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Original Research Article

Neoadjuvant chemoradiation may be associated with improved pathologic response in pancreatic cancer

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ABSTRACT

Background: Neoadjuvant therapy is increasingly utilized in the management of pancreatic adenocarcinoma. The type of neoadjuvant therapy and its effect on pathologic response remains understudied.
Methods: A retrospective review was performed on patients who underwent neoadjuvant therapy followed by pancreatectomy. Multivariable regressions were used to determine associations between neoadjuvant therapy regimens and pathologic response.
Results: Seventy-five patients with pathologic responses available for review received FOLFIRINOX (61%) or gemcitabine with nab-paclitaxel (39%). Demographics, histologic differentiation, and utilization of chemoradiation were similar between the groups. Multivariable logistic regression demonstrated that chemoradiation was associated with an increased likelihood of a complete or near-complete pathologic response and a decreased rate of lymphovascular invasion and lymph node positivity. Neither chemotherapy regimen nor number of cycles administered were associated with pathologic response.
Conclusions: Neoadjuvant chemoradiation may be associated with complete or near-complete pathologic response regardless of chemotherapy regimen in pancreatic cancer patients.

Introduction

Standard treatment for patients with operable pancreatic cancer has historically been resection followed by adjuvant therapy. One challenge with this treatment paradigm is that due to postoperative complications and delayed recovery, up to 40% of patients do not receive any adjuvant therapy and only 20% of patients receive a full course of chemotherapy at the recommended dose.[1]

In an attempt to increase the proportion of patients who receive appropriate chemotherapy for pancreatic cancer, neoadjuvant therapy is being administered with increasing frequency. Nationwide utilization of neoadjuvant therapy among patients with non-metastatic pancreatic adenocarcinoma has increased from 8.3% in 2003 to 12.1% in 2011.[2] This may offer a number of advantages. Preoperatively, patients are likely in better physical condition and are more likely to tolerate chemotherapy compared to post-operative administration. Chemotherapy is also less effective among patients with a poor performance status.[3] Furthermore, preoperative chemotherapy may treat micrometastatic disease, selecting patients who respond and sparing rapidly progressing patients from a non-beneficial pancreatectomy.[3]

With an understanding of the rationale for neoadjuvant therapy, many groups have investigated its efficacy. Neoadjuvant therapy is associated with reduced rates of lymph node positivity, which has been shown to be associated with recurrence rates and overall survival.[4] Additionally, it allows for examination of the pathologic response to therapy, which has been reported as a prognostic indicator and can help guide further treatment.[5] Although rare, a small subset of patients achieves a complete pathologic response to therapy, which often predicts improved long-term survival.[5,6] The neoadjuvant regimen which leads to the highest likelihood of a complete pathologic response remains unknown. This study investigates two commonly used chemotherapeutic regimens as neoadjuvant therapy in pancreatic cancer, as well as the impact of chemoradiation on pathologic response.

Methods

Study population: We performed a retrospective review of an

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institutional database which includes data on all patients who underwent a pancreatectomy between January 1, 2009 and May 25, 2020. Demographic, clinical, and pathologic data were collected. Type of neoadjuvant therapy, duration of therapy, and use of chemoradiation were recorded. Patients were included whether they were initially deemed resectable, borderline resectable, or locally advanced. Patients with locally advanced and borderline resectable tumors uniformly receive neoadjuvant therapy. Those with radiographically resectable disease generally receive neoadjuvant therapy, though select patients with no adverse prognostic features may undergo up-front surgery. Patients were excluded if pathologic response scores were not available for review.

Outcomes: The primary outcome of this study was the pathologic response to neoadjuvant therapy as determined by the College of American Pathologists score. The pathologic responses are categorized as follows: complete response (score 0, no viable tumor cells), near-complete response (score 1, single viable cells or small clusters of viable cells), partial response (score 2, cancer with evidence of regression, but more than small clusters of viable cells), or no response (score 3, extensive residual cancer).[7] Secondary outcomes included assessment of perineural invasion, lymphovascular invasion, margin positivity, and rate of lymph node positivity.

