02-2009	none
57	male	Pancreas	no	GEM	25-11-2008	08-06-2009	17-08-2009	none
63	male	Pancreas	no	GEM	26-09-2008	07-11-2008	11-04-2009	none
75	female	Pancreas	no	GEM	29-05-2008	17-07-2008	10-06-2010	none
77	male	Pancreas	no	GEM	21-05-2008	04-09-2008	02-06-2009	none
70	male	Pancreas	no	GEM	11-01-2008	04-03-2008	14-04-2008	none
44	male	Pancreas	no	GEM	10-10-2007	17-03-2008	23-05-2008	none
67	male	Pancreas	no	GEM	27-07-2007	14-09-2007	10-11-2007	none
72	male	Pancreas	no	GEM	02-04-2007	28-05-2007	06-08-2007	none
60	male	Pancreas	no	GEM	27-12-2006	17-08-2007	20-02-2008	none
57	female	Pancreas	no	GEM	22-11-2006	10-01-2007	24-04-2007	none
72	female	Pancreas	no	GEM	30-03-2006	13-06-2006	04-02-2007	none
69	male	Pancreas	no	GEM	10-08-2012	11-01-2013	13-04-2013	none
63	female	Pancreas	no	GEM plus elrotinib	16-09-2010	11-01-2012	29-02-2012	none
71	male	Pancreas	no	GnP	20-02-2018	21-08-2018	31-08-2018	none
70	male	Pancreas	no	GnP	28-11-2017	16-01-2018	27-03-2018	none
60	male	Pancreas	no	GnP	02-10-2017	26-02-2018	12-03-2018	none
72	female	Pancreas	no	GnP	08-09-2017	16-03-2018	27-05-2018	none
61	male	Pancreas	no	GnP	16-01-2018	21-02-2018	12-05-2018	none
68	male	Pancreas	no	GnP	06-09-2017	09-01-2018	26-01-2018	none
69	female	Pancreas	no	GnP	21-03-2017	27-04-2017	22-01-2018	none
66	male	Pancreas	no	GnP	22-11-2017	31-08-2018	31-08-2018	none
65	female	Pancreas	no	GnP	10-03-2017	01-05-2017	28-07-2017	none
65	male	Pancreas	no	GnP	31-01-2017	20-07-2017	08-10-2017	none
75	male	Pancreas	no	GnP	20-09-2016	31-01-2017	28-03-2017	none
75	female	Pancreas	no	GnP	26-09-2016	17-10-2016	15-11-2016	none
73	female	Pancreas	no	GnP	30-08-2016	20-12-2016	20-03-2017	none
81	male	Pancreas	no	GnP	28-07-2016	13-10-2016	18-01-2017	none
62	male	Pancreas	no	GnP	03-03-2017	06-04-2017	13-05-2017	none
67	male	Pancreas	no	GnP	22-06-2016	21-09-2016	16-12-2016	none
77	female	Pancreas	no	GnP	12-05-2015	04-08-2015	03-09-2015	none
74	male	Sarcoma	yes	GD	14-10-2015	29-02-2016	29-08-2018	cephem
38	female	Sarcoma	yes	GD	11-12-2014	17-06-2015	27-08-2015	cephem
51	female	Sarcoma	yes	GD	13-08-2015	22-02-2016	15-03-2016	cephem
58	female	Pancreas	yes	GEM	07-06-2017	04-09-2017	15-11-2017	cephem
75	female	Biliary tract	yes	GnP	27-09-2017	22-02-2018	04-08-2018	cephem

(*Continued*)

Table S2 (Continued).

Age	Sex	Primary site	Operation history	GEM-containing regimen	GEM containing regimen		Date of death	Antibiotics treatment
					Date of start	Date of discontinuation		
78	male	Pancreas	yes	GnP	30-10-2017	19-01-2018	26-09-2018	cephem
50	male	Pancreas	yes	GnP	03-10-2016	21-06-2017	27-03-2018	cephem
63	female	Pancreas	yes	GnP	23-07-2015	07-01-2016	30-06-2016	cephem
67	female	Pancreas	yes	GnP	18-07-2017	19-03-2018	12-04-2018	cephem
59	female	Pancreas	yes	GnP	29-06-2016	26-12-2016	22-01-2017	cephem
31	male	Sarcoma	yes	GD	19-12-2013	11-12-2014	22-06-2015	new quinolone
64	male	Sarcoma	yes	GD	16-04-2014	20-06-2014	25-11-2015	new quinolone
51	male	Sarcoma	yes	GD	10-11-2015	15-12-2015	04-10-2016	new quinolone
61	female	Biliary tract	yes	GEM	24-11-2016	27-04-2017	13-01-2018	new quinolone
78	female	Pancreas	yes	GEM	09-11-2009	26-04-2010	26-07-2010	new quinolone
66	female	Pancreas	yes	GEM plus erlotinib	20-06-2008	04-11-2008	09-01-2009	new quinolone
45	Fe male	Biliary tract	Yes	GnP	08-07-2015	10-06-2016	04-10-2016	new Quinolone
46	Female	Pancreas	Yes	GnP	22-03-2013	26-02-2015	31-08-2018	New quinolone
63	Male	Pancreas	Yes	GnP	22-08-2013	24-10-2013	06-02-2014	New quinolone
63	Male	Pancreas	Yes	GnP	30-01-2014	09-04-2014	21-08-2016	New quinolone
58	Male	Pancreas	Yes	GnP	10-08-2015	14-10-2015	14-03-2016	New quinolone
69	Male	Pancreas	Yes	GnP	07-06-2017	02-02-2018	31-08-2018	New quinolone
64	FEMALE	Biliary tract	Yes	GC	24-05-2016	08-02-2017	14-12-2017	None
62	Male	Biliary tract	Yes	GC	25-08-2015	12-04-2016	01-01-2017	None
36	Male	Biliary tract	Yes	GCS	21-07-2006	24-03-2008	21-05-2009	None
75	Male	Sarcoma	Yes	GD	24-08-2012	30-04-2013	03-02-2014	None
61	Female	Sarcoma	Yes	GD	21-07-2017	31-08-2018	31-08-2018	None
38	Male	Sarcoma	Yes	GD	30-01-2015	06-03-2015	27-04-2015	None
44	Male	Sarcoma	Yes	GD	18-08-2016	27-10-2016	16-12-2016	None
80	Female	Sarcoma	yes	GD	10-02-2014	08-04-2014	12-05-2014	None
56	Female	Sarcoma	Yes	GD	21-02-2017	10-04-2017	09-05-2017	None
59	Male	Sarcoma	Yes	GD	04-06-2008	05-08-2008	05-09-2008	None
70	Male	Biliary tract	Yes	GEM	26-03-2007	14-05-2007	06-08-2007	None
60	Male	DK	Yes	GEM	04-02-2010	27-05-2010	09-09-2010	None
66	Male	DK	Yes	GEM	26-02-2010	17-09-2010	11-02-2012	None
78	Female	DK	Yes	GEM	09-02-2006	28-03-2006	02-05-2006	None
60	Male	Pancreas	Yes	GEM	12-11-2013	28-01-2014	04-06-2014	None
67	Female	Pancreas	Yes	GEM	08-11-2011	20-12-2011	20-12-2011	None
63	Male	Pancreas	Yes	GEM	05-11-2009	14-10-2010	18-01-2011	None
57	Female	Pancreas	Yes	GEM	30-09-2009	19-11-2009	18-06-2010	None
62	Female	Pancreas	Yes	GEM	20-11-2006	26-01-2007	15-04-2007	None
41	Female	Pancreas	Yes	GEM	13-04-2012	17-08-2012	09-01-2013	None
74	Male	Pancreas	Yes	GnP	12-02-2015	16-12-2015	12-01-2016	None
62	Male	Pancreas	Yes	GnP	05-06-2015	14-09-2016	20-01-2017	None
54	Male	Pancreas	Yes	GnP	10-04-2015	06-07-2015	22-01-2016	None
81	Male	DK	Yes	GEM	16-01-2015	03-06-2016	31-08-2018	β-lactamase inhibitor

Abbreviations: CUP, Cancer of unknown primary; NEC, Neuroendocrine carcinoma; GEM, Gemcitabine; GnP, GEM+nabPTX; GC, GEM plus cisplatin; GD, GEM plus docetaxel; GCS, GEM plus cisplatin plus S-1.