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Benefit of Gemcitabine/Nab-Paclitaxel Rescue of Patients With Borderline Resectable or Locally Advanced Pancreatic Adenocarcinoma After Early Failure of FOLFIRINOX

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Abstract

Objectives: Neoadjuvant therapy (NT) is used for advanced pancreatic ductal adenocarcinoma (PDAC). No clear guidelines exist for switching therapies when patients do not respond to initial NT. We sought to characterize patients who underwent early switch from FOLFIRINOX to gemcitabine/nab-paclitaxel (GA) as NT for PDAC.

Methods: We identified patients at a single institution switched from FFX to GA within the first 4 months of NT for PDAC during 2012–2017. We compared clinicopathologic data and oncologic outcomes.

Results: Of 25 patients who met criteria, 21 showed a serologic or radiographic response to GA; 11 (52%) reached resection. Responders had decreased carbohydrate antigen (CA) 19-9 levels from pre-treatment to post-GA ($P = 0.036$). Resected responders had significantly decreased CA 19-9 comparing pre-switch to post-GA ($P = 0.048$). The only predictor of GA response was pre-chemotherapy CA 19-9 < 1000 U/mL ($P = 0.021$). Predictors of reaching resection were head/uncinate tumor ($P = 0.010$) and presenting stage lower than locally advanced ($P = 0.041$).

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Conclusion: When patients do not respond to neoadjuvant FOLFIRINOX, early switch to GA should be considered. Future efforts should be directed toward identifying markers that will allow correct choice of initial therapy rather than attempting to rescue patients who respond poorly to first-line therapy.

Keywords

pancreatic ductal adenocarcinoma; neoadjuvant therapy; gemcitabine-abraxane; FOLFIRINOX; chemotherapy switch

INTRODUCTION

Pancreatic adenocarcinoma (PDAC) is currently the third leading cause of cancer death in the United States¹ and is projected to be the second leading cause by 2030.² Despite improvements from new chemotherapy regimens, the 5-year overall survival (OS) remains low.¹ Multimodality therapy including surgical resection represents the only hope for potential cure, but only 10–20% of patients present with anatomically resectable disease.³ Up to 50% of patients present with localized disease that is beyond anatomically resectable, referred to as borderline resectable (BR) or locally advanced (LA).⁴ International guidelines now recommend treating these patients with preoperative, or neoadjuvant, therapy (NT), with a goal of down-staging tumor burden to allow resection. In addition, patients with anatomically resectable tumors may also benefit from NT, as is reflected in recent guidelines on treatment sequencing.^{5–7}

Despite the increased use of NT, there are limited data to guide chemotherapy selection. Most clinicians are influenced by data from the metastatic setting, which have shown efficacy for two systemic therapy combinations, FOLFIRINOX (infusional 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin, or FFX) and gemcitabine/nab-paclitaxel (gemcitabine-Abraxane®, or GA).^{8,9} There is a prevalent belief that FFX is more efficacious, likely based on cross-trial comparison of treatment arms from trials done in the metastatic setting. While these trials had different patient population, making such comparisons problematic, this belief persists and most robust patients with a diagnosis of BR or LA PDAC are started on FFX as the first-line agent for preoperative chemotherapy.¹⁰

While data directing selection of a first-line agent for NT of PDAC are limited, data guiding the choice of second-line regimens in the neoadjuvant setting are even more limited.¹¹ Even in the metastatic setting, very little data support specific second-line options,¹² although recent guidelines from the American Society of Clinical Oncology recommend the use of GA after FFX has failed in the metastatic setting.¹³ Within this context, we analyzed the oncologic outcomes of PDAC patients who experienced failure of FFX early in the neoadjuvant setting owing to lack of clinical or radiographic response and/or toxicity and were then switched to GA with the intent of eventual definitive local therapy.

MATERIALS and METHODS

Patient Population

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this retrospective cohort study of patients with non-metastatic PDAC treated with chemotherapy with plans for intended local therapy. The institution's prospectively maintained pancreatic tumor database¹⁴ was queried for patients seen during January 1, 2012, through December 31, 2017, and all patients with non-metastatic PDAC who were treated with FFX and then switched to GA within the first 4 months of therapy were included. The last date of follow-up was May 31, 2018. Patients who manifested metastatic disease after FFX therapy were excluded, leaving patients who underwent a therapeutic switch in NT with the continued intent of reaching local therapy.