Statistical analysis: Patients were categorized by chemotherapy regimen: FOLFIRINOX (single treatment every two-week cycle) or gemcitabine plus nab-paclitaxel (treatments on day 1, 8, and 15 of a four-week cycle). Those who received single agent chemotherapy or multiple different chemotherapy regimens were excluded due to relatively low numbers and significant heterogeneity in neoadjuvant treatment details. Comparisons of continuous dependent variables were performed using the Wilcoxon rank-sum test and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Pathologic responses were categorized by two separate grouping strategies: no response (score 3) versus any response (score 0,1,2) and a minimal or no response (score 2,3) versus a complete or near-complete response (score 0,1). Multivariable logistic regressions were performed to analyze the effect of treatment variables on pathologic response, lymphovascular invasion, perineural invasion, lymph node positivity, and margin positivity. Variables included in multivariable regressions were chosen based on those determined to be clinically relevant. Odds ratios and 95% confidence intervals were calculated. A p-value of <0.05 was used for statistical significance throughout and StataSE v16.0 (Statacorp LLC, College Station, TX) was used to perform statistical analyses. This study was approved by the Institutional Review Board at University Hospitals Cleveland Medical Center.

Results

Demographic and clinical data: Of 852 possible patients, 110 had a confirmed diagnosis of pancreatic ductal adenocarcinoma and received neoadjuvant therapy. Seventy-five patients met inclusion criteria. Forty-six (61%) patients received neoadjuvant therapy with FOLFIRINOX while 29 (39%) received gemcitabine with nab-paclitaxel. There were no differences in age, sex, or race between the two treatment groups as shown in Table 1. Patients who received FOLFIRINOX had a better performance status as compared to those who received gemcitabine and nab-paclitaxel, although the Charlson comorbidity index was similar between groups. There were also no differences in clinical tumor- or nodal-stage at diagnosis between the two groups, although there was a trend toward smaller tumors in those who received gemcitabine with nab-paclitaxel compared to the FOLFIRINOX group (2.3 cm vs 2.7 cm, $p = 0.052$). Patients in the FOLFIRINOX group completed more cycles of neoadjuvant chemotherapy compared to patients who received gemcitabine with nab-paclitaxel (6 vs 3, $p < 0.001$). Few patients in either group received neoadjuvant chemoradiation (17% FOLFIRINOX vs 14% gemcitabine with nab-paclitaxel, $p = 0.679$), with a median dose of 50.4 Gy in both groups. After completion of neoadjuvant therapy, both groups had a reduction in tumor size based on preoperative imaging (size difference: 0.4 cm FOLFIRINOX vs −0.5 cm gemcitabine with nab-paclitaxel, $p = 0.848$).

Pathologic characteristics: Resected tumors were larger on pathologic examination in those who received FOLFIRINOX compared to those who received gemcitabine with nab-paclitaxel (3.0 cm vs 2.1 cm, $p = 0.046$) as shown in Table 2. Both groups had larger tumors on final pathology compared to their preoperative imaging studies. There were no differences in the number of positive lymph nodes (2 positive nodes for FOLFIRINOX vs 2 positive nodes for gemcitabine with nab-paclitaxel, $p = 0.837$), the total number of lymph nodes evaluated (27 vs 23, $p = 0.835$), nor the rate of lymph node positivity (67% vs 76%, $p = 0.433$). Additionally, there were no differences in rates of perineural invasion (80% FOLFIRINOX vs 86% gemcitabine with nab-paclitaxel, $p = 0.493$), lymphovascular invasion (69% vs 52%, $p = 0.137$), or margin positivity (17.8% vs 7.1%, $p = 0.176$). Most patients had no identifiable pathologic response to therapy (score 3: 50% FOLFIRINOX vs 45% gemcitabine with nab-paclitaxel) or a partial response (score 2: 39% vs 45%). A minority had a near-complete response (score 1: 9% vs 10%). Only one patient (1% of study population) had a complete pathologic response after receiving 12 cycles of FOLFIRINOX without chemoradiation.

