Hong Kong J Radiol. 2020;23:27-33 | https://doi.org/10.12809/hkjr2017076

ORIGINAL ARTICLE

Gemcitabine Plus Nanoparticle Albumin-bound Paclitaxel for Patients with Inoperable Pancreatic Cancer: Experience at a Single Oncology Centre

TY Lee, MHC Lam, KM Cheung, HC Cheng, RKC Ngan, KH Wong

Department of Clinical Oncology, Queen Elizabeth Hospital, Jordan, Hong Kong

ABSTRACT

Objective: *To review the outcomes of gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel for patients with inoperable pancreatic cancer.*

Methods: *The data of patients treated with this regimen at a single oncology centre in Hong Kong between December 2014 and December 2017 were retrospectively reviewed. Patient data assessed included serial tumour markers (carbohydrate antigen 19-9 and/or carcinoembryonic antigen) and ultrasound, computed tomography, or positron emission tomography-computed tomography scans. The primary objective was to evaluate progression-free and overall survival. The secondary objective was to evaluate the rate of treatment-related toxicities. All adverse events were graded with the Common Terminology Criteria for Adverse Events version 5.*

Results: *The data of a total of 35 patients were analysed. The median age was 61 years and the majority (77%) had stage IV disease. Histological diagnosis was available in 74% of patients. The median number of cycles received was three. A total of 31% of patients required dose reduction of nab-paclitaxel. Median progression-free survival was 4.9 months (95% confidence interval [CI] = 3.4-6.4), and median overall survival was 7.5 months (95% CI = 5.6-9.4). Overall, 51% of patients received second-line or third-line chemotherapy following disease progression. Grade ≥3 neutropoenia occurred in 29% of patients and febrile neutropoenia in 6%. Grade ≥3 peripheral neuropathy occurred in 9% of patients.*

Conclusion: *Gemcitabine plus nab-paclitaxel doublet chemotherapy is an effective and safe treatment for inoperable pancreatic cancer. Data from our centre are comparable to literature published to date. However, prognosis remains poor for this disease.*

Key Words: *Neoplasm metastasis; Pancreatic neoplasms; Paclitaxel; Deoxycytidine/ analogs & derivatives*

Correspondence: *Dr TY Lee, Department of Clinical Oncology, Queen Elizabeth Hospital, Jordan, Hong Kong*
Email: lukelee2@gmail.com

Submitted: 3 Feb 2019; Accepted: 23 Apr 2019.

Contributors: TYL, HCC, RKCN and KHW designed the study. TYL, MHCL and KMC acquired the data. TYL drafted the manuscript. All authors contributed to data analysis, and had critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest: As editors of the journal, TY Lee, MHC Lam, and RKC Ngan were not involved in the peer review process. Other authors have no conflicts of interest to disclose.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Approval: The study was approved by the Kowloon Central / Kowloon East institution's Research Ethics Committee (Ref KC/KE-18-0177/ER-1) and was conducted in compliance with the Declaration of Helsinki.

中文摘要

吉西他濱—納米白蛋白結合型紫杉醇治療不宜手術的胰腺癌患者：單一腫瘤學中心的經驗

李天恩、林河清、張嘉文、鄭海清、顏繼昌、黃錦洪

目的：探討吉西他濱—納米白蛋白結合型紫杉醇對不宜手術的胰腺癌患者的治療效果。

方法：回顧分析2014年12月至2017年12月在香港一所腫瘤中心接受該方案治療的患者數據。評估的患者數據包括系列腫瘤標誌物（碳水化合物抗原19-9和／或癌胚抗原）以及超聲波掃描、電腦斷層掃描或正電子掃描。研究主要評估無惡化存活期和總存活期，其次評估與治療相關的毒性反應的比率。所有不良事件均按照CTCAE第5版進行分級。

結果：共分析35例患者的資料。年齡中位數為61歲，大多數患者（77%）屬第四期。74%患者可進行組織學診斷。化療周期的中位數為3。31%患者須減少納米白蛋白結合型紫杉醇劑量。中位無惡化存活期為4.9個月（95%置信區間3.4-6.4個月），總體存活期中位數為7.5個月（95%置信區間5.6-9.4個月）。總體而言，51%患者病情惡化後接受二線或三線化療。29%患者出現≥3級中性粒細胞減少症，6%患者出現發熱中性粒細胞減少症。9%患者出現≥3級圍神經病變。

