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

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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

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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.
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. 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. 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.

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. Combination regimens have since been studied and were shown to improve treatment outcomes, including FOLFIRINOX in the phase III ACCORD 11 trial, modified FOLFIRINOX, and gemcitabine plus capecitabine.

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). Longer-term follow-up data further confirmed the efficacy of the treatment regimen. 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, 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/m² and nab-paclitaxel 125 mg/m² 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).
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 neutropenia and leucopenia developed in 29% and 11% of patients, respectively. Febrile neutropenia was noted in 6% of patients, whereas non-neutropenic 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 1. Characteristics of the patients at baseline.*

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

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.
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 × 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, NCCN, and NICE 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 capcitabine, GnP, and FOLFIRINOX.
FOLFIRINOX has been shown to confer a significant improvement in survival at the expense of increased toxicity.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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,\textsuperscript{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 neutropenia rate was 6%. This is similar to the result of the MPACT trial (3%),\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{29,30}

**CONCLUSION**

GnP is an effective and safe first-line treatment for Asian patients with inoperable pancreatic cancer.\textsuperscript{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.

REFERENCES