Data Collection

The following variables were collected from the database: age, sex, body mass index, serum bilirubin at presentation, NT details, and pathologic data from surgical specimens. Serum carbohydrate antigen (CA) 19-9 levels were collected at specific time points throughout each patient's treatment course: before chemotherapy (Pre-Chemo); prior to switching (Pre-Switch); and at first (Post-GA1), second (Post-GA2), and third (Post-GA3) restaging after GA when applicable. Tumor-vessel interface for relevant vessels at the time of patients' initial computed tomography (CT) scan were determined by a single dedicated pancreatic radiologist (S.J.). Initial radiographic tumor stage was characterized as potentially resectable (PR), BR based on anatomy (BR-A), or LA according to criteria for the ongoing ALLIANCE trial A021501, which allow tumor interface with the portal vein in PR patients, notably more liberal than the traditional Society of Surgical Oncology/Society for Surgery of the Alimentary Tract/National Comprehensive Cancer Network consensus.^{15,16} We then used the MD Anderson clinical staging system to define BR patients as type A (BR-A; anatomic criteria), type B (BR-B; biological findings suspicious for extra-pancreatic disease), and BR type C (BR-C; comorbidities with potential reversibility) PDAC as applicable.¹⁷

Determination of Response and Reason for Therapy Switch

Therapy response was defined as either a radiographic or a serologic. Serologic response was any decrease in serum CA 19-9 of at least 50% from a starting value above the normal range. Radiographic response was determined by the radiologist reading each report and gathered from radiographic reports. Any radiographic response was deemed "response." The reason for therapy switch was determined by review of multi-disciplinary clinic notes in the electronic medical record.

Neoadjuvant Therapy

Each patient's treatment plan was determined by a multi-disciplinary team of medical, surgical, and radiation oncologists. Patients were seen by both the surgical oncologist and medical oncologist before NT. In general, patients who were selected for FFX therapy were given oxaliplatin at 85 mg/m², irinotecan at 150–180 mg/m², 5-fluorouracil bolus of 400

mg/m², leucovorin at 400 mg/m², and 2400 mg/m² infusional 5-fluorouracil over the course of 2 days. FFX was given in a 2-week cycle; the number of cycles received was reported. Typical practice at our institution during the study period was to give 4 cycles of FFX, then restage patients with computed tomography (CT) scan and labs. If the patient was tolerating FFX therapy and responding at the 2-month restaging, this regimen was continued for an additional 4 cycles before local therapy. Local therapy was either definitive radiotherapy with or without radiosensitizer when resection was still not possible or preoperative radiotherapy (as appropriate) with or without radiosensitizer followed by resection. This treatment algorithm is very similar to the original ALLIANCE protocol for BR PDAC, in which patients receive either seven cycles of FFX plus radiation or eight cycles of FFX without radiation.¹⁸ Rarely, if therapy was not tolerated and/or if treating oncologists felt that a patient's disease was not responding to FFX, then the patient was switched to GA and continued on preoperative chemotherapy for another 2–4 months before being considered for preoperative radiotherapy and eventual resection. There was an institutional tendency to avoid switching regimens early if possible to allow the alternative regimen to be saved for later use. Some patients who were switched to GA were treated in 2-weeks cycles, which is our institutional preference, while others were treated with a 3 weeks on, 1 week off schedule as recommended by Von Hoff.⁸ Therefore, GA was reported as months of GA therapy as opposed to number of cycles.

Statistical Analysis

Continuous variables were reported as medians with interquartile range (IQR). We compared clinicopathologic variables between response groups using nonparametric tests such as the Mann-Whitney test for continuous variables and a chi-square or Fisher exact test for categorical data. Survival estimates were calculated using Kaplan-Meier analysis and compared using log-rank test. All statistics were performed using SPSS, version 24 (IBM, Armonk, NY). A *P* value of <0.05 was considered significant.

RESULTS

Patient Characteristics

We identified patients who were seen at our institution during the study period for non-metastatic PDAC and were started on FFX with the intent of definitive local therapy. Of these patients, we identified 25 who failed FFX and were switched to GA with continued curative intent. Of the 25 patients included in the final analysis, 21 showed a response to GA (RESP), while four did not (nonRESP). Eleven of the 21 (52%) responding patients underwent resection (RESP-RESECT), while 10 did not (RESP-nonRESECT) (Fig. 1). Baseline clinicopathologic characteristics did not significantly differ between cohorts (Table 1).

Initial Tumor Characteristics

On initial CT scan, six (24%) patients had PR, 14 (56%) had BR, and 5 (20%) had LA disease. On clinical staging, 20 (80%) patients had BR disease (7 BR-A, 11 BR-B, and 2 BR-C), and 5 (20%) had LA disease. Each patient's tumor location, tumor-vessel interfaces, and presenting stage are shown in Supplementary Table 1. Tumor location significantly

differed between outcome groups: head and uncinate tumors were less frequent in RESP-nonRESECT patients (4/10 [40%]) than in the RESP-RESECT (10/11 [91%]) and nonRESP (4/4 [100%]; $P = 0.004$) groups. These 3 groups did not significantly differ with respect to initial radiographic stage ($P = 0.153$) but did differ with respect to clinical stage ($P = 0.043$). RESP-nonRESECT and nonRESP patients more frequently presented with LA disease (36%) than did the RESP-RESECT patients (0%; $P = 0.027$).

Response to FFX

Serologic—After a median of 4 cycles of FFX, 16 of 25 (64%) patients had an evaluable change in CA 19-9 from presentation to pre-switch of chemotherapy. Of those without an evaluable change two presented with bilirubin >2 mg/dL and were not re-checked before initiation of chemotherapy, three were non-producers of CA 19-9, three had normal pre-chemotherapy CA 19-9, and one did not have a repeat CA 19-9 before switching. Of these 16 patients, 15 did not have a serologic response, while one patient had an initial serologic response after 4 cycles, then had an increase in CA 19-9 after 2 additional cycles of FFX and was determined to no longer be showing a response to FFX (Supplementary Table 2).

Radiographic—All but 1 of the 25 patients had restaging CT prior to therapy switch (1 patient stopped FFX after only 2 cycles owing to poor tolerance and was switched to GA without restaging). On restaging CT, 14 (58%) patients showed progression or a mixed response, nine (38%) showed stable disease, and only 1 (4%) showed a response. The outcome groups did not significantly differ in radiographic response to FFX ($P = 0.752$) (Supplementary Table 2).

Reason for Therapy Switch

Overall, 16 (64%) patients were switched to GA solely due to poor response to FFX, 6 (24%) solely due to poor tolerance, and 3 (12%) due to both poor response and poor tolerance. These reasons did not significantly differ between outcome groups ($P = 0.914$). Similarly, reason for switch did not predict response to GA ($P = 0.735$) or eventual resection ($P = 0.993$).

GA Therapy Details and Response

Patients received a median of 4 months of GA, with a median of 2.5 months in the nonRESP group, 3 months in the RESP-RESECT group, and 4 months in the RESP-nonRESECT group ($P = 0.163$).

Serologic Response—At the first post-GA restaging, after a median of 4 cycles of GA, 19 patients had an evaluable change in CA 19-9 from Pre-Switch; 3 were non-producers of CA 19-9, and 3 had a normal CA 19-9 levels throughout therapy. Of the 19 patients with an evaluable change, 14 (74%) had a serologic response (9/9 RESP-RESECT patients, 5/6 RESP-nonRESECT patients, and 0/4 nonRESP patients). Of note, the single RESP-nonRESECT patient without a serologic response had a 44% decrease in CA 19-9, a radiographic response at the first restaging, and a further decrease in CA 19-9 at the next restaging.

Radiographic Response—All 25 patients had a CT at the first post-GA restaging. Only 3 patients (12%) showed progression, 2 (8%) showed mixed response, and 3 (12%) showed stable disease, while the majority of patients, 16 (64%), showed a response on CT. Except for 2 in the RESP-RESECT group with stable disease (18%) and two in the RESP-nonRESECT group with stable disease (10%) or stable disease (10%), all in the responding groups showed a radiographic response. In the nonRESP group, all but one patient with a mixed response (25%) showed radiographic progression (75%) (Supplementary Table 2).

Overall, the response rate to GA in our cohort was 21/25 (84%). Four patients had a serologic response to GA only, 7 patients had a radiographic response to GA only (6 of these were either non-producers or had normal levels of CA 19-9), and 10 patients had both a serologic and radiographic response.

