Original Article

Dose-modified gemcitabine plus nab-paclitaxel front-line in advanced pancreatic ductal adenocarcinoma with baseline hyperbilirubinemia

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Background: Von Hoff *et al.* demonstrated survival improvement with gemcitabine (GEM) + nab-paclitaxel (NabP) for metastatic pancreatic ductal adenocarcinoma (PDAC) compared to GEM alone. GEM + NabP resulted in a median overall survival (OS) and progression-free survival (PFS) of 8.5 and 5.5 months, respectively. Patients with baseline hyperbilirubinemia were excluded. Primary objective was OS. Secondary objectives included time on treatment (TOT), disease control rate, dosing practices, delays/admissions, and adverse effects.

Methods: Patients with borderline resectable, locally advanced, or metastatic PDAC who initiated front-line GEM-NabP during July 01, 2013–July 01, 2017 were reviewed. Patients with a baseline total bilirubin ≥2 mg/dL were included.

Results: Twelve patients total were included. Median age was 71 years old. Median baseline total bilirubin was 2.4 mg/dL (range, 2.1–5.2 mg/dL). 58% had metastatic disease. Median doses were NabP 100 mg/m^2 + GEM 600 mg/m^2 IV with a fixed-dose rate infusion (10 mg/m^2/min). GEM-NabP was given biweekly or 3 weeks on 1 week off. Median OS, TOT, and disease control rate were 13.9, 5.2 months, and 58%, respectively. Fifty percent of patients required a dose delay. Metastatic patients only (n=7) had median OS and TOT of 6.9 and 2.1 months, respectively. No admissions related to toxicity were found.

Conclusions: Our analysis revealed safety with NabP (median dose =100 mg/m^2) + GEM (median dose =600 mg/m^2 at fixed-dose rate) given predominately biweekly in patients with a baseline elevated total bilirubin (≥2 mg/dL).

Keywords: Pancreatic neoplasms; nab-paclitaxel; gemcitabine; carcinoma; pancreatic ductal; hyperbilirubinemia

Submitted Aug 15, 2019. Accepted for publication Oct 12, 2019.
doi: 10.21037/jgo.2019.10.05
View this article at: http://dx.doi.org/10.21037/jgo.2019.10.05

Introduction

Pancreatic ductal adenocarcinoma (PDAC) accounts for 80–90% of pancreatic cancers (1). Maintaining a dismal prognosis, PDAC represents the third most common cause of cancer-related deaths common amongst both men and women in the United States with an overall 5-year survival rate of ~5–8% (1-3). The 5-year overall survival (OS) rate declines further to <3% in the advanced setting (4). By 2030, pancreatic cancer is projected to be the second most fatal malignancy (5).

In 1997, gemcitabine (GEM) monotherapy was established as the standard front-line therapy with modest survival outcomes for metastatic patients (6). Various GEM-based chemotherapy combinations were evaluated following monotherapy approval; however, these studies failed to define a clinically utilized standard combination. Therefore, in 2011, Conroy *et al.* provided a pivotal study altering metastatic PDAC treatment (7). They reported on a phase II-III multicenter, randomized controlled trial comparing a fluoropyrimidine combination regimen of 5-fluorouracil + leucovorin + oxaliplatin + irinotecan (FOLFIRINOX) to GEM alone. Median OS and progression-free survival (PFS) were improved in the FOLFIRINOX arm with a median OS of 11.1 months and PFS of 6.4 months reported in the FOLFIRINOX arm compared to median OS of 6.8 months and PFS of 3.3 months in the GEM arm (P<0.001). Shortly after these improved outcomes with FOLFIRINOX over GEM, Von Hoff *et al.* (MPACT trial) reported the results of a multicenter phase III randomized trial comparing GEM + nab-paclitaxel (NabP) to GEM alone in metastatic PDAC (8). The combination regimen was dosed giving NabP at 125 mg/m^2 intravenous (IV) followed by GEM 1,000 mg/m^2 IV over 30 minutes both given days 1, 8, and 15 every 4 weeks. Similar to FOLFIRINOX, the combination regimen improved outcomes compared to GEM alone. Median OS was 8.5 months in the combination arm compared to 6.7 months in the GEM monotherapy arm (P<0.001). Median PFS showed an almost 2 months improvement with median PFS at 5.5 months in the combination arm compared to 3.7 months in the monotherapy arm (P<0.001). In the combination group, 41% of patients required a reduction in the NabP dose, and 47% required a GEM dose reduction. Neutropenia and leukopenia were the most frequently noted grade ≥3 adverse events in the combination arm.

Both combination regimens (FOLFIRINOX and NabP + GEM) are incorporated currently in front-line treatment of locally advanced/metastatic PDAC (1,2). Von Hoff *et al.*'s pivotal MPACT trial excluded patients with an elevated baseline total bilirubin (8). Further, NabP prescribing information lacks a starting dose recommendation for PDAC patients with hepatic impairment [AST <10× upper limit of normal (ULN) and total bilirubin >1.5× ULN] stating "not recommended" in these situations (9). The purpose of this retrospective review was to review the safety and efficacy of GEM-NabP in patients with baseline hyperbilirubinemia.

Methods

We performed a single institution, retrospective chart review of patients with clinically borderline resectable, locally advanced, or metastatic PDAC who received GEM-NabP front-line. Adult patients who initiated this regimen during July 01, 2013–July 01, 2017 were reviewed for baseline hyperbilirubinemia (total bilirubin >2 mg/dL) at start of therapy. Patients were included if they were seen at our center along with radiographic evaluation follow-up. OS was our primary objective. Secondary objectives were time on treatment (TOT) and response defined as disease control (any response + stable disease) *vs.* progression on first radiographic evaluation. Further outcomes were dosing practices, delays, any grade 3/4 hematologic toxicities, admissions, adverse effects, and reasons for stopping treatment.

Data collection included patient demographics and tumor characteristics. These factors were age, gender, clinical disease stage (borderline resectable, locally advanced, or metastatic), and location of primary tumor (head; tail; body). Baseline total bilirubin value, stent placement (yes; no), start date of GEM-NabP treatment along with doses, chemotherapy schedule used, cycle number when doses were escalated, and number of cycles received were reported. Additionally, date of progression, date of death, or last follow-up were collected. Number of treatment delays, reason for delay, hospital admissions related to toxicity, need for growth factor support, and adverse effects (per grade) along with reasons for stopping GEM-NabP (radiographic progression, clinical progression, performance status decline, and/or toxicity) were collected.

Ethics

Our study was approved by the institutional review board

Table 1 Overall demographics

Demographics	N (%)
Age, median [range], years old	71 [56–81]
Gender	
Male	6 (50.0)
Female	6 (50.0)
Clinical stage	
Borderline resectable	2 (16.7)
Locally advanced unresectable	3 (25.0)
Metastatic	7 (58.3)
Pancreatic mass location	
Head	9 (75.0)
Body	3 (25.0)
Baseline total bilirubin, median [range], mg/dL	2.4 [2.1–5.2]
Gemcitabine starting dose	
500 mg/m^2	1 (8.3)
600 mg/m^2	11 (91.7)
Nab-paclitaxel starting dose	
65 mg/m^2	4 (33.3)
100 mg/m^2	6 (50.0)
125 mg/m^2	2 (16.7)
Schedule	
Biweekly	9 (75.0)
Three weeks on, one week off	3 (25.0)
Number of cycles, median [range]	8 [1–27]
Nab-paclitaxel dose escalation	
Not increased	6 (50.0)
Increased	5 (41.7)
N/A (started at full dose)	1 (8.3)

N/A, not applicable.

and a waiver of consent was granted due to patients lost to follow-up, no longer at the institution, or expired. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work area appropriately investigated and resolved.

Statistical analysis

Statistical analysis was performed using descriptive statistics. Continuous variables were described using median and range while categorical data was summarized using frequencies and percentages. OS, the primary objective, was calculated as start of GEM-NabP to death or last follow-up date. TOT was defined as treatment start date to treatment discontinuation for progressive disease, performance status decline, toxicity, patient preference, transition to local therapy for locally advanced patients, or death/last follow-up. Disease control was defined as any response + stable disease at first radiographic scan. Common Terminology Criteria for Adverse Effects (CTCAE) version 4 was utilized to determine adverse effect grade retrospectively when applicable.

Results

Twelve total patients were included in the analysis with a median age of 71 years old (range, 56–81 years old) with a 50:50 split on gender. Overall demographics are reported in *Table 1*. Fifty-eight point three percent were metastatic. Most patients' (75%) primary pancreatic tumor was located in the head of the pancreas. Median baseline bilirubin was 2.4 mg/dL. The median number of cycles given was eight (range, 1–27 cycles). Each cycle was given every 2 weeks or on a 3 week on 1 week off schedule. Most (75%) received this in a biweekly fashion. Median doses reported were NabP 100 mg/m^2 IV (range, 65–125 mg/m^2) plus GEM 600 mg/m^2 (range, 500–600 mg/m^2) given at a fixed dose rate (10 mg/m^2/min). Of note, standard practice at our institution is to administer gemcitabine in a fixed-dose rate with doses ranging from 600 to 750 mg/m^2. The hyperbilirubinemia case in most cases (n=11) was biliary obstruction. These cases received biliary stent placement to relieve obstruction. One patient had extensive liver metastases unable to have a biliary stent placed to relieve obstruction. Forty-one point seven percent of patients had doses escalated as bilirubin elevations subsided. The median cycle number for dose escalation to full NabP dose (125 mg/m^2) was cycle two (range cycle number 2–8). Neither of the borderline resectable patients were able to proceed with surgery. All three locally advanced patients received capecitabine plus radiation therapy after stabilization of disease on GEM + NabP.

Table 2 Outcomes

Outcome	N (%)
Efficacy	
Overall survival, median (range), months	13.9 (1.35–30.3)
Time on treatment, median (range), months	5.2 (0.46–25.2)
Radiographic scan result	
Disease control	7 (58.3)
Progression/toxicity	5 (41.7)
Safety	
Number of treatment delays	6 (50.0)
Toxicity	
Neuropathy	
Grade 1	5 (41.7)
Grade 2	0
Grade 3	1 (8.3)
Fatigue	
Grade 1	5 (41.7)
Grade 2	2 (16.7)
ANC decline	
Grade 1 (pegfilgrastim added)	3 (25.0)
Grade 3 (pegfilgrastim added)	1 (8.3)
Thrombocytopenia	
Grade 1	1 (8.3)
Grade 2	1 (8.3)
Liver Function Test Elevation	
Grade 3	1 (8.3)

ANC, absolute neutrophil count.

Outcomes are listed in *Table 2*. Median OS, TOT, and disease control were 13.9, 5.2 months, and 58%, respectively. One patient had yet to progress at time of data collection. Most patients stopped therapy due to radiographic or clinical progression. The three locally advanced patients stopped GEM + NabP to proceed with consolidative chemoradiation. One patient stopped therapy due to a decline in performance status and toxicity. Focusing on only those with metastatic disease (n=7), clinical outcomes were less favorable (median OS =6.9 months; median TOT =2.1 months, 28% disease control rate on first scan).

Fifty percent of all patients required a dose delay; however only 41.7% required a dose delay attributed to chemotherapy adverse effects. Two patients were admitted due to infection unrelated to chemotherapy toxicity and were not neutropenic at the time. All but one patient had a biliary stent placed to relieve dilation/obstruction. The one patient without a stent placed stopped treatment due to grade 3 liver function elevation. Reasons for dose delays were grade 2 fatigue (2 patients), grade 3 neutropenia (1 patient), grade 1 thrombocytopenia (1 patient), grade 2 thrombocytopenia (1 patient), and reports of fever and chills (1 patient). Toxicities are listed in *Table 2*. The median absolute neutrophil nadir and platelet nadir were 2.17 k/uL (range, 0.71–4.76 k/uL) and 138 k/uL (range, 54–242 k/uL). Patients with delays due to thrombocytopenia had platelet count recovery in time for the planned next treatment and the patient delayed due to grade 3 neutropenia recovered counts after 7 days. Secondary growth factor prophylaxis was given to this patient for future cycles. Most frequent adverse effects were grade 1 fatigue and grade 1 neuropathy.

Discussion

Advanced PDAC patients with baseline hyperbilirubinemia were excluded in the pivotal PDAC phase III trials that have established current practice (7,8). FOLFIRINOX represents a challenge for these patients, as prescribing information for irinotecan does not recommend its use in patients with a total bilirubin >2 mg/dL (10). Performance status in this population may additionally represent a barrier to FOLFIRINOX administration. Gemcitabine prescribing information lacks guidance with dosing in this setting; however, literature has provided recommended adjustments (11-13). Taxanes are primarily hepatically metabolized which raises safety concerns when prescribing these agents in the presence of hepatic dysfunction due to potential prolonged clearance and increased systemic exposure (12-15). Dose adjustments or taxane avoidance to avoid myelosuppression and treatment-related death are suggested based on limited data.

Existing safety and efficacy data for PDAC patients with hyperbilirubinemia utilizing GEM + NabP is limited. Our study showed a 41.7% dose delay due to chemotherapy. Reasons for dose delays (i.e., neutropenia, thrombocytopenia, and fatigue) in our small subset of patients were similar to those in the MPACT study in which dose delays were frequent (71% ≥1 NabP dose delay) (16). Phase I pharmacokinetic safety study

evaluating GEM+ NabP in PDAC patients with cholestatic hyperbilirubinemia unfortunately was terminated early due to infrequent enrollment (17). A recent retrospective analysis by Pelzer *et al.*, reported 29 patients with advanced PDAC treated with Gem + NabP with hyperbilirubinemia (total bilirubin ≥1.2 mg/dL) (18). Similar to our study, patients in this analysis were mostly metastatic and had their primary tumor in the head of the pancreas. The majority (68%) of patients received Gem + NabP in the first or second-line setting. The remainder received GEM + NabP in the third or fourth-line setting. Most patients (62%) had a total bilirubin ≥1.2–3 mg/dL. Fourteen percent had total bilirubin >3–5 mg/dL and 24% had a total bilirubin >5 mg/dL. The majority of patients received full dose of GEM (1,000 mg/m^2) + NabP (125 mg/m^2) 3 weeks on 1 week off. The authors did not identify any unexpected toxicities. They concluded that GEM + NabP did not cause severe early toxicity in patients with hyperbilirubinemia. Vogel *et al.* provided a recent review and German expert opinion regarding GEM + NabP use in PDAC patients with hyperbilirubinemia (19). The panel concluded that hyperbilirubinemia is a result of multiple types of hepatic dysfunction and the etiology should be determined prior to starting therapy. The panel suggested reduced starting doses for GEM + NabP based on the degree of hyperbilirubinemia coupled with the reason for hepatic impairment.

Conclusions

Despite our limited sample size our data adds to the available literature recognizing the safe administration of GEM + NabP in PDAC patients with hyperbilirubinemia at baseline bilirubin ranging from 2.1–5.2 mg/dL. Median doses were NabP 100 mg/m^2 + GEM 600 mg/m^2, administered at fixed dose rate (10 mg/m^2/minute) given biweekly or in a 3 weeks on 1 week off fashion. We recommend determining the underlying etiology for hyperbilirubinemia with attempts to correct the underlying cause prior to GEM + NabP if possible, and we encourage continued reporting in this area to determine efficacy in this patient population. We recommend a cautious dose modification and close monitoring approach with these patients until more data is available.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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Cite this article as: Rogers JE, Mizrahi JD, Shroff RT, Nelson DA, Tu J, Javle MM, Wolff RA, Pant S. Dose-modified gemcitabine plus nab-paclitaxel front-line in advanced pancreatic ductal adenocarcinoma with baseline hyperbilirubinemia. J Gastrointest Oncol 2020;11(1):55-60. doi: 10.21037/jgo.2019.10.05