結論：吉西他濱—納米白蛋白結合型紫杉醇治療不宜手術的胰腺癌患者安全和有效。本研究數據與文獻相若，惟疾病的預後仍然欠佳。

INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies, constituting the sixth leading cause of all cancer deaths in Hong Kong despite not falling into the top ten malignancies by incidence.[1] Surgical resection is the only potentially curative treatment. However, because presentation of pancreatic cancer is commonly late, fewer than one-fifth of patients are considered suitable candidates for pancreatectomy.[2] Even after successful surgical resection, prognosis remains poor with the 5-year survival after margin-negative surgery being approximately 10% for node-positive disease and 30% for node-negative disease.[3]

Systemic chemotherapy is the treatment of choice for unresectable locally advanced or metastatic pancreatic cancer. Gemcitabine has been the standard first-line therapeutic agent since 1997, when it demonstrated superiority over 5-fluorouracil.[4] Combination regimens have since been studied and were shown to improve treatment outcomes, including FOLFIRINOX in the phase III ACCORD 11 trial,[5] modified FOLFIRINOX,[6] and gemcitabine plus capecitabine.[7]

In the multinational phase III MPACT trial published in 2013, the combination regimen gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel (GnP) was demonstrated to be superior to gemcitabine alone, in terms of overall survival (OS, primary endpoint, median 8.5 vs. 6.7 months, $p < 0.001$), progression-free survival (PFS, median 5.5 vs. 3.7 months, $p < 0.001$), and independently reviewed overall response rate (23% vs. 7%, $p < 0.001$).[8] Longer-term follow-up data further confirmed the efficacy of the treatment regimen.[9] Since then, GnP has become one of several first-line treatment regimens for patients with good performance status. However, despite its proven efficacy, combination treatment is associated with significantly greater toxicities and costs. The most common grade ≥3 adverse events with this regimen include leucopoenia, neutropoenia, peripheral neuropathy, and fatigue.

In the MPACT trial,[8] Asian patients accounted for <2% of the study population. Data pertaining to the efficacy and safety of GnP are therefore much needed in order to support its use in local populations. Therefore, the aim of this retrospective study was to investigate the outcomes and safety of GnP for Asian patients with inoperable pancreatic cancer.

METHODS

All patients with inoperable pancreatic cancer treated

with GnP as first-line or second-line therapy at Queen Elizabeth Hospital between December 2014 and December 2017 were retrospectively reviewed. Prescription and dispensing records from the hospital pharmacy computer system were used to retrieve data on patients treated with the combination regimen. A total of 35 patients were identified and included in this study. Demographic and survival data were extracted from the hospital's electronic clinical management system and medical records.

GnP was given as per departmental protocol. The regimen consisted of an intravenous infusion of gemcitabine 1000 mg/m^2 and nab-paclitaxel 125 mg/m^2 on days 1, 8, and 15 every 4 weeks. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was not routinely provided. Four patients (11.4%) started with a lower initial dose (80%-85% dose) after consideration of the individual functional and disease status. Treatment was continued until the development of either disease progression or unacceptable toxicity. Patients were assessed every 2 weeks during the chemotherapy period with standardised blood tests. Follow-up visits were scheduled to take place once every 3 weeks for patients who received second-line or third-line chemotherapy after GnP, or every 3 to 8 weeks for patients who did not receive second-line chemotherapy and those who completed second-line chemotherapy until death.