CA 19-9 Over Time

Median Pre-Chemo CA 19-9 was significantly higher for nonRESP patients (1991 U/mL, range 273–3847 U/mL) than for RESP-nonRESECT patients (285 U/mL, IQR 11–564 U/mL) or RESP-RESECT patients (364 U/mL, IQR 82–1040 U/mL) ($P = 0.001$). Pre-Switch CA 19-9 remained higher for nonRESP patients than for RESP patients ($P = 0.001$) and after the switch to GA ($P < 0.001$ for both Post-GA1 and Post-GA2) (Table 1). No group showed a significant change from Pre-Chemo to Pre-Switch CA 19-9 levels, but RESP patients showed a significant change from Pre-Chemo levels (364 U/mL; IQR, 34–634 U/mL) to Post-GA1 (48 U/mL, IQR, 22–108 U/mL; $P = 0.036$), while the nonRESP patients did not show a significant change between those time points (1991 U/mL; IQR, 477–3609 U/mL vs 2223 U/mL; IQR, 795–7671 U/mL; $P = 0.492$) (Fig. 2). While nonRESP patients showed a significant increase in median CA 19-9 from Pre-Chemo to Post-GA2 (5854 U/mL; range, 5141–6566 U/mL; $P = 0.042$), RESP patients continued to show a significant decrease in median CA 19-9 from Pre-Chemo to Post-GA2 (37 U/mL; IQR, 17–179 U/mL; $P = 0.013$) (Fig. 2).

Median CA 19-9 values were not significantly different between RESP-RESECT and RESP-nonRESECT groups at any time point. However, the RESP-RESECT group showed a significant decrease in median CA 19-9 from both Pre-Chemo (364 U/mL; IQR, 82–1040 U/mL) and Pre-Switch (531 U/mL; IQR, 125–1336 U/mL) time points to the second restaging (33.5 U/mL; IQR, 17.8–182 U/mL; $P = 0.028$ and $P = 0.005$, respectively), while the RESP-nonRESECT median CA 19-9 did not change significantly throughout the treatment course. CA 19-9 curves for individual patients in each group are depicted in Figure 3.

Predictors of Response and Resection

The only significant predictor of response to GA was a pre-chemotherapy CA 19-9 level of <1000 U/mL (RESP: 88% vs nonRESP: 25%; $P = 0.010$). Predictors of reaching resection were tumor location in the head/uncinate (vs body/tail) (RESP-RESECT: 91% vs nonRESECT: 50%; $P = 0.030$) and presenting stage lower than LA (RESP-RESECT: 100% vs nonRESECT: 64%; $P = 0.027$).

Pathologic Findings

Pathologic results in RESP-RESECT patients are summarized in Supplementary Table 3. Nine (81.8%) of 11 patients had an R0 resection, and 3 (27.3%) were N0.

Survival

At a median follow up of 17.0 months, RESP-RESECT patients had a significantly longer estimated progression-free survival after the switch to GA (15.2 months) than either RESP-nonRESECT (6.5 months) or nonRESP (1.4 months) patients ($P < 0.001$) (Fig. 4). RESP-RESECT patients also had a significantly longer estimated overall survival (23.7 months) than either RESP-nonRESECT (15.9 months) or nonRESP (5.6 months) patients ($P < 0.001$) (Fig. 5).

DISCUSSION

In this single institution retrospective cohort study performed at an institution with a bias against early chemotherapy switching, we identified 25 patients who received GA as NT for PDAC after experiencing a poor response to and/or poor tolerance of FFX. While the majority of patients were switched due to a poor response to FFX, 21 of 25 patients showed response to GA. Only one patient in this cohort showed a radiographic response to FFX, but 64% showed a radiographic response after GA. Similarly, despite no improvements in CA 19-9 after FFX, there was a substantial decrease in CA 19-9 after GA in the patients whose disease responded to GA. This decrease persisted through roughly 4 months of GA in the RESP group and persisted even further in the RESP-RESECT group. The only significant predictor of response to GA was a pre-chemotherapy CA 19-9 level of <1000 U/mL. Predictors of resection after the switch to GA were head/uncinate tumor location and PR/BR presentation (vs. LA). Patients whose disease responded to GA and who reached resection had an estimated median OS of almost 2 years. Therefore, when patients undergoing NT for localized PDAC do not show a response to initial FFX, early switch to GA may result in a measurable response and should be considered.

The use of NT is becoming standard for patients with BR and LA PDAC, as reflected by recent guidelines from the NCCN and ASCO.^{5,6,8,9,19–21} These guidelines do not recommend a specific regimen, but instead allow either GA or FFX as first-line NT. This ambiguity reflects the lack of data directly comparing FFX to GA for the treatment of PDAC in any setting. Nevertheless, FFX is generally accepted as the preferred initial regimen for NT in patients with very good performance status, as is recommended for metastatic disease.¹⁰ The assumption that FFX is superior may be partially based on the assumption that a regimen with more toxicity is more efficacious. More likely, it is based on comparisons of the phase III trials of these two regimens for metastatic PDAC. In their respective trials, FFX therapy resulted in a median OS of 11.1 months compared to only 8.5 months for GA therapy, while both control groups had roughly the same OS (6.8 months and 6.7 months, respectively).^{8,9} This type of cross-trial comparison is, however, problematic given the difference in patient populations.

Even less clear than which regimen should initially be chosen is what to do when patients do not respond to first-line therapy. This issue is particularly important because many patients with BR and LA disease will not reach definitive resection without significant treatment response. In addition, most patients started on FFX NT will continue this therapy for at least 4 months, even without evidence of response at initial restaging. This practice is in line with the protocol for the ALLIANCE trial A021501, which is randomizing patients with BR PDAC to NT with either 7 cycles of modified FFX or 7 cycles of FFX followed by radiation therapy.¹⁵ Patients in this trial are being restaged after 4 cycles of FFX, but only to ensure no development of metastatic disease. This high-profile and important trial demonstrates the commonly used clinical practice of not only choosing FFX as first-line for NT but also continuing this therapy for a full 4 months as long as patients do not develop metastatic disease. This reflects the general assumption that FFX is more effective than GA and that in cases where FFX fails to elicit a response, GA will also fail.

Despite this general assumption, 84% of patients in our cohort did at least initially experience a response to GA after failing FFX. This finding is particularly important because most patients switched therapy because of a lack of response to FFX rather than poor tolerance. Moreover, almost half of these patients had enough response to GA to reach definitive resection. Furthermore, patients in this cohort were switched after a median of only 4 cycles of FFX, essentially at the time of first restaging, rather than continuing FFX for an additional 2 months. Continuing ineffective therapy could not only delay more effective therapy but also worsen toxicities, which could eliminate the option of surgery.

In addition to radiographic and serologic responses, our cohort showed much better survival than one would expect in these patients with generally aggressive disease who not only were chosen for NT, but also failed first-line therapy. Without a change in therapy, one would anticipate that most of these patients would have had very short survival. The OS in our cohort, however, was 17 months, and the resected group reached nearly 2 years. Thus, an OS of nearly 2 years in the 11 patients who reached resection is not only a statistically significant improvement but also, we submit, a clinically relevant improvement that provides hope to patients who might not see an initial response at the 2-month restaging visit.

While demonstrating that some patients respond better to GA than FFX is important, this finding will be truly meaningful only when we can effectively select the correct regimen for patients upfront. In our cohort, a presenting CA 19-9 <1000 U/mL predicted eventual GA response. This finding likely speaks less to anything specific about GA or FFX and more to the importance of the BR-B clinical stage and the concept that a markedly elevated CA 19-9 level (>1000 U/mL) identifies patients with very aggressive biology even when radiographic evidence does not show gross metastatic disease.¹⁷ We emphasize, however, that this criterion should not be used as a justification to avoid a therapy switch in the setting of FFX failure, as 2 patients who presented with CA 19-9 >1000 U/mL not only showed a response to GA but also had enough of a response to undergo definitive resection, and one of these patients was still alive over 3 years later. Predictors of eventual resection included tumors in the pancreatic uncinate or head and presenting at a stage less than LA anatomy. These predictors underscore the importance of using accurate initial clinical staging to inform the goals of NT and the realistic likelihood of eventual resection. In addition, these data

demonstrate that the margin for error is even thinner in patients with more advanced disease, which may not be amenable to “rescue” after failure of first-line therapy, making selection of the correct first-line therapy even more crucial. Ultimately, improved predictors of response to these two therapies are needed to help us select the correct therapy for patients at presentation.

The current study has some important limitations. First, this is a retrospective study, leaving the possibility of additional patients who were omitted. We mitigated this limitation by querying our prospective database of all patients with localized disease entering our multidisciplinary (not just the surgical oncology) clinic. Second, some information, such as reason for switching therapies, had to be retrospectively ascertained from clinic notes, leaving room for incorrect interpretation. The size of our cohort and short follow-up (due to the relatively recent use of FFX and GA) in some cases may limit the generalizability of our conclusions. Finally, there is inherent selection bias, as this cohort was switched “early” to a second-line therapy despite many oncologists’ belief that it is better to continue with the initial chemotherapy regimen even in the face of marginal or poor response as long as there is a lack of clear progression or metastatic disease. Despite these limitations, we have shown that many cases of PDAC will respond to NT with early GA rescue after failure of FFX to induce response, and some will do so dramatically. Before our current study, to our knowledge, there has been only a single report of 2 patients who were treated with GA after failure of FFX and were then able to reach resection.¹¹ The present study represents the largest cohort study to date that addresses this important question, and provides evidence that early change to GA after failure of initial FFX NT may benefit patients.

CONCLUSIONS

While FFX is currently considered the first-line NT in PDAC, some patients appear to respond better to GA. When patients do not respond as hoped to FFX at the time of initial restaging, a therapeutic switch to GA should be considered rather than saving GA for metastatic disease in the future. Translational efforts should be directed at identifying markers to identify up front which patients will respond better to FFX compared with GA rather than testing response empirically as we do now. Such markers will help us select the best tailored initial NT rather than attempting to rescue patients who experience a poor response to first-line therapy and suffer the opportunity cost of time on the non-ideal therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.
Oncologic outcome groups.

FIGURE 2.

Median CA 19-9 over time for RESP and nonRESP Groups. *RESP vs nonRESP CA 19-9, $P < 0.05$. #Change from Pre-Chemo CA 19-9, $P < 0.05$.

FIGURE 3.

Individual CA 19-9 curves showing percentage change over time for RESP-RESECT (A), RESP-nonRESECT (B), and nonRESP (C) patients. Pre-Chemo indicates before chemotherapy; Pre-Switch, prior to switching chemotherapy (Pre-Switch); PostGA1, PostGA2, PostGA3, At first, second, and third restaging after GA, respectively.

FIGURE 4.
Progression-free survival.

FIGURE 5.
Overall survival.

TABLE 1.**Patient Factors**

	All Patients (n = 25)	Responders-Resected (n = 11)	Responder-Nonresected (n = 10)	Nonresponders (n = 4)	P
Age at diagnosis, median (range), y	66 (50–80)	66 (52–80)	66 (50–78)	68 (56–76)	0.865
BMI, median (range), kg/m ²	25.4 (20.0–35.2)	24.5 (20.0–35.2)	26.5 (20.6–29.6)	23.0 (20.7–31.2)	0.814
Sex, n (%)					0.563
Female	14 (56)	6 (55)	5 (50)	3 (75)	
Male	11 (44)	4 (36)	6 (60)	1 (25)	
Ethnicity, n (%)					0.464
Asian	1 (4)	0 (0)	1 (10)	0 (0)	
African American	2 (8)	0 (0)	2 (20)	0 (0)	
Hispanic	1 (4)	1 (9)	0 (0)	0 (0)	
White	21 (84)	10 (91)	7 (70)	4 (100)	
Pre-existing comorbidity, n (%)					0.204
None	6 (24)	4 (36)	1 (10)	1 (25)	
Mild	11 (44)	5 (45)	5 (50)	1 (25)	
Moderate	7 (28)	2 (18)	4 (40)	1 (25)	
Severe	1 (4)	0 (0)	0 (0)	1 (25)	
CA 19-9, median (IQR), U/mL					
Pre-Chemo	487 (96–1000)	364 (82–1040)	479 (16–587)	1991 (476–3609)	0.001
Pre-Switch	574 (247–1382)	531 (125–1335)	420 (208–642)	2278 (692–6458)	0.001
Post-GA1	51 (31–530)	45 (22–299)	51 (20–59)	2223 (795–7671)	<0.001
Post-GA2	50 (16–201)	34 (18–182)	69 (6–679)	5854 (5141–5853)	<0.001

IQR indicates interquartile range; Pre-Chemo, before any chemotherapy; Pre-Switch, before switch to gemcitabine/nab-paclitaxel; Post-GA1, first post-gemcitabine/nab-paclitaxel restaging; Post-GA2, second post-gemcitabine/nab-paclitaxel restaging.