Pathologic characteristics were also compared for those who received neoadjuvant chemoradiation and those who received chemotherapy alone. Chemoradiation was associated with a reduced number of positive lymph nodes (0 vs 3, $p < 0.001$) and a decreased total number of lymph nodes evaluated (18 vs 28, $p = 0.006$). The lymph node positivity rate was lower in those receiving chemoradiation (25% vs 79%, $p < 0.001$). There was no difference in margin positivity rate (9.1% vs 14.5%, $p = 0.532$). Only one patient (8%) who received chemoradiation had no response to therapy, compared to 55% in those without chemoradiation.

Multivariable analysis of factors associated with pathologic response: Chemotherapy type (gemcitabine with nab-paclitaxel versus FOLFIRINOX) was not associated with pathologic response, nor was the number of completed cycles (Table 3). Patients who received chemoradiation had a greater likelihood of achieving any response (score 0,1,2) (odds ratio = 13.999, $p = 0.016$) and, more importantly, a complete or near-complete response (score 0,1) (odds ratio = 8.893, $p = 0.008$). Neither chemotherapy regimen, nor number of cycles, were associated with rates of perineural invasion, lymphovascular invasion, lymph node positivity, or margin positivity (Table 4). However, receipt of neoadjuvant chemoradiation was associated with decreased rates of lymphovascular invasion (odds ratio = 0.240, $p = 0.045$) and lymph node positivity (odds ratio = 0.051, $p = 0.001$).

Discussion

In this limited sample of patients receiving neoadjuvant therapy for pancreatic cancer, there was no difference in pathologic response between FOLFIRINOX and gemcitabine plus nab-paclitaxel. Similarly, the chemotherapy regimen was not associated with pathologic findings, including rates of perineural invasion, lymphovascular invasion, lymph node positivity, or margin positivity. In contrast, chemoradiation was associated with a more favorable pathologic response to therapy, reduced rates of lymphovascular invasion, and decreased rates of lymph node positivity.

Previously, the neoadjuvant experience from M.D. Anderson Cancer Center showed that less than 3% of patients who received

Table 1
Summary of demographic and clinical details. Values are reported as median (range) or number (percentage), as appropriate, unless otherwise noted. Bold values indicate statistical significance.

	FOLFIRINOX	Gemcitabine nab-paclitaxel	p-value
Number of patients	46 (61%)	29 (39%)	–
Age (years)	70 (43–87)	69 (54–83)	0.396
Female	26 (56%)	20 (69%)	0.281
Race			0.284
White	36 (80%)	27 (93%)	
Black	6 (13%)	1 (3%)	
Other	3 (7%)	1 (3%)	
Charlson comorbidity index	5 (2–8)	5 (3–8)	0.974
Eastern Cooperative Oncology Group (ECOG) performance status (mean, standard deviation)	0.63 (0.54)	1.08 (0.41)	**0.001**
Initial size (cm)	2.7 (1.0–13.3)	2.3 (0–7.8)	0.052
Clinical tumor-stage			0.185
1	8 (18%)	6 (21%)	
2	23 (51%)	17 (61%)	
3	12 (27%)	2 (7%)	
4	2 (4%)	3 (11%)	
Clinical nodal-stage			0.326
0	36 (84%)	20 (74%)	
1	7 (16%)	7 (26%)	
Tumor extent at diagnosis			0.441
Radiographically resectable	18 (40.0%)	16 (55.2%)	
Borderline resectable	19 (42.2%)	9 (31.0%)	
Locally advanced	8 (17.8%)	4 (13.8%)	
Preoperative size (cm)	2.2 (0–6.4)	1.9 (0–5)	0.297
Difference in size, preoperatively (cm)	−0.4 (−8.0–2.3)	−0.5 (−3.7–0.8)	0.848
Number of chemotherapy cycles	6 (1–12)	3 (2–6)	**<0.001**
Neoadjuvant chemoradiation	8 (17%)	4 (14%)	0.679
Radiation dose (Gray)	50.4 (33.0–50.4)	50.4 (50.4)	1.000
Operation			0.936
Whipple pancreaticoduodenectomy	30 (65%)	18 (62%)	
Distal pancreatectomy	8 (17%)	5 (17%)	
Total pancreatectomy	8 (17%)	6 (21%)	
Time from diagnosis to surgery (days)	171 (45–278)	154 (80–286)	0.168
Histologic grade			0.279
Well differentiated	2 (5%)	5 (17%)	
Moderately differentiated	25 (68%)	16 (55%)	
Poorly differentiated	10 (27%)	8 (28%)	
Adjuvant chemotherapy	28 (60.9%)	20 (69.0%)	0.477
Time from surgery to adjuvant chemotherapy (days)	68 (30–330)	71 (59–180)	0.353