Assessment was by means of serial measurements of tumour markers (carbohydrate antigen 19-9 [CA19-9] and/or carcinoembryonic antigen) and serial imaging studies, including ultrasound, computed tomography, or positron emission tomography–computed tomography at the physician's discretion. A biochemical response was defined as a ≥50% reduction in CA19-9 levels from baseline. In instances where the serum CA19-9 level was normal at baseline, carcinoembryonic antigen level and its subsequent changes were taken into consideration. Disease response on imaging was assessed using RECIST version 1.1.[10]

The primary objective was to evaluate the PFS and OS using the Kaplan-Meier method. PFS was defined as the time from the date of starting GnP to disease progression or death from any cause. OS was defined as the time from the date of starting GnP to the date of death from any cause. For the purpose of data analysis, the survival status of all patients was updated on the data cut-off date 31 July 2018. Data from surviving patients would be censored on the date of last follow-up. The log rank test was used to test for associations between survival and demographic or clinical characteristics of the patients. Hazard ratios were estimated based on the univariate Cox proportional hazards regression model. Two-tailed tests were performed and a p value of <0.05 was considered statistically significant.

The secondary objective was to evaluate treatment-related toxicities. All adverse events were graded according to CTCAE (Common Terminology Criteria for Adverse Events) of National Cancer Institute, version 5.0.[11]

Version 4 of the STROBE guidelines for cohort studies was used in the preparation of this manuscript.[12] The study was approved by the Kowloon Central/Kowloon East Research Ethics Committee (Ref KC/KE-18-0177/ER-1) and was conducted in compliance with the Declaration of Helsinki.

RESULTS

The demographic and clinical characteristics of the patients are summarised in Table 1. In all, 37% of patients were aged ≥65 years. Most patients (89%) had a score of 1 on the Eastern Cooperative Oncology Group (ECOG) performance scale. Histological diagnosis was confirmed in 74% of patients. The majority of patients (83%) had metastatic disease. Approximately 10% of patients had disease recurrence following prior radical Whipple procedure.

Among the 35 patients included in this study, 32 (91%) received GnP as a first-line regimen, while the remaining three had had first-line chemotherapy with either FOLFIRINOX or XELOX. The median number of GnP chemotherapy cycles received was three and the maximum number of cycles received was eight. Around one-third of patients required dose reduction for nab-paclitaxel due to toxicities. The range of dose reduction varied between 20% and 40%. In cases where treatment was aborted, the main reasons included disease progression (66%) and treatment-related toxicities (26%). One patient withdrew consent for further treatment due to financial difficulty. Another two patients opted out of chemotherapy to receive traditional Chinese medicine instead based on personal preference. Approximately half (51%) of all patients received second-line or third-line chemotherapy subsequent to disease progression, with the majority (13/18) receiving doublet chemotherapy of capecitabine plus oxaliplatin. The median duration of follow-up was 7.5 months (range, 1.4-31.5 months).

Table 1. Characteristics of the patients at baseline.*

Characteristic	All patients (n = 35)
Age, median (range), years	61 (49-78)
<65 years	22 (63%)
≥65 years	13 (37%)
Sex	
Male	20 (57%)
Female	15 (43%)
Race or ethnic group	
Asian	35 (100%)
ECOG	
1	31 (89%)
2	4 (11%)
Histology	
Adenocarcinoma	25 (71%)
Carcinoma, NOS	1 (3%)
Not available	9 (26%)
Pancreatic tumour location	
Head	15 (43%)
Neck	2 (6%)
Body	11 (31%)
Tail	7 (20%)
No. of metastatic sites	
0	6 (17%)
1	17 (49%)
2	8 (23%)
≥3	4 (11%)
Site(s) of metastatic disease	
Liver	23 (66%)
Lung	6 (17%)
Peritoneum	6 (17%)
Bone	4 (11%)
Previous therapy	
Whipple procedure	4 (11%)
Prior first-line chemotherapy	3 (9%)
Stenting	1 (3%)
Baseline CA19-9 level, U/mL	
Median	2923
Normal	6 (17%)
ULN to <59× ULN	10 (29%)
≥59× ULN	19 (54%)

Abbreviations: CA19-9 = carbohydrate antigen 19-9; carcinoma, NOS = carcinoma, not otherwise specified; ECOG = Eastern Cooperative Oncology Group performance status scores (range 0-5, with lower scores indicating better performance status); ULN = upper limits of normal.
* Data are shown as No. (%), unless otherwise specified.

