

Retrospective analysis of efficacy and safety of Gemcitabine-based chemotherapy in patients with metastatic pancreatic adenocarcinoma experiencing disease progression on FOLFIRINOX

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Background: Metastatic pancreatic adenocarcinoma (MPA) represents a highly lethal condition. Despite the improvements seen with FOLFIRINOX, there is no randomized data to guide treatment selection beyond this regimen. We aimed to evaluate the outcomes of patients with MPA progressing on FOLFIRINOX who were treated with Gemcitabine-based chemotherapy afterwards.

Methods: We included patients aged 18 years or older, treated for MPA with FOLFIRINOX in the first-line setting and who experienced disease progression, with Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and treated with at least one cycle of Gemcitabine-based chemotherapy in second or further lines of treatment. We used descriptive statistics to characterize the study population and Cox proportional-hazards models to describe factors associated with survival. As an exploratory analysis, we compared the outcomes of patients treated with single-agent Gemcitabine with those of patients undergoing Gemcitabine-based polychemotherapy.

Results: The study population consisted of 42 patients. Median age was 59 years and 78.6% of patients presented ECOG 0–1. Thirty-three patients (78.6%) were treated with Gemcitabine-based chemotherapy in the second-line setting and 27 patients (64.3%) were treated with single-agent Gemcitabine. Objective response rate and disease control rate were 2.4% and 33.4%, respectively. Median progression-free survival (PFS) and median overall survival (OS) were 2.9 and 5.5 months, respectively. Six-month PFS and OS rates were 19.2% and 46.2%, respectively. We observed no significant difference in OS according to the type of Gemcitabine-based chemotherapy, despite numerically improved disease control rate and PFS for those treated with Gemcitabine-based polychemotherapy. In multivariate analysis, ECOG 2 (*vs.* ECOG 0–1) was the only factor significantly associated with inferior PFS and OS.

Conclusions: a subgroup of patients with MPA derives benefit from treatment with Gemcitabine-based regimens after FOLFIRINOX. There is a suggestion that Gemcitabine-based combinations, in particular Gemcitabine plus Nab-Paclitaxel, provide superior outcomes compared to single-agent Gemcitabine. Additionally, treatment in this setting should be offered carefully to patients with ECOG 2, as they present shorter survival and increased risk of toxicity.

Keywords: Metastatic; pancreatic; neoplasm; Gemcitabine; FOLFIRINOX

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Introduction

Advanced pancreatic adenocarcinoma still carries a dismal prognosis; less than 1% of patients are alive 5 years after the discovery of metastasis (1). Despite recent advances in cytotoxic chemotherapy in the first-line setting (2,3), virtually all patients experience disease progression when treated with FOLFIRINOX or Gemcitabine plus Nab-Paclitaxel. Hence, patients frequently need additional treatments to palliate symptoms and extend survival.

After single-agent Gemcitabine, only one randomized trial has properly compared survival outcomes of patients undergoing second-line treatment with those of patients not actively treated (4). In the CONKO-003, treatment with OFF (Oxaliplatin, 5-fluorouracil and folinic acid) was associated with increased overall survival (OS). Three additional randomized controlled trials have evaluated the role of polychemotherapy after Gemcitabine monotherapy, and two of them favored 5-fluorouracil-based combinations over single-agent 5-fluorouracil in this scenario (5-7). Thus, there is a shortage of prospective studies assessing the role of second-line treatment, especially that of Gemcitabine-based chemotherapy after disease progression on FOLFIRINOX (8).

Likewise, most data regarding the use of Gemcitabine-based chemotherapy after FOLFIRINOX stem from retrospective studies. They report response rates (RRs) ranging from 10% to 30% and median OS times ranging from 3.6 to 12.4 months (8-16). In these studies, patients treated with Gemcitabine plus Nab-Paclitaxel seemed to fare better than those treated with Gemcitabine monotherapy. However, such studies were performed in rather heterogeneous populations, including patients treated with FOLFIRINOX for locally advanced disease, and individuals who had FOLFIRINOX interrupted due to toxicity concerns—not experiencing disease progression. Consequently, further studies are needed to evaluate the potential benefits and harms of Gemcitabine-based chemotherapy in this setting.

Herein we report the results of a retrospective study including 42 patients with metastatic pancreatic adenocarcinoma (MPA) treated with Gemcitabine-based chemotherapy following disease progression on FOLFIRINOX. We aimed to assess the efficacy and the toxicity profile of Gemcitabine-based chemotherapy in this setting.

Methods

Design

This is a retrospective study carried out in a single cancer-specialized hospital in Brazil. It was based on routinely collected data retrieved from the electronic charts of patients with MPA submitted to Gemcitabine-based chemotherapy following disease progression on FOLFIRINOX. Data were collected from August 2017 to January 2018. This study was approved by the A.C. Camargo Cancer Center Internal Ethics Review Board (CAAE 88206718.7.0000.5432).

Patients

We included patients with the following characteristics: age ≥ 18 years, with pathologically confirmed diagnosis of MPA from January 1st 2010 to December 31th 2016 and disease progression on first-line FOLFIRINOX according to RECIST 1.1, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and treatment with at least one cycle of Gemcitabine-based chemotherapy in second or further lines of chemotherapy. Patients who underwent treatment outside A.C. Camargo Cancer Center were excluded.

Treatment

Patients were treated with FOLFIRINOX in the first-line setting, with either standard or attenuated doses. In further lines of treatment, Gemcitabine was used as single-agent or in combination. We considered patients as been treated with single-agent Gemcitabine when no other cytotoxic agent was used along with it at any time. Gemcitabine-based combination regimens included Gemcitabine plus Nab-Paclitaxel, Gemcitabine plus Cisplatin and GEMOX (gemcitabine plus Oxaliplatin). Gemcitabine monotherapy consisted of Gemcitabine IV 1,000 mg/m² on days 1, 8 and 15 of a 28-day cycle. Gemcitabine plus Nab-Paclitaxel consisted of Gemcitabine IV 1,000 mg/m² and Nab-Paclitaxel IV 125 mg/m² on days 1, 8 and 15 of a 28-day cycle. Gemcitabine + Cisplatin consisted of Gemcitabine 1,000 mg/m² IV and Cisplatin IV 35 mg/m² on days 1 and 8 of a 21-day cycle. GEMOX consisted of Gemcitabine IV 1,000 mg/m² and Oxaliplatin 100 mg/m² on days 1 and 15 of a 28-day cycle.

Procedures

Radiological tumor response data were retrieved from original radiological reports and there was no independent radiological imaging review. Assessment of tumor response was performed every 2 to 3 months using multi-detector computer tomography or magnetic resonance imaging. Biochemical tumor response was assessed according to changes in serum CA 19-9 after the beginning of Gemcitabine-based treatment. Such measurements took place every two to three months. Patients with baseline serum CA 19-9 ≤ 37 U/mL were considered to have a normal tumor marker level.

Predictor variables

We collected data on the following baseline patients' characteristics: age, gender, ECOG performance status, Age-Adjusted Charlson Comorbidity Score (AACCS), body mass index (BMI), tumor site (head/neck *vs.* body/tail), number of metastatic sites, serum CA 19-9 before the start of Gemcitabine-based chemotherapy (U/mL), neutrophil-to-lymphocyte ratio (NLR) before the start of Gemcitabine-based chemotherapy, use of prior adjuvant Gemcitabine, number of previous lines of treatment for metastatic disease, duration of progression-free survival (PFS) interval (according to RECIST 1.1) while on FOLFIRINOX in the first-line setting, time interval from the last cycle of FOLFIRINOX to start of Gemcitabine-based chemotherapy, type of Gemcitabine-based chemotherapy, and deployment of granulocyte colony stimulating factors (G-CSF) during Gemcitabine-based chemotherapy. Patients for whom performance status data were not available had their performance inferred from the descriptions of patients' capabilities found in the medical records. We also collected information regarding additional lines of treatment after failure of Gemcitabine-based chemotherapy, including the number of further lines of treatment and the chemotherapy regimens used.

Outcome variables

The co-primary outcomes of the study were the OS and the PFS of patients diagnosed with MPA and treated with Gemcitabine-based chemotherapy after progression on first-line FOLFIRINOX. As secondary outcomes, we assessed the radiological RR and the disease control rate (DCR) according to RECIST 1.1, the biochemical RR

using the changes in CA 19-9 levels, and the toxicity profile. We assessed OS from the start of FOLFIRINOX (OS1) and from the start of Gemcitabine-based chemotherapy (OS2). OS was defined as the time from start of treatment (either FOLFIRINOX or Gemcitabine-based chemotherapy) to death from any cause. PFS was defined as the time from start of Gemcitabine-based chemotherapy to disease progression according to RECIST 1.1 or death (whatever occurred first). Patients were censored at the last follow-up visit in the absence of an event. DCR was defined as the proportion of patients experiencing objective response or stable disease at the first tumor response evaluation. We defined biochemical response as at least a 50% reduction in CA 19-9 level from baseline. Patients with normal levels of serum tumor markers at diagnosis were considered ineligible for this analysis. Toxicity was graded according to the Common Toxicity Criteria for Adverse Events version 4.0. The safety analysis included the assessment of treatment delays (any delay), need for dose reduction during treatment, treatment discontinuation (and its reasons), severe treatment-related toxicity (treatment-related complication mandating hospital admission) and treatment-related mortality. As an exploratory analysis, we compared the outcomes of patients treated with single-agent Gemcitabine with those of patients undergoing Gemcitabine-based polychemotherapy.

Statistical analysis

We used absolute values and ratios to describe the distribution of categorical variables and Fisher's exact test to compare the distributions of such variables. We used median values and the interquartile ranges (IQR) to describe the distribution of numerical variables. We generated curves to describe time-to-event variables (OS and PFS) according to the Kaplan-Meier method. Survival curves were compared using the log-rank test. We used Cox proportional-hazard model to performed univariate analysis of OS and PFS. We selected variables with P value < 0.25 in the univariate analysis for the multivariate model. As baseline NLR and serum CA 19-9 showed right-skewed distributions, for didactic purposes, we transformed these variables to the logarithmic base (Log_{10}) in the regression model. Also, due to the relatively modest sample size, we used ECOG performance status (0–1 *vs.* 2) and number of previous lines of treatment (1 *vs.* ≥ 2) as dichotomous variables. We considered two-tailed P values < 0.05 as statistically significant. Statistical analysis was performed

Table 1 Characteristics of the study population

| Characteristics | Gemcitabine-based chemotherapy (N=42) | Gemcitabine monotherapy (N=27) | Gemcitabine-based combination (N=15) |
|---|---------------------------------------|--------------------------------|--------------------------------------|
| Age, median (IQR) (years) | 59.0 (53.0–64.0) | 58.0 (53.0–60.5) | 62.0 (53.0–66.5) |
| Sex, n (%) | | | |
| Male | 25 (59.5) | 15 (55.6) | 10 (66.7) |
| Female | 17 (40.5) | 12 (44.4) | 5 (33.3) |
| ECOG, n (%) | | | |
| 0 | 8 (19.0) | 5 (18.5) | 3 (20.0) |
| 1 | 25 (59.5) | 14 (51.9) | 11 (73.3) |
| 2 | 9 (21.4) | 8 (29.6) | 1 (6.7) |
| AACCS, median [IQR] | 8 [7–8] | 8 [7–8] | 8 [7–8.5] |
| BMI, median (IQR) (kg/m ²) | 23.3 (19.8–27.0) | 23.3 (19.8–26.7) | 23.2 (21.2–30.5) |
| Tumor site, n (%) | | | |
| Head/neck | 15 (35.7) | 10 (37.0) | 5 (33.3) |
| Body/tail | 27 (64.3) | 17 (63.0) | 10 (66.7) |
| Number of metastatic sites, median [IQR] | 2 [1–3] | 2 [1–3] | 2 [1–3] |
| CA 19-9, median (IQR) (U/mL) | 997.0 (218.1–3,177.0) | 510.0 (166.0–3,328.0) | 1,289.0 (467.0–2,623.0) |
| Neutrophil-to-lymphocyte ratio, median (IQR) | 4.0 (2.1–5.8) | 2.6 (1.6–4.5) | 4.3 (3.5–6.5) |
| Prior adjuvant gemcitabine, n (%) | | | |
| Yes | 2 (4.8) | 2 (7.4) | 0 (0.0) |
| No | 40 (95.2) | 25 (92.6) | 15 (100.0) |
| Previous lines of treatment, n (%) | | | |
| 1 | 33 (78.6) | 21 (77.8) | 12 (80.0) |
| 2 | 8 (19.0) | 5 (18.5) | 3 (20.0) |
| 3 | 1 (2.4) | 1 (3.7) | 0 (0.0) |
| Duration of progression-free survival under FOLFIRINOX, median (IQR) (months) | 8.1 (4.2–10.2) | 8.5 (4.4–10.2) | 6.5 (3.7–9.7) |

with the software R Project version 3.4.0.

Results

Overall, 104 patients with MPA underwent treatment with FOLFIRINOX in the first-line setting in our institution. We identified 59 patients who received Gemcitabine-based chemotherapy after FOLFIRINOX. Seventeen patients were excluded for the following reasons: ECOG ≥ 3 (11 patients), no progression on FOLFIRINOX according to RECIST 1.1 (two patients) and treatment outside A.C.

Camargo Cancer Center (four patients). As a result, 42 patients constitute the study population.

Table 1 depicts patients' characteristics at the start of Gemcitabine-based chemotherapy. Median age was 59.0 years (IQR: 53.0–64.0). Twenty-five (59.5%) patients were male and most patients presented ECOG 0 (N=8; 19.0%) or ECOG 1 (N=21; 59.5%). Most primary tumors were located in the body or tail of the pancreas (N=27; 64.3%). The median CA 19-9 level was 997.0 U/mL (IQR: 218.1–3,177.0) and the median NLR was 4.0 (IQR: 2.1–5.8). Most patients (N=33; 78.6%) had Gemcitabine-based

Table 2 Radiological and biochemical response to Gemcitabine based-chemotherapy

| Response | Gemcitabine-based chemotherapy (N=42), n (%) | Gemcitabine monotherapy (N=27), n (%) | Gemcitabine-based combination (N=15), n (%) |
|----------------------------|--|---------------------------------------|---|
| RECIST 1.1 | | | |
| Objective response | 1 (2.4) | 0 (0.0) | 1 (6.7) |
| Complete response | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Partial response | 1 (2.4) | 0 (0.0) | 1 (6.7) |
| Stable disease | 13 (31.0) | 7 (25.9) | 6 (40.0) |
| Progressive disease | 22 (52.4) | 16 (59.3) | 6 (40.0) |
| Not available | 6 (14.3) | 4 (14.8) | 2 (13.3) |
| CA 19-9[§] | | | |
| Response [#] | 5 (11.9) | 3 (11.1) | 2 (13.3) |
| No response | 20 (47.6) | 11 (40.7) | 9 (60.0) |
| Do not express CA 19-9 (%) | 6 (14.3) | 4 (14.8) | 2 (13.3) |
| Not available | 11 (26.2) | 9 (33.3) | 2 (13.3) |

[§], normal CA 19-9 defined as ≤ 37 U/mL; [#], response defined as $\geq 50\%$ reduction from baseline.

chemotherapy as second-line treatment.

Treatments

In the first-line setting, patients were treated with FOLFIRINOX for a median of 12.0 cycles (IQR: 8.2–16.0 cycles). Median PFS under FOLFIRINOX treatment was 8.1 months (IQR: 4.2–10.2 months). All patients discontinued FOLFIRINOX due to radiological disease progression according to RECIST 1.1. The median time between the last cycle of FOLFIRINOX and the start of Gemcitabine-based chemotherapy was 1.2 months (IQR: 0.8–2.8 months).

Among 42 patients treated with Gemcitabine-based chemotherapy, 27 received treatment with single-agent Gemcitabine and 15 underwent treatment with Gemcitabine-based polychemotherapy. In the second group, eight patients were treated with Gemcitabine plus Nab-Paclitaxel, five patients with Gemcitabine plus Cisplatin and two patients with GEMOX. Overall, patients were submitted to a median of 3 cycles of chemotherapy (IQR: 3–4 cycles). The median number of cycles of single-agent Gemcitabine was 3 (IQR: 2.5–3). Conversely, individuals submitted to polychemotherapy underwent a median of 4 cycles of treatment (IQR: 3–6 cycles). Seven patients (16.7%) received decreased doses of chemotherapy from

the start (14.8% for single-agent Gemcitabine *vs.* 20% for Gemcitabine-based combinations). Primary prophylaxis with G-CSF was not used by any patient. During the time span of the study, Nab-Paclitaxel was not promptly available in Brazil as this medication had to be imported. As a consequence, after progression on FOLFIRINOX, patients swiftly started treatment with Gemcitabine and Nab-Paclitaxel was incorporated without tumor progression after a median 31.5 days from the start of Gemcitabine (IQR: 21.0–46.2 days).

RR and DCR

Table 2 illustrates radiological and biochemical responses to Gemcitabine-based chemotherapy. Among 42 patients, only one patient (2.4%) experienced partial response according to RECIST 1.1. This patient was treated in second-line setting with Gemcitabine plus Nab-Paclitaxel after treatment with FOLFIRINOX for 2.2 months. DCR for all patients was 33.4%. Patients undergoing Gemcitabine-based polychemotherapy presented numerically higher DCR (46.7% *vs.* 25.9%; $P=0.19$). Besides, the attainment of disease control at the first radiological response assessment was associated with increased OS [hazard ratio (HR) =0.28; 95% CI, 0.12–0.64; $P=0.002$].

Five patients (11.9%) showed biochemical response

to treatment. There was no significant difference in the percentage of patients achieving biochemical response according to the type of Gemcitabine-based chemotherapy (single-agent *vs.* combination; $P=1.00$).

Survival outcomes and prognostic factors

Median follow-up time was 20.8 months and four patients were lost to follow-up. At last follow-up, 40 patients (95.2%) had Gemcitabine-based chemotherapy permanently interrupted. Treatment was discontinued due to disease progression in 32 patients, due to clinical deterioration in five patients and due to limiting toxicity in three patients. Thirty-nine patients experienced death or disease progression. Median PFS from the start of Gemcitabine-based chemotherapy was 2.9 months (95% CI, 2.5–4.1 months) (Figure 1A). PFS rates at 3 and 6 months were 48.6% and 19.2%, respectively. At last follow-up, 35 patients were dead. Median OS from the start of Gemcitabine-based chemotherapy (OS2) was 5.5 months (95% CI, 3.8–7.3 months) (Figure 1B). OS rates at 6 and 12 months were 46.2% and 12.3%, respectively. Median OS from the start of FOLFIRINOX in the first-line setting (OS1) was 14.6 months (95% CI, 12.0–16.3 months). OS rates from the start of first-line chemotherapy at 12 and 18 months were 68.2% and 28.6%, respectively.

In the multivariate model, ECOG performance status was the only variable independently associated with PFS (ECOG 2: HR =2.97; 95% CI, 1.22–7.22; $P=0.01$) (Table 3). Indeed, median PFS for patients with ECOG 0–1 at start of Gemcitabine-based chemotherapy was 3.2 months (95% CI, 2.7–4.7 months), while patients with ECOG 2 presented median PFS of 1.9 months (95% CI, 0.4–NA months) (Figure 2A). For OS, again, ECOG performance status was the only independent prognostic factor (ECOG 2: HR =5.98; 95% CI: 1.87–19.0; $P=0.002$) (Table 4). Median OS for patients with ECOG 0–1 at the start of Gemcitabine was 7.1 months (95% CI, 4.6–8.7 months) and 2.2 months (95% CI, 0.4–NA months) for those with ECOG 2 (Figure 2B).

There were no statistically significant differences in OS or PFS according to the type of Gemcitabine-based chemotherapy performed (single-agents *vs.* combination) in multivariate analysis. We also compared survival outcomes of patients treated with single-agent Gemcitabine to those of patients treated with Gemcitabine plus Nab-Paclitaxel. Again, we did not observe statistically significant differences in PFS (HR =0.58, 95% CI, 0.25–1.31; $P=0.19$) or OS

(HR =0.96, 95% CI, 0.38–2.40).

Toxicity

Table 5 describes the toxicity profile of Gemcitabine-based chemotherapy. Grade 3–5 toxicities were observed in 47.6% of patients. Figures were higher for patients undergoing treatment with polychemotherapy (66.7% *vs.* 37.0%; $P=0.10$). The most important grade 3–5 non-hematological toxicities were fatigue (14.3%) and decreased appetite (19.0%). The hematological toxicity was mild, with less than 10% incidence of grade 3–5 toxicities, except for thrombocytopenia (11.9%). Thirty-six patients (85.7%) experienced treatment delays and 19 patients (45.2%) needed chemotherapy dose reductions during the course of treatment. Severe toxicities were observed in seven patients (16.7%) and there were no treatment-related deaths.

Further treatments

Table 6 describes the additional treatments undertaken after Gemcitabine failure. Fifteen patients (35.7%) were submitted to further treatments. Numerically, more patients treated with single-agent Gemcitabine underwent additional treatments (44.4% *vs.* 20.0%; $P=0.18$). The most commonly used regimen following progression on Gemcitabine was paclitaxel monotherapy.

Discussion

Chemotherapy plays an important role in the treatment of MPA, providing symptom palliation and benefits in OS (17). So far, the most encouraging results in the first-line setting have been achieved using the FOLFIRINOX regimen. In the pivotal ACCORD 11/PRODIGE 4 trial (2), the median OS for those treated with FOLFIRINOX was 11.1 months, and in a recently presented randomized phase II trial (SWOG S-1313) evaluating the role of recombinant human hyaluronidase, patients treated with modified FOLFIRINOX presented a median OS of 14.4 months. That is the longest survival ever reported for patients with MPA in a randomized clinical trial.

Nevertheless, virtually all patients treated with FOLFIRINOX will experience disease progression, and evaluation of the potential benefits and harms of further treatments is paramount. After Gemcitabine monotherapy, second-line treatments based on 5-fluorouracil have been established as standards of care for those with adequate

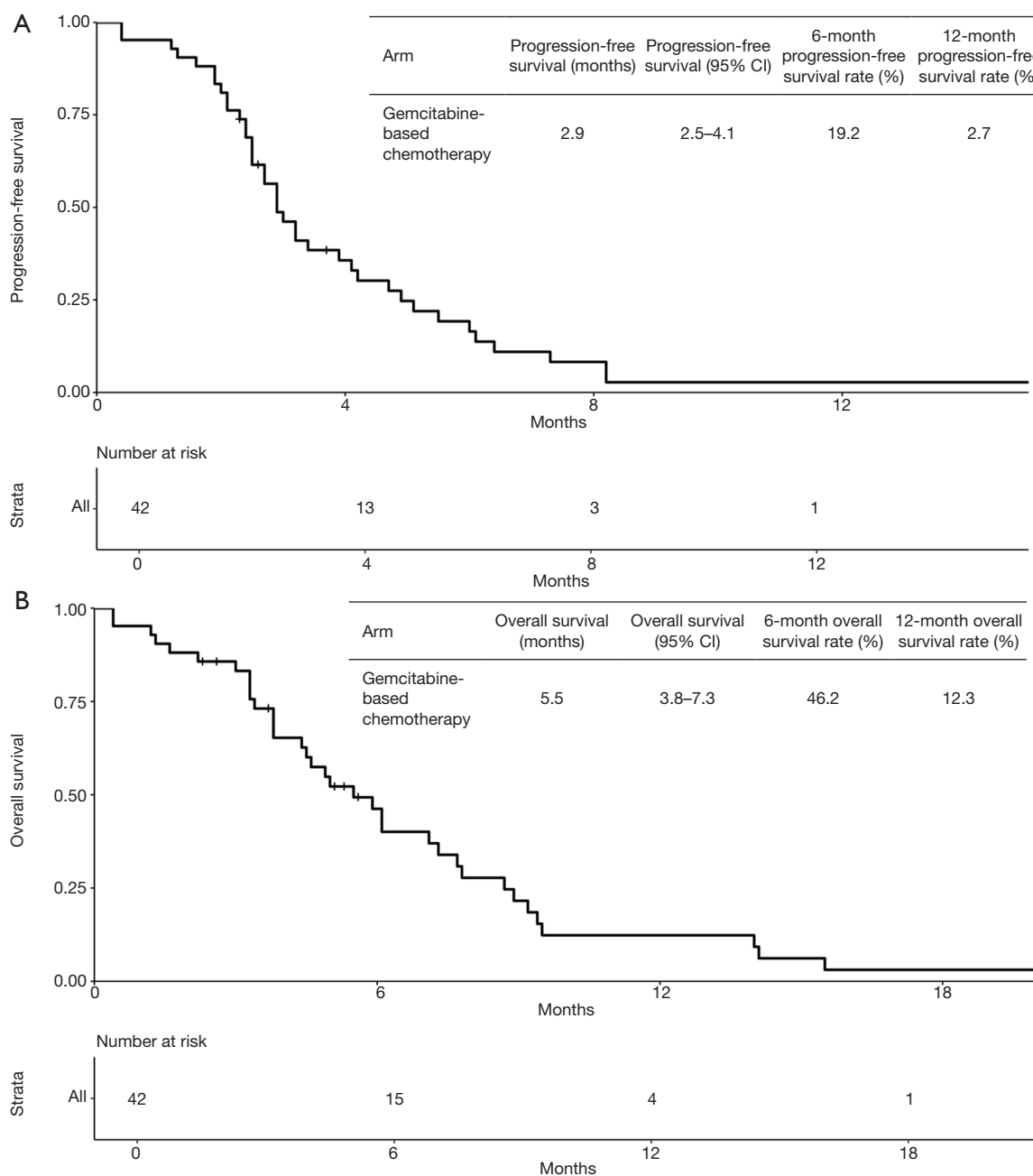


Figure 1 Progression-free survival (A) and overall survival (B) of patients with metastatic pancreatic adenocarcinoma treated with Gemcitabine-based chemotherapy after disease progression on FOLFIRINOX.

performance status based in randomized phase III trials (4-7). However, there are no randomized trials evaluating the role of additional lines of treatment following FOLFIRINOX. Recently, researchers have made significant progress in the understanding of the molecular mechanisms

underlying the pathogenesis of pancreatic cancer and impressive results were seen in subgroups of patients treated with Immunotherapy (18), NTKR inhibitors (19) and PARP inhibitors (20). Nevertheless, only a very small number of patients derive benefit from such targeted strategies and

Table 3 Prognostic factors for progression-free survival

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---------------------|-----------|---------|-----------------------|-----------|---------|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Age | 1.01 | 0.96–1.05 | 0.74 | – | – | – |
| Sex | | | | – | – | – |
| Male | 1 | – | – | | | |
| Female | 1.28 | 0.66–2.46 | 0.45 | | | |
| ECOG | | | | | | |
| 0–1 | 1 | – | – | 1 | – | – |
| 2 | 3.43 | 1.49–7.89 | 0.003 | 2.97 | 1.22–7.22 | 0.01 |
| AACCS | 1.01 | 0.72–1.40 | 0.94 | – | – | – |
| BMI | 0.98 | 0.92–1.05 | 0.74 | – | – | – |
| Tumor site | | | | – | – | – |
| Head/neck | 1 | – | – | | | |
| Body/tail | 1.46 | 0.74–2.88 | 0.26 | | | |
| Number of metastatic sites | 1.09 | 0.79–1.52 | 0.57 | – | – | – |
| Log ₁₀ (CA 19-9) (U/mL) | 1.01 | 0.71–1.44 | 0.93 | – | – | – |
| Log ₁₀ (neutrophil-to-lymphocyte ratio) | 1.64 | 0.47–5.67 | 0.42 | – | – | – |
| Previous lines of treatment | | | | – | – | – |
| 1 | 1 | – | – | | | |
| ≥2 | 0.96 | 0.44–2.11 | 0.92 | | | |
| Type Gemcitabine-based chemotherapy | | | | | | |
| Gemcitabine (monotherapy) | 1 | – | – | 1 | – | – |
| Gemcitabine (combination) | 0.58 | 0.30–1.14 | 0.11 | 0.73 | 0.35–1.50 | 0.40 |
| Progression-free survival under FOLFIRINOX (months) | 0.99 | 0.93–1.05 | 0.87 | – | – | – |

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; BMI, body mass index.

this highlights the necessity to further explore the role of available chemotherapeutic agents in MPA after disease progression on FOLFIRINOX.

In our study, despite the low objective RR, a significant proportion of patients experienced disease control when treated with Gemcitabine-based chemotherapy. Other studies have shown similar results with RRs ranging from 10% to 30% and DCRs ranging from 26% to 60% (8,10-16,21). We also showed that at 6 months, nearly 20% of patients treated with Gemcitabine-based chemotherapy are progression-free. Accordingly, other studies have shown PFS rates at 6 months ranging from 16% to 83% (8,15,21). That said, a

subgroup of patients definitely benefits from Gemcitabine-based chemotherapy following disease progression on FOLFIRINOX.

Despite these results, chemotherapy clearly does not aid all patients and some might even experience significant treatment-related toxicities. Thus, patient selection is crucial in deciding whether or not to provide these patients further cytotoxic treatments. In this regard, we showed that performance status is an extremely important factor to bear in mind. Patients with ECOG performance status 2 had a median OS of only 2.2 months, significantly shorter than the median OS of those with ECOG performance

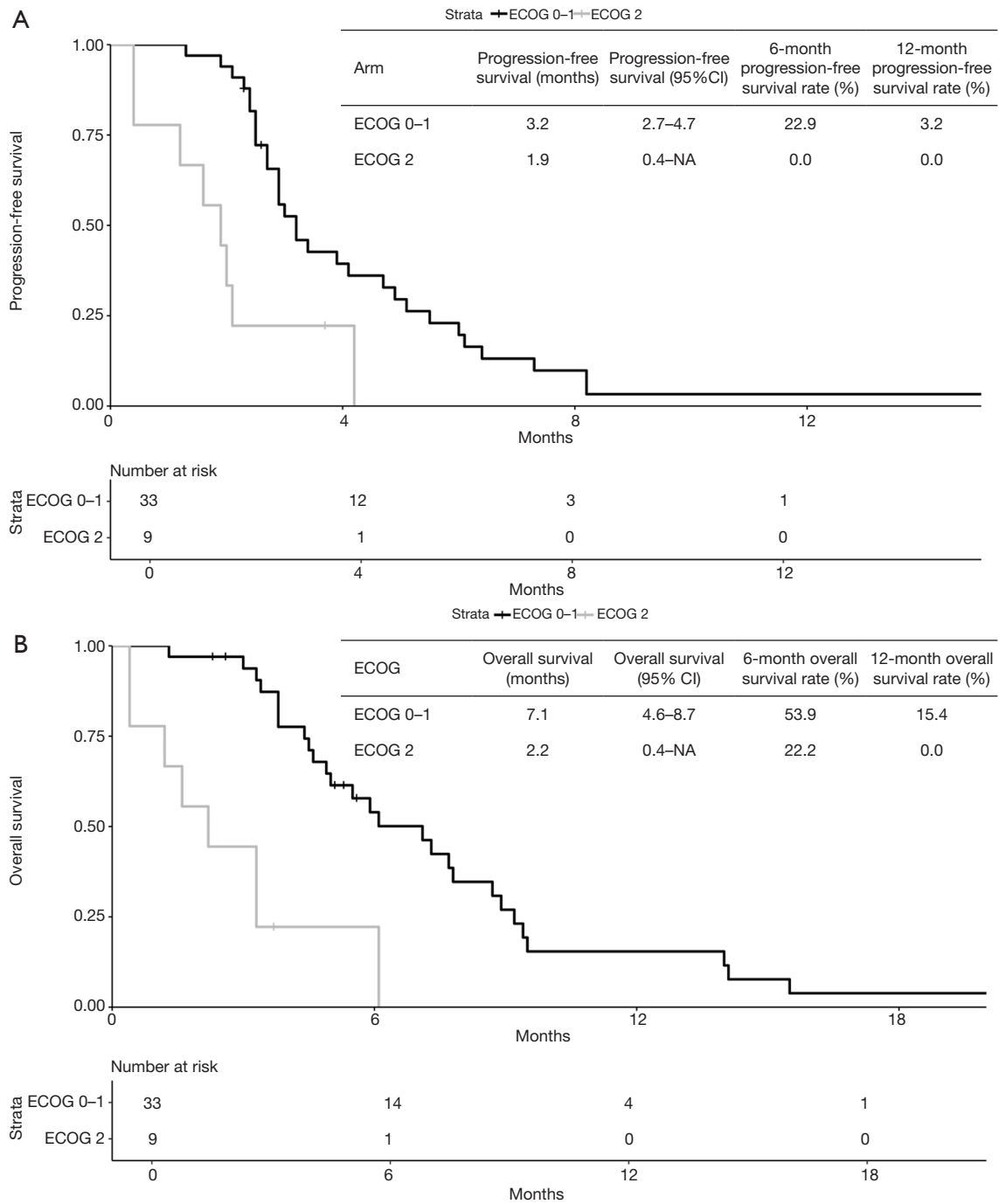


Figure 2 Progression-free survival (A) and overall survival (B) of patients with metastatic pancreatic adenocarcinoma treated with Gemcitabine-based chemotherapy after progression on FOLFIRINOX according to ECOG performance status at the start of Gemcitabine-based treatment (ECOG 0-1 vs. ECOG 2). P=0.001 for progression-free survival and P<0.001 for overall survival. ECOG, Eastern Cooperative Oncology Group.

Table 4 Prognostic factors for overall survival

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---------------------|------------|---------|-----------------------|------------|---------|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Age | 0.99 | 0.95–1.04 | 0.93 | – | – | – |
| Sex | | | | – | – | – |
| Male | 1 | – | – | | | |
| Female | 1.34 | 0.65–2.74 | 0.41 | | | |
| ECOG | | | | | | |
| 0–1 | 1 | – | – | 1 | – | – |
| 2 | 6.07 | 2.46–14.90 | <0.001 | 5.98 | 1.87–19.00 | 0.002 |
| AACCS | 1.05 | 0.72–1.53 | 0.76 | – | – | – |
| BMI | 0.99 | 0.92–1.06 | 0.85 | – | – | – |
| Tumor site | | | | – | – | – |
| Head/neck | 1 | – | – | | | |
| Body/tail | 0.85 | 0.43–1.70 | 0.66 | | | |
| Number of metastatic sites | 1.29 | 0.88–1.87 | 0.18 | 0.87 | 0.54–1.42 | 0.59 |
| Log ₁₀ (CA 19-9) (U/mL) | 0.86 | 0.56–1.32 | 0.49 | – | – | – |
| Log ₁₀ (neutrophil-to-lymphocyte ratio) | 3.42 | 0.90–12.9 | 0.06 | 1.73 | 0.30–9.95 | 0.53 |
| Previous lines of treatment | | | | – | – | – |
| 1 | 1 | – | – | | | |
| ≥2 | 1.26 | 0.56–2.84 | 0.56 | | | |
| Type Gemcitabine-based chemotherapy | | | | – | – | – |
| Gemcitabine (monotherapy) | 1 | – | – | | | |
| Gemcitabine (combination) | 1.17 | 0.56–2.42 | 0.66 | | | |
| Progression-free survival under FOLFIRINOX (months) | 0.96 | 0.90–1.03 | 0.27 | – | – | – |

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; BMI, body mass index.

status 0–1 (7.1 months). Other studies assessing the role of Gemcitabine-based chemotherapy in the second-line setting after FOLFIRINOX (21) or after other chemotherapeutic regimens (22,23) have also demonstrated the importance of using patients' performance status to weight out potential benefits of chemotherapy. Moreover, in a recent large study evaluating factors associated with improved survival in the second-line treatment for advanced pancreatic adenocarcinoma, performance status proved to be the single most important factor predicting outcome (23). As a result, before deciding to offer patients further treatment after progression on FOLFIRINOX, a meticulous evaluation of

patients' clinical status must be performed.

Some studies have shown that other factors can predict benefits from Gemcitabine-based chemotherapy after FOLFIRINOX. In special, it has been suggested early progression on FOLFIRINOX is a harbinger of greater efficacy during second-line Gemcitabine-based chemotherapy (8,11,13). In our study, we could not replicate this finding, perhaps due to the modest sample size. But interestingly, the sole patient presenting radiological response to chemotherapy was one treated with Gemcitabine plus Nab-Paclitaxel after experiencing disease progression only 2.2 months after the start of

Table 5 Grade 3 or higher toxicity with Gemcitabine-based chemotherapy

| Toxicity | Gemcitabine-based chemotherapy (grade ≥ 3) (N=42), n (%) | Gemcitabine monotherapy (grade ≥ 3) (N=27), n (%) | Gemcitabine-based combination (grade ≥ 3) (N=15), n (%) |
|-----------------------------|---|--|--|
| Any toxicity grade ≥ 3 | 20 (47.6) | 10 (37.0) | 10 (66.7) |
| Non-hematologic toxicity | | | |
| Nausea | 1 (2.4) | 0 (0.0) | 1 (6.7) |
| Vomiting | 1 (2.4) | 0 (0.0) | 1 (6.7) |
| Constipation | 3 (7.1) | 2 (7.4) | 1 (6.7) |
| Diarrhea | 1 (2.4) | 0 (0.0) | 1 (6.7) |
| Mucositis | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Fatigue | 6 (14.3) | 2 (7.4) | 4 (26.7) |
| Decreased appetite | 8 (19.0) | 4 (14.8) | 4 (26.7) |
| Hematologic toxicity | | | |
| Anemia | 4 (9.5) | 1 (3.7) | 3 (20.0) |
| Leukopenia | 1 (2.4) | 0 (0.0) | 1 (6.7) |
| Neutropenia | 4 (9.5) | 3 (11.1) | 1 (6.7) |
| Thrombocytopenia | 5 (11.9) | 2 (7.4) | 3 (20.0) |
| Febrile neutropenia | 1 (2.4) | 0 (0.0) | 1 (6.7) |
| Treatment delay | 36 (85.7) | 23 (85.2) | 13 (86.7) |
| Dose reduction | 19 (45.2) | 11 (40.7) | 8 (53.3) |
| Severe toxicity | 7 (16.7) | 2 (7.4) | 5 (33.3) |
| Treatment mortality | 0 (0.0) | 0 (0.0) | 0 (0.0) |

FOLFIRINOX. Components of FOLFIRINOX and Gemcitabine (and Nab-Paclitaxel) present different mechanisms of action, theoretically rendering them non-cross-resistant. These data strengthen the role of Gemcitabine-based chemotherapy after early disease progression on FOLFIRINOX. However, care must be taken in interpreting the results of studies assessing the relationship between the duration of disease control with FOLFIRINOX and subsequently with Gemcitabine-based chemotherapy as some results are not statistically significant (described as trends) and large retrospective studies have not shown a significant correlation between these two outcomes (23).

Another way to assist in selecting patients for further treatment could rely on the molecular characteristics of the tumor. The expression of the human equilibrative nucleoside transporter-1 (hENT1) as assessed by immunohistochemistry has been shown to predict the

benefit of adjuvant Gemcitabine after pancreatic cancer resection (24). Nonetheless, the results of studies assessing its role in the metastatic setting have been disappointing, as they have found poor correlation between hENT immunohistochemical expression and benefits from Gemcitabine (25,26). The lack of predictive capability may be associated with the use of different antibodies (27) and may be circumvented by deploying other techniques, such as RT-PCR (28). Moreover, recent data point to increased anti-cancer activity of Gemcitabine plus Nab-Paclitaxel in patients with tumors lacking class III β -tubulin as assessed by immunohistochemistry (29). These data pave the way to an optimal approach to select patients for Gemcitabine-based chemotherapy based on molecular features of the tumors and additional research is needed to fully describe the role of these and other potential markers of treatment efficacy.

After patients failing treatment with FOLFIRINOX

Table 6 Treatment regimens after Gemcitabine-based chemotherapy

| Treatment characteristic | Gemcitabine-based chemotherapy (N=42) | Gemcitabine monotherapy (N=27) | Gemcitabine-based combination (N=15) |
|----------------------------|---------------------------------------|--------------------------------|--------------------------------------|
| Further treatment, n (%) | | | |
| Yes | 15 (35.7) | 12 (44.4) | 3 (20.0) |
| No | 27 (64.3) | 15 (55.6) | 12 (80.0) |
| Lines of further treatment | | | |
| Median | 0 | 0 | 0 |
| Range | 0–2 | 0–2 | 0–1 |
| Type of treatment, n (%) | | | |
| Paclitaxel | 6 (14.3) | 5 (18.5) | 1 (6.7) |
| Nab-Paclitaxel | 1 (2.4) | 1 (3.7) | 0 (0.0) |
| Capecitabine | 2 (4.8) | 2 (7.4) | 0 (0.0) |
| FOLFOX | 2 (4.8) | 2 (7.4) | 0 (0.0) |
| FOLFIRI | 3 (7.1) | 2 (7.4) | 1 (6.7) |
| FOLFIRINOX | 2 (4.8) | 2 (7.4) | 0 (0.0) |
| CDDP + Gemcitabine | 2 (4.8) | 1 (3.7) | 1 (6.7) |
| Others | 1 (2.4) | 1 (3.7) | 0 (0.0) |

have been properly selected to undergo Gemcitabine-based chemotherapy, there remains a doubt regarding the optimal regimen to be used. In our study, there was no significant difference in OS based on the type of Gemcitabine-based chemotherapy used (single-agent *vs.* polychemotherapy). Nevertheless, in the univariate analysis of PFS, there was a suggestion that polychemotherapy may achieve better results than single-agent Gemcitabine. Additionally, disease control ratio was numerically higher in patients treated with Gemcitabine-based combinations. Retrospective series evaluating the activity of single-agent Gemcitabine have shown objective RRs around 10.0% and DCRs ranging from 26.0% to 40.0% (10,11,21). These figures seem lower than the ones found in retrospective studies of Gemcitabine-based combos, especially those including Nab-Paclitaxel. Retrospective studies assessing the activity of Gemcitabine plus Nab-Paclitaxel after FOLFIRINOX have demonstrated RRs up to 30% and DCRs up to 60% (8,12,13,15,16).

Survival results also seem to be superior using Gemcitabine plus Nab-Paclitaxel. This combination has yielded median PFS times between 2.8 and 5.1 months and median OS times between 5.7 and 12.4 months

(8,12,13,15,16). Also, the longest median OS attained so far in MPA (18 months) was seen in an observational study in which patients were treated sequentially with FOLFIRINOX and Gemcitabine plus Nab-Paclitaxel (8). These data, along with the increased activity of Gemcitabine plus Nab-Paclitaxel shown in the first-line setting (30), set this combination as a valuable option for those progressing on FOLFIRINOX.

Nonetheless, polychemotherapy is associated with increased toxicity. In our study, combined regimens presented increased incidence of severe side-effects. This is in line with the findings of randomized trials evaluating Gemcitabine-based combinations in the first-line setting (2,30) and with retrospective analyses showing that, after FOLFIRINOX, Gemcitabine plus Nab-Paclitaxel is associated with higher rates of grades 3–5 adverse events than single-agent Gemcitabine (13,21). Thus, the improved activity of this regimens comes at the expense of increased toxicity and this information is paramount when choosing chemotherapy regimens for those with worse clinical conditions, as they are prone to more severe toxicities.

Our study presents limitations. It is a retrospective study with a relatively modest sample size. Also, patients treated

with Gemcitabine plus Nab-Paclitaxel presented at least some delay in starting Nab-Paclitaxel, possibly hampering outcomes in these patients. Nonetheless, our study portrays the outcomes of a homogenous cohort of patients treated in a single center, with detailed information. We believe our study adds significant information to the current knowledge, especially regarding the importance of performance status in selecting patients for second-line treatment after FOLFIRINOX and the benefits and harms of combination chemotherapy in this setting.

To summarize, some patients with MPA derive significant benefit from treatment with Gemcitabine-based chemotherapy following progression on FOLFIRINOX. Numerically, the benefit seems to be greatest using Gemcitabine-based polychemotherapy. Nevertheless, care should be taken when treating patients with combined regimens as there is an increased risk of toxicity. In this regard, we should use performance status to aid in treatment selection. Patients with ECOG performance 2 present short survival times in this setting. Were these patients to be treated, due to their limited survival outcomes and putatively increased risk of toxicity, we favor single-agent Gemcitabine over polychemotherapy.

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Footnote

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

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