neoadjuvant therapy had a complete pathologic response.[5] The results presented here are consistent with that finding. However, the effect of specific treatment strategies on the pathologic response has been inconsistent in the literature. The prior study from M.D. Anderson found no association between neoadjuvant treatment regimens (chemotherapy and/or chemoradiation) and pathologic response.[5] A separate study revealed that of eleven patients who achieved a complete pathologic response, all received neoadjuvant chemotherapy and chemoradiation.[8] A study from Johns Hopkins University examining patients who underwent neoadjuvant chemoradiation showed a complete response in 10% of patients; however, the chemotherapy regimen was not associated with pathologic response.[6] A recent report from Ohio State University demonstrated that patients who underwent neoadjuvant FOLFIRINOX were more likely to achieve a complete or near-complete pathologic response compared to gemcitabine with

Table 2
Summary of pathologic outcomes. Values are reported as median (range) or number (percentage), as appropriate. Bold values indicate statistical significance.

	FOLFIRINOX	Gemcitabine nab-paclitaxel	p-value	Chemoradiation	No Chemoradiation	p-value
Number of patients	46 (61%)	29 (39%)	–	12 (16%)	63 (84%)	–
Tumor size (cm)	3.0 (0–7.0)	2.1 (0–7.0)	**0.046**	2.1 (0–5.5)	2.9 (0–7.0)	0.120
Difference in size (diagnosis)	−0.1 (−7.8–4.3)	0 (−3.6–4.2)	0.972	−0.2 (−4.0–4.2)	0 (−7.8–4.3)	0.585
Difference in size (pre-op)	0.4 (−1.9–7.0)	0.7 (−3.0–4.2)	0.671	0.3 (−3.0–4.2)	0.5 (−1.6–7.0)	0.413
Positive lymph nodes	2 (0–11)	2 (0–9)	0.837	0 (0–2)	3 (0–11)	**<0.001**
Total lymph nodes	27 (9–62)	23 (4–74)	0.835	18 (4–42)	28 (10–74)	**0.006**
Lymph node positivity	31 (67%)	22 (76%)	0.433	3 (25%)	50 (79%)	**<0.001**
Positive margin	8 (17.8%)	2 (7.1%)	0.176	1 (9.1%)	9 (14.5%)	0.532
Perineural invasion	36 (80%)	25 (86%)	0.493	9 (75%)	52 (84%)	0.432
Lymphovascular invasion	31 (69%)	15 (52%)	0.137	5 (42%)	41 (66%)	0.192
Pathologic response			0.820			**0.001**
Complete response	1 (2%)	–		0	1 (2%)	
Near-complete response	4 (9%)	3 (10%)		4 (33%)	3 (5%)	
Partial response	18 (39%)	13 (45%)		7 (58%)	24 (38%)	
No response	23 (50%)	13 (45%)		1 (8%)	35 (55%)	

Table 3
Multivariable logistic regression analyzing impact of clinical variables on pathologic response. Bold values indicate statistical significance.

Score 0,1	Odds ratio	95% Confidence interval		p-value
Gemcitabine/nab-paclitaxel vs FOLFIRINOX	1.584	0.223	11.263	0.646
Number of chemotherapy cycles	1.064	0.811	1.398	0.653
Neoadjuvant chemoradiation	8.893	1.751	45.181	**0.008**
Score 0,1,2	**Odds ratio**	**95% Confidence interval**		**p-value**
Gemcitabine/nab-paclitaxel vs FOLFIRINOX	2.036	0.626	6.626	0.238
Number of chemotherapy cycles	1.124	0.947	1.335	0.182
Neoadjuvant chemoradiation	13.999	1.645	119.146	**0.016**

Table 4
Multivariable logistic regression analyzing impact of treatment details on rates of perineural invasion, lymphovascular invasion, lymph node positivity, and margin positivity. Bold values indicate statistical significance.

Perineural invasion	Odds ratio	95% Confidence interval		p-value
Gemcitabine/nab-paclitaxel vs FOLFIRINOX	1.338	0.306	5.853	0.699
Number of chemotherapy cycles	0.980	0.800	1.201	0.849
Neoadjuvant chemoradiation	0.534	0.119	2.395	0.413
Lymphovascular invasion	**Odds ratio**	**95% Confidence interval**		**p-value**
Gemcitabine/nab-paclitaxel vs FOLFIRINOX	0.311	0.093	1.046	0.059
Number of chemotherapy cycles	0.939	0.786	1.123	0.492
Neoadjuvant chemoradiation	0.240	0.059	0.967	**0.045**
Lymph node positivity	**Odds ratio**	**95% Confidence interval**		**p-value**
Gemcitabine/nab-paclitaxel vs FOLFIRINOX	0.673	0.156	2.904	0.596
Number of chemotherapy cycles	0.851	0.698	1.037	0.110
Neoadjuvant chemoradiation	0.051	0.009	0.279	**0.001**
Margin positivity	**Odds ratio**	**95% Confidence interval**		**p-value**
Gemcitabine/nab-paclitaxel vs FOLFIRINOX	0.394	0.065	2.387	0.311
Number of chemotherapy cycles	1.004	0.814	1.239	0.968
Neoadjuvant chemoradiation	0.384	0.038	3.896	0.418
Locoregional tumor extent				
Borderline resectable vs resectable	2.419	0.500	11.706	0.272
Locally advanced vs resectable	2.695	0.014	8.493	0.357

nab-paclitaxel.[9] Additionally, chemoradiation was associated with decreased rates of lymph node positivity and favorable pathologic responses.[9]

The present data support two principal conclusions. First, few patients who undergo neoadjuvant therapy for pancreatic cancer achieve a complete or near-complete pathologic response (11% in the current study). This is in comparison to esophageal and rectal cancers, in which complete pathologic responses have been reported in over 20% of patients who receive neoadjuvant therapy.[10,11] Scientists submit that the hypoxic, hypovascular, and nutrient deprived tumor microenvironment of pancreatic cancer renders traditional chemotherapeutics less effective through activated resistance pathways.[12] The second important finding is that the addition of chemoradiation seems to be associated with improvements in pathologic response to therapy and other tumor characteristics. This finding is supported by the Alliance Trial A021101 which examined the feasibility and safety of neoadjuvant FOLFIRINOX with chemoradiation for borderline resectable pancreatic cancer. The study revealed that 33% of patients achieved a near-complete pathologic response and an additional 13% had a complete response.[13]

Our study has several limitations worth highlighting. This was not a randomized clinical trial. Similar to other single institution studies on neoadjuvant therapy in pancreatic cancer, we are limited by a small sample size, particularly with regard to the number of patients who received chemoradiation. Further, chemoradiation use was not standardized and in general was used when there was a concern about an arterial margin. Similarly, the choice of chemotherapy regimen was not standardized, but in general gemcitabine with nab-paclitaxel was utilized when there was a concern regarding patient performance status. Finally, the ultimate outcome of studies of neoadjuvant therapy for cancer is overall survival. Given that the majority of patients who received neoadjuvant therapy at our institution were treated recently, survival data are not mature yet.

Conclusions

Few patients undergoing neoadjuvant therapy for pancreatic cancer achieve a complete or near-complete pathologic response; however, the addition of chemoradiation seems to be associated with an increased likelihood of a favorable response. Our institutional preference has historically been to deprioritize chemoradiation. These findings suggest an alternative strategy may be warranted and support further investigations to more clearly define the optimal neoadjuvant therapy regimen and its association with survival.

Summary

Neoadjuvant therapy is increasingly utilized for patients with pancreatic cancer. The specific chemotherapy regimen is not associated with differences in pathologic response to therapy; however, neoadjuvant chemoradiation may be associated with an increased likelihood of a favorable pathologic response and reduced rates of lymphovascular invasion and lymph node positivity.

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