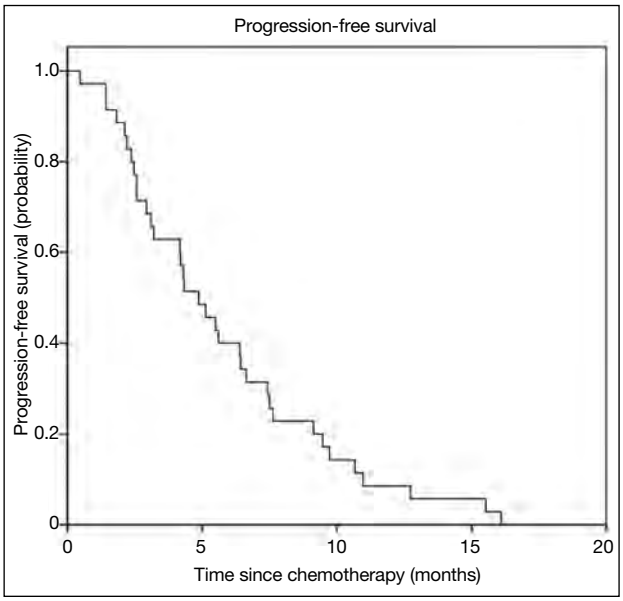

Figure 1. Progression-free survival of 35 patients with inoperable pancreatic cancer receiving gemcitabine plus nanoparticle albumin-bound paclitaxel.

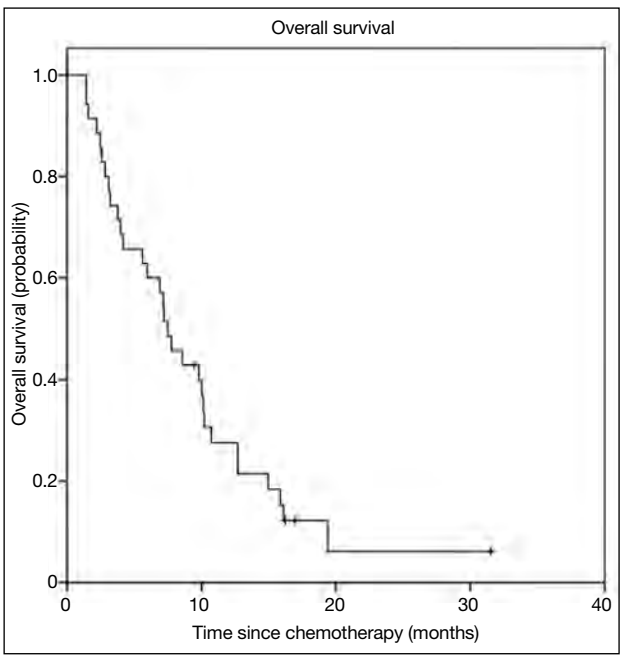

Figure 2. Overall survival of 35 patients with inoperable pancreatic cancer receiving gemcitabine plus nanoparticle albumin-bound paclitaxel.

The median PFS was 4.9 months (95% confidence interval [CI] = 3.4-6.4 months) [Figure 1], and the median OS was 7.5 months (95% CI = 5.6-9.4) [Figure 2]. Biochemical partial response was noted in 34% of patients and radiological partial response in 20%. In all, 14% of patients had both biochemical and radiological partial response. The treatment outcomes are summarised in Table 2.

Grade ≥3 neutropoenia and leucopoenia developed in 29% and 11% of patients, respectively. Febrile neutropoenia was noted in 6% of patients, whereas non-neutropoenic fever occurred in 17% of patients. The most frequently reported grade ≥3 non-haematological toxicities were fatigue (26%) and peripheral neuropathy (9%). There were no cases of grade 4 neuropathy. All significant adverse events are summarised in Table 3.

Table 2. Summary of treatment outcomes.*

Characteristic	All patients, (n = 35)
No. of cycles of GnP, median (range)	3 (0.3-8)
Dose reduction for gemcitabine	
No	26 (74%)
Yes	9 (26%)
Dose reduction for nab-paclitaxel	
No	24 (69%)
Yes	11 (31%)
Reason of stopping treatment	
Disease progression	23 (66%)
Toxicities of treatment	9 (26%)
Patient's preference	
Cost of treatment	1 (3%)
Alternative treatment (traditional Chinese medicine)	2 (6%)
Subsequent chemotherapy	
With	
Capecitabine + oxaliplatin	13 (37%)
5-fluorouracil + oxaliplatin	1 (3%)
Gemcitabine	2 (6%)
Capecitabine	1 (3%)
S1 + folinic acid	1 (3%)
Without	17 (49%)
Overall survival, median (95% CI), months	7.5 (5.6-9.4)
Progression-free survival, median (95% CI), months	4.9 (3.4-6.4)
Biochemical response	
Partial response	12 (34%)
by CA19-9	11 (31%)
by CEA	1 (3%)
Static disease	7 (20%)
Radiological response	
Partial response	7 (20%)
Static disease	9 (26%)

Abbreviations: 95% CI = 95% confidence interval; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; GnP = gemcitabine plus nab-paclitaxel.
* Data are shown as No. (%), unless otherwise specified.

Table 3. Common adverse events of grade ≥3.*

Event	All patients (n = 35)
Grade ≥3 haematological adverse event†	
Neutropoenia	10 (29%)
Leucopoenia	4 (11%)
Thrombocytopoenia	3 (9%)
Anaemia	5 (14%)
Grade ≥3 non-haematological adverse event‡	
Diarrhoea	0
Fatigue	9 (26%)
Peripheral neuropathy	3 (9%)
Grade ≥3 hyperbilirubinaemia†	2 (6%)
Febrile neutropoenia‡	2 (6%)
Non-neutropoenic fever‡	6 (17%)

* Data are shown as No. (%).
† Assessment of the event was made on the basis of laboratory values.
‡ Assessment of the event was made on the basis of investigator assessment of treatment-related adverse events.

Table 4. Univariate analysis of overall survival based on the following characteristics.

Variables	Hazard ratio (95% CI)	p Value
Baseline CA19-9		
Normal	1	-
ULN to <59× ULN	2.7 (0.7-10.1)	0.143
≥59× ULN	4.6 (1.3-16.1)	0.016
Age ≥65 years	0.81 (0.39-1.71)	0.58
Male sex	1.29 (0.63-2.63)	0.48
ECOG 2	3.62 (1.16-11.3)	0.027
Presence of liver metastasis(es)	2.68 (1.21-5.96)	0.015
Presence of lung metastasis(es)	1.83 (0.73-4.64)	0.20
Presence of peritoneal metastasis(es)	2.74 (1.06-6.94)	0.037

Abbreviations: 95% CI = 95% confidence interval; CA19-9 = carbohydrate antigen 19-9; ECOG = Eastern Cooperative Oncology Group performance status scores (range 0-5, with lower scores indicating better performance status); ULN = upper limit of the normal.

Univariate analysis was used to investigate the relationship between baseline CA19-9 level and survival. The OS was found to be lower for those with higher baseline level of CA19-9 (≥59× upper limits of normal [ULN]) versus those with normal baseline CA19-9 (hazard ratio [HR] = 4.6, 95% CI = 1.3-16.1, p = 0.016). The results are summarised in Table 4.

Further univariate analysis of OS based on different demographic features was performed using the log rank test. It was found that patients with ECOG 2 had poorer survival (HR = 3.62, 95% CI = 1.16-11.3, p = 0.027). The presence of hepatic metastatic disease (HR = 2.68, 95% CI = 1.21-5.96, p = 0.015) or peritoneal metastases (HR = 2.74, 95% CI = 1.06-6.94, p = 0.037) were associated with worse OS. The results are summarised in Table 4.

DISCUSSION

Systemic combination chemotherapy is the current standard treatment for patients with unresectable locally advanced or metastatic pancreatic cancer who have good performance status. GnP has been incorporated into various international guidelines, including ESMO,[13] NCCN,[14] and NICE[15] guidelines.

The current guidelines at our institution offer a number of chemotherapy regimens to be used as first-line therapy for advanced or metastatic pancreatic exocrine carcinoma. These include single-agent gemcitabine or S-1, combination chemotherapy regimens such as gemcitabine plus capecitabine, GnP, and FOLFIRINOX.

FOLFIRINOX has been shown to confer a significant improvement in survival at the expense of increased toxicity.[16] Therefore, FOLFIRINOX is generally offered to a highly selected patient group, consisting primarily of young fit patients with very good performance status. Most of our patients with ECOG 1-2 are offered less intensive combination chemotherapy regimens of either gemcitabine plus capecitabine, or GnP. nab-Paclitaxel is a self-financed item in public hospitals in Hong Kong; therefore, only those patients who can afford nab-paclitaxel will receive GnP, and others will be given gemcitabine plus capecitabine. Single-agent gemcitabine or S-1 is often given to systemically more frail patients. In this retrospective study, only patients receiving GnP therapy were reviewed.

The data on PFS and OS from this retrospective study are comparable to the published outcomes of the MPACT trial. The median PFS was 4.9 months (95% CI = 3.4-6.4) in this study, compared to 5.5 months (95% CI = 4.5-5.9) in the MPACT trial.[8] The median OS was 7.5 months (95% CI = 5.6-9.4) in this study, versus 8.5 months (95% CI = 7.9-9.5) in the MPACT trial. This finding is also consistent with another phase II study performed in a Chinese population, in which the median PFS was 5.5 months (95% CI = 5.3-7.2) and median OS was 9.2 months (95% CI = 7.6-11.1).[17]

Advanced age itself is not an absolute contra-indication for combination chemotherapy, and such regimens are generally well tolerated in older patients. The oldest patient in this study was aged 78 years, with an ECOG performance status of 1, who received a total of eight cycles of GnP without any need for dose reduction. This finding also concurs with the MPACT trial,[8] which included patients aged >80 years.

The doublet regimen GnP was well tolerated by patients in the current study. Although primary G-CSF prophylaxis was not routinely given to our patients, the febrile neutropoenia rate was 6%. This is similar to the result of the MPACT trial (3%),[8] in which 26% of patients received G-CSF. No new safety issues were observed.

The baseline CA19-9 level was elevated in approximately 83% of patients, and the majority (54%) had a level ≥59× ULN. CA19-9 has historically been widely used as a surrogate marker for disease progression during follow-up assessments after radical surgery or during ongoing chemotherapy.[18] However, there has yet to be a universal consensus as to the extent to which CA19-9 may be used as a surrogate marker for response evaluation during chemotherapy.[19] Serial monitoring of CA19-9 level was performed in our patients, and we defined a biochemical response as a 50% reduction from baseline, as proposed in the literature.[20-22] Based on this definition, a biochemical response was observed in 34% of our patients.

The OS was found to be lower for those with higher baseline levels of CA19-9 (≥59× ULN) than those with normal baseline levels. This observation was consistent with previous studies, which suggested higher baseline CA19-9 levels to be generally associated with worse clinical outcomes.[23-25]

Univariate analysis showed that patients with worse pretreatment performance status (ECOG 2), presence of liver metastasis(es), or peritoneal disease had poorer OS. These findings were consistent with prior reported data.[26-28] However, owing to the limited sample size in this study, further multivariate analysis was not possible.

There are a number of limitations in the current study. Firstly, the sample size in this retrospective study was relatively small, as many of our patients in the public health care system cannot afford the self-financed drug (nab-paclitaxel) or had co-morbidities that rendered them unfit for doublet chemotherapy. This may have led to selection bias as only relatively well-off patients, who might inherently be more health-cautious, have better performance status, greater social support, and earlier access to healthcare could afford the treatment. Because of the relatively small sample size, the results of univariate analysis should be interpreted with caution owing to the limited statistical power. Similarly, further descriptive analysis on the OS according to the second- or third-line regimens was difficult owing to the small sample size, whereby most regimens of the subsequent chemotherapy were given to only one or two patients. Lastly, three patients in the study received GnP as a second-line regimen. These patients might therefore have experienced lower response rates and worse survival outcomes that could potentially have an adverse effect on the study results.[29,30]

CONCLUSION

GnP is an effective and safe first-line treatment for Asian patients with inoperable pancreatic cancer.[31] Data from the present study are consistent and comparable with the literature published to date. Higher baseline CA19-9 level was a negative prognostic factor. Future studies should focus on determining the optimal combination

regimen and sequence of treatment for patients with inoperable or metastatic pancreatic cancer.

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