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Second-line Modified GTX versus Gemcitabine-Nab-Paclitaxel (GmAb) Following First-Line FOLFIRINOX in Advanced Pancreatic Cancer: A Retrospective Analysis at the American University of Beirut Medical Center (AUBMC)

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Abstract

Background: Pancreatic cancer is characterized by its generally poor prognosis and ranks seventh worldwide in cancer-related mortality. We previously conducted a prospective study on the use of modified GTX regimen (a combination of gemcitabine, docetaxel, and capecitabine), which has appreciable activity and is well-tolerated, in this setting. We compared the efficacy of GTX regimen versus Gemcitabine-nab-paclitaxel (GmAb) as second-line chemotherapy in advanced pancreatic cancer patients receiving first-line therapy with FOLFIRINOX.

Method: This retrospective chart review aimed to collect and record data corresponding to patients diagnosed with advanced pancreatic cancer at the American University of Beirut Medical Center who received FOLFIRINOX as first-line chemotherapy and who then had GTX or GmAb as second-line treatment between 2013 and 2019. We measured the progression-free survival, overall survival, and toxicity of GTX versus GmAb as second-line treatment for pancreatic adenocarcinoma at AUBMC.

Results: The median overall survival for the GmAb group was around 52 months, which is greater than that of the GTX group, which was 25 months. 26.7% of patients who received GTX required dose reduction starting from cycle one, while only 3.1% of those who received GmAb required dose reduction from cycle one. 38.7% of patients who received GmAb did not have anemia throughout the course of treatment, while the majority of patients who received GTX, 93.3%, had grade I anemia.

Conclusion: Our data show that GmAb is a possibly better second-line treatment option than GTX with better tolerance to the dose, less anemia, and a better survival profile. More studies are needed with a larger sample size and a prospective design to prove such a possible difference between the two regimens.

Keywords: Gemcitabine, FOLFIRINOX, Pancreatic neoplasms, Second-line chemotherapy

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Introduction

Pancreatic cancer is characterized by a generally poor prognosis and ranks seventh worldwide in cancer-related mortality. It accounts for about 3% of all cancers in the US and Europe and about 7% of all cancer deaths.[1, 2] While surgical resection represents the best curative management approach, only 10% of patients are resectable at diagnosis, and the remaining either have metastatic disease (50%) or locally advanced disease (30%).[1-3] Despite surgical resection, the 5-year overall survival (OS) remains limited to around 20%, and 30% of patients tend to develop early recurrence, with the majority eventually relapsing.[2] Moreover, induction chemotherapy followed by radiation therapy is the recommended first-line approach for locally advanced unresectable disease. The preferred regimens for pancreatic cancer remain FOLFIRINOX or gemcitabine and nab-paclitaxel.[4] However, there are almost no prospective studies regarding second-line regimens. As such, there is no consensus regarding a standard approach in the second-line setting for advanced pancreatic cancer.

Specifically, there is a paucity of studies that explore the possible regimens following the use of fluoropyrimidine-based regimens. This is of particular importance with the increasing use of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) in the first-line setting. There is considerable interest in the choice of second-line chemotherapy, especially gemcitabine-containing regimens. We have previously conducted a prospective study on the use of the modified GTX regimen (a combination of gemcitabine, docetaxel, and capecitabine), which has appreciable activity and is well-tolerated in this setting.[5,6]

Here, we compared the efficacy of the GTX regimen versus gemcitabine-nab-paclitaxel (GmAb) as second-line chemotherapy in advanced pancreatic cancer patients receiving first-line therapy with FOLFIRINOX.

Aim and hypothesis

Our aim was to compare the use of the GTX regimen and GmAb as second-line chemotherapy in patients with advanced pancreatic cancer. We hypothesized that comparing the use of GTX or GmAb as second-line chemotherapy in advanced pancreatic cancer patients could guide treatment choice in this setting.

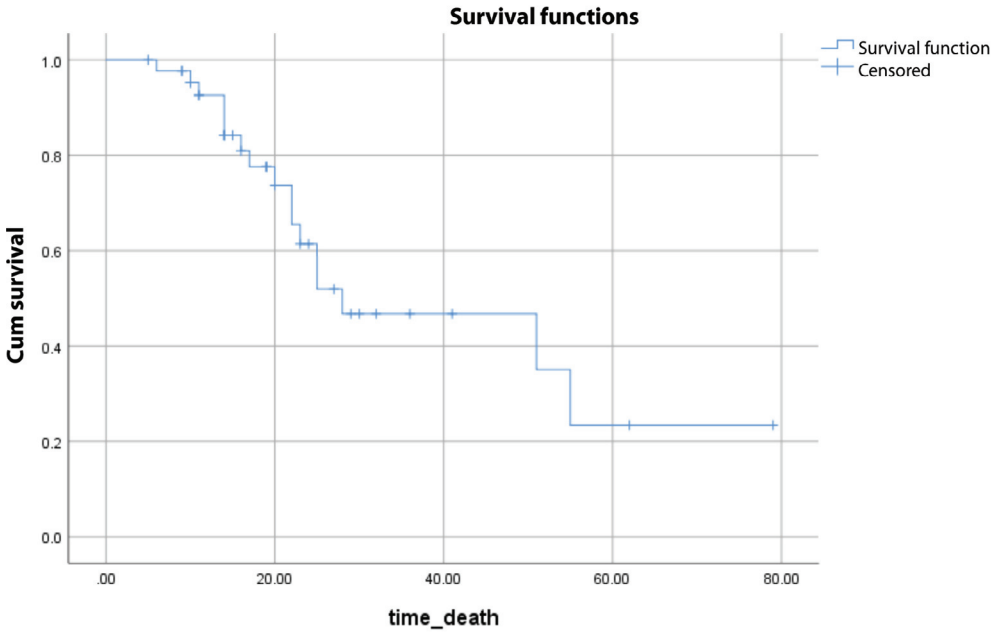

Figure 1. Kaplan-Meier survival curve for the whole patient population (GTX and GmAb)
Cum: Cumulative; GTX: Combination of gemcitabine, docetaxel and capecitabine; GmAb: Combination of gemcitabine and nab-paclitaxel

Materials and Methods

This is a retrospective chart review that aimed to collect and record data from patients diagnosed with advanced pancreatic cancer at the American University of Beirut Medical Center who received FOLFIRINOX as first-line chemotherapy and then had GTX or GmAb as second-line treatment between 2013 and 2019. Informed consent was obtained from the participants, and data collected and recorded included patient demographics (age, gender, nationality), descriptive characteristics (past medical and surgical history, risk factors), disease characteristics (staging, grading), imaging findings, treatment plans, tumor responses to treatment, and adverse events. The data cut-off was at June 15, 2021. The ethics approval to review the charts was obtained from the Institutional Review Board at the American University of Beirut (IRB ID: BIO-2019-0092). Data was collected from the patients' Paper Medical Charts and Electronic Health Records corresponding to eligible patients. They were recorded on Data Collection Sheets and stored in a locked cabinet. We measured the progression-free survival (PFS), OS, and toxicity of GTX versus GmAb as second-line treatment for pancreatic adenocarcinoma at AUBMC. Inclusion criteria were patients aged 18 years or older with an ECOG performance status of 0, 1, or 2, with histologically proven pancreatic adenocarcinoma, metastatic or locally advanced unresectable disease, who progressed on first-line FOLFIRINOX and received GTX or GmAb as second-line treatment. Exclusion criteria were having an ECOG performance status greater than 2 and second-line therapy not involving GTX or GmAb. All patients who progressed on first-line FOLFIRINOX were recruited by their primary oncologists to receive second-line chemotherapy when they had a performance status of 0, 1, or 2 and agreed to continue treatment. There was no pre-set number of planned chemotherapy cycles in the patient population, as the treatment in their second-line course was planned until progression of disease and as long as tolerated. Outcome was assessