

Neoadjuvant *Nab*-paclitaxel and Gemcitabine in Borderline Resectable or Locally Advanced Unresectable Pancreatic Adenocarcinoma in Patients Who Are Ineligible for FOLFIRINOX

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Abstract. *Background/Aim:* Combination nab-paclitaxel/gemcitabine (AG) is superior to gemcitabine in patients with metastatic pancreatic cancer (PC). There are limited data for AG in borderline resectable (BR) or locally advanced pancreatic cancer (LAPC). Herein, we report our experience with neoadjuvant AG for BR/LAPC in patients ineligible for FOLFIRINOX. *Patients and Methods:* This retrospective series, included patients with BR/LAPC who received AG as neoadjuvant therapy for 3-4 months followed by radiation, then re-evaluation for surgery. *Results:* Between 10/2013-2/2018, 32 patients (22 BR, 10 LAPC) were treated with this approach. Median age was 70 years. Nine patients were converted to resectability by imaging; six had R0 resections (19%), five (16%) achieved a partial response and 24 (75%) had stable disease. *Conclusion:* In this small series, the R0 resection rate and response rate were 19% and 16% respectively. These data suggest that neoadjuvant AG may be an alternate option for patients ineligible for FOLFIRINOX.

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer deaths in the United States with a projected 44,330 deaths occurring in 2018 (1). With a 5-year overall survival (OS) rate of 8%, it carries a bleak prognosis largely due to the advanced stage at presentation in most patients (1). Surgical resection in the context of multimodality therapy is the only treatment that carries a potential for cure but only 10-20% have anatomically resectable disease at presentation, and up to 50% of newly diagnosed patients present with non-metastatic unresectable disease. Based upon the extent of vascular involvement, these patients are defined as borderline resectable (BR) or locally advanced, pancreatic cancer (LAPC) (2). The main treatment goal for patients with initially unresectable pancreatic cancer is conversion to resectability with recent data showing that a margin-negative resection after neoadjuvant therapy is associated with better survival than those who did not have surgery (2, 3).

One of the most efficacious therapies for metastatic PDAC is the FOLFIRINOX regimen (5-fluorouracil, oxaliplatin, leucovorin and irinotecan). Conroy *et al.* demonstrated that FOLFIRINOX improved OS compared to gemcitabine, with a median OS of 11.1 months vs. 6.8 months in patients with metastatic disease (4). Patients were included in this study only if they were less than 75 years old and had an excellent performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1. Subsequent studies have shown that neoadjuvant FOLFIRINOX

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followed by combined chemoradiation therapy may be feasible as neoadjuvant therapy (5, 6). This algorithm can result in a microscopic margin-negative (R0) resection rate of approximately 18% in patients with initially LAPC, and higher for those who are BR (6, 7). Von Hoff *et al.* have also shown an improved OS in patients with metastatic PDAC treated with gemcitabine plus *nab*-paclitaxel (AG) compared to gemcitabine alone with a median OS of 8.5 months compared to 6.7 months (7). This was one of the first trials to ever show a significant survival advantage for a gemcitabine-based doublet in the subgroup of patients with a Karnofsky performance status of 70-80 (equivalent to an ECOG performance status of 2). This regimen has also recently been used in the neoadjuvant setting for potentially resectable PDAC. Ielpo *et al.* demonstrated a 68% resection rate along with a median OS and disease-free survival of 31 months and 18 months respectively (8).

Following the phase III trial of AG in patients with advanced disease, we began using this regimen followed in some cases by chemoradiation in patients with BRPC or LAPC who were deemed ineligible for FOLFIRINOX neoadjuvant therapy due to age, poor performance status or comorbidities. Within this context, the aims of this retrospective study were to determine the R0 resection rate, response rate, progression free survival (PFS), and toxicity in this patient population.

Patients and Methods

A retrospective analysis was performed at the University of Kentucky Markey Cancer Center in Lexington, Kentucky and the University of Miami, Sylvester Cancer Center, Miami, FL of all patients with BRPC or LAPC who received first-line treatment with AG. Patients were identified by searching the pancreatic cancer database which was approved by the Institutional Review Board (IRB) of both institutions.

The medical, radiation and surgical oncologists in the group developed an algorithm for uniform treatment of this group of patients as follows. Patients were selected for treatment with AG if they had a histological or cytological diagnosis of pancreatic adenocarcinoma, an Eastern Cooperative Group performance status (ECOG PS) of 0-3, adequate organ function, BRPC or LAPC, or deemed ineligible for FOLFIRINOX neoadjuvant therapy. The decision about ineligibility for FOLFIRINOX was based on the judgement of the treating medical oncologist and usually was because of advanced age, poor performance status (PS) or significant medical comorbidities. For patients who presented with biliary obstruction, adequate biliary drainage was required prior to initiation of this chemotherapy. The radiographic determination of resectability was made by standardized multidisciplinary review. The NCCN (National Comprehensive Cancer Network) criteria for resectability were applied (9). The data used to determine resectability included pretreatment contrast-enhanced CT scans (CECT's) and endoscopic ultrasound (EUS) in all patients.

The treatment regimen was the same as published in the MPACT trial for metastatic PDAC (7). This consisted of gemcitabine 1,000 mg/m² and *nab*-paclitaxel 125 mg/m²

administered on days 1, 8 and 15 every 28 days for at least 2-4 cycles. Treatment continued until progression of disease, intolerable toxicity or maximum response. Toxicities were assessed at every visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4. Criteria for dose modification were similar to those described in the MPACT trial. Response assessment by CECT's were performed every 8 weeks on therapy or sooner if progression was suspected by symptoms or rising serum CA19-9.

After every CECT scan during treatment, each patient's case was reviewed at a multidisciplinary conference to determine whether the reason for defining the patient as BRPC or UR LAPC had improved. Since size was not the only criterion used in this evaluation, traditional response criteria (such as RECIST) were not employed. If two consecutive scans during treatment showed similar findings with no improvement, this was considered to be the maximum response. Maximum tolerability was defined as the point when excessive toxicities warranted stopping AG, even if a patient had not achieved their maximum response. Because an algorithm of real-time monitoring of response and toxicity was used, there was no predefined minimum or maximum number of cycles.

At maximum response or maximum tolerability, patients who appeared to be resectable by imaging criteria were offered surgical exploration and resection (within 6-8 weeks after chemotherapy) followed by postoperative chemoradiation. Patients who remained UR at maximum response or tolerability of AG were offered chemoradiation. For radiation sensitization, patients received concurrent capecitabine. Intensity-modulated radiation therapy (IMRT) was delivered in a standard fashion to a total dose of 50.4 Gy in 28 fractions or 52.5 Gy in 25 fractions. At the end of chemoradiation, patients were re-evaluated with CECT's to determine resectability. Post-CCRT treatment was left to the discretion of the treating physicians. Dose intensity was defined as the percentage of the full dose that was delivered.

The primary endpoint for this analysis was R0 resection rate. Secondary endpoints included Overall survival (OS), progression free survival (PFS), response rate, and toxicity. An R0 resection was defined as at least 1 mm free margins. Patients known to be alive were censored at the time of last contact. All patients who received at least one cycle of AG were included in the analysis. PFS was defined as the duration in months from the date of the first cycle of AG until the date of documented progression, recurrence, or death, whichever was soonest. OS and PFS were estimated by the Kaplan-Meier method with corresponding two-sided 95% confidence interval (CI) for survival proportions based on Greenwood's variance and the log-transform method. Statistical significance was defined as *p*<0.05, and all tests were two-sided. Tests were performed using the IBM SPSS statistics software version 24 (IBM, NY, USA).

Results

Between 10/2013-2/2018, 32 treatment-naïve BRPC or UR LAPC patients were treated with AG. Baseline characteristics are shown in Table I. The median age was 70 years (range=44-90 years). Fifty percent of the patients were deemed BR and 31% UR on initial diagnosis, 19% of the patients were resectable, but had other comorbidities (equivalent to the MD Anderson Cancer Center borderline resectable group C). ECOG PS ranged from 0-3 with 19%

Table I. *Baseline characteristics.*

	N (%)
Age (median, range), years	70 (44-90)
Gender	
Male	10 (31%)
Female	22 (68%)
ECOG performance status	
0	5 (16%)
1	21 (66%)
2	4 (13%)
3	2 (6%)
Reason for neoadjuvant therapy	
Unresectable	10 (31%)
Borderline resectable	16 (50%)
Resectable but comorbidities	6 (19%)
Requiring biliary stent	
Yes	21 (66%)
No	11 (34%)

of patients having a PS of 2 or 3. Forty-four percent of patients were administered between 6-9 doses of AG while 16% received less than 6 doses and 40% received greater than 10 doses. The median number of administered doses was 9. In total, 319 doses of AG were given to the patients, with 231 (72%) at reduced doses. Reasons for dose reductions were similar to the published AG regimen (6, 7) along with worsening clinical status. The mean dose intensity for gemcitabine and *nab*-paclitaxel was 78% and 76% respectively.

Treatment outcomes are summarized in Table II. Prior to radiation therapy, the best radiological response was a partial response based on RECIST criteria in 5/32 (16%) of patients; 75% (24/32) of patients had stable disease while 9% (3/32) had progression of disease prior to radiation. Sixty-one percent of patients received neoadjuvant chemoradiation. Overall six (19%) patients achieved an R0 resection after neoadjuvant treatment and surgical exploration. Out of these six patients four had BRPC. Three patients were deemed unresectable at surgical exploration, one due to peritoneal metastases, one due to liver metastases, and the other was due to a grossly abnormal liver and biopsy showed necrotizing cholangitis of the right posterior section. Three patients were deemed to be surgical candidates after neoadjuvant therapy but declined surgery after discussing the risks and benefits. These patients were elderly, had complications during neoadjuvant therapy, and had concerns about postoperative quality of life. Three patients were considered medically unfit for surgery. Fourteen patients (44%) had disease progression during or on the first scan after the neoadjuvant chemotherapy with or without chemoradiation program. Three patients are still receiving

Table II. *Treatment outcomes.*

Best radiological response to AG (prior to radiation)	N(%)
Partial response	5 (16%)
Stable disease	24 (75%)
Progression	3 (9%)
Radiation therapy received	18 (56%)
Surgery	
R0 resection	6 (19%)
Unresectable on exploration	3 (9%)
Refused surgery	3 (9%)
Medically unfit for surgery	3 (13%)
Disease progression on neoadjuvant therapy	14 (44%)
Ongoing response pending radiation therapy and or surgery	3 (9%)

AG: *Nab*-paclitaxel/gemcitabine.

neoadjuvant chemotherapy with good ongoing response with plan to proceed to surgery with or without radiation.

The median overall survival (OS) was 13.1 (95%CI=9.2-17.0) months for all 32 treated patients. Median OS for 6 resectable patients (BR type C) was not reached at the time of this analysis while it was 12 months (95%CI=8.4-15.6) for BR and 10.4 months (95%CI=3.3-16.8) for UR patients. PFS for all 32 treated patients was 8.8 months (95%CI=5.4-12.2). Median PFS for 6 resectable patients was not reached at the time of this analysis and PFS for BR and UR was 8.4 (95%CI=5.5-11.3) and 7.4 (95%CI=2.4-12.1) months respectively (Table III).

Discussion

Systemic therapy for advanced PDAC has improved over the last 5 years with the FOLFIRINOX and AG regimens both showing superiority over gemcitabine monotherapy (3, 6). The systemic treatment of BRPC and LAPC is evolving as the newer regimens are being applied to these patients who have potential consolidative local treatment options after neoadjuvant therapy. Although prospective phase III studies are ongoing, none has been reported yet to confirm the role of FOLFIRINOX or AG in BRPC and UR LAPC. Recently Hammel *et al.* presented the data from a phase II LAPACT trial of AG for patients with UR LAPC with an R0 resection rate of 7% and a median PFS of 10.2 months (10). Treatment guidelines in the US have now incorporated chemotherapy with FOLFIRINOX or AG as options for patients with non-metastatic disease (5, 6, 11). Due to concerns about the tolerability of FOLFIRINOX, it is usually only applied to younger patients with good performance status (9).

Herein we report results of the AG regimen in BRPC and UR LAPC patients deemed ineligible for FOLFIRINOX neoadjuvant therapy. In this small series, the R0 resection

Table III. *Survival results.*

	N	Median (months)	95%CI (months)	p-Value
OS, all patients	32	13.1	9.2-17.0	
OS				
Resectable with comorbidities	6	Not reached		
Borderline resectable	16	12.0	8.4-15.6	
Unresectable	10	10.4	3.3-16.8	0.201
OS				
ECOG 0	5	Not reached		
ECOG 1	21	13.8	9.0-18.6	
ECOG 2-3	6	10.4	0.5-20.3	0.335
OS				
No radiation	14	6.4	Not calculable	
Radiation	18	13.1	10.3-15.9	0.702
PFS, all patients	32	8.8	5.4-12.2	
PFS				
Resectable with comorbidities	6	Not reached		
Borderline resectable	16	8.4	5.5-11.3	
Unresectable	10	7.4	2.4-12.1	0.111
PFS				
ECOG 0	5	Not reached		
ECOG 1	21	8.8	5.7-11.9	
ECOG 2-3	6	7.4	4.0-10.8	0.369
PFS				
No radiation	14	5.8	Not calculable	
Radiation	18	8.8	6.2-11.5	0.990

CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PFS: progression-free survival.

rate was 19% and the response rate was at least 16%, despite frequent dose reductions and relatively low dose intensity. As a comparison, a recent study of highly selected, good performance status UR/BRPC patients treated with neoadjuvant FOLFIRINOX followed by radiation also achieved an R0 resection rate of 20% (6, 12). Although FOLFIRINOX demonstrates superior efficacy over gemcitabine in metastatic PDAC, there are still concerns about its tolerability, leading many investigators to modify the treatment regimen (9, 11). In our cohort, 72% of AG doses had to be reduced, but no patient was taken off chemotherapy due to intolerance despite having patients with ECOG PS up to 3 and ages up to 90.

Historically, elderly and/or poor PS patients with PDAC, both of whom represent a clinically significant proportion of real-world patients outside of clinical trial populations, have been excluded from curative-intent strategies (13). Our data suggest that these patients may now have a possibility for potentially curative resection with the use of neoadjuvant AG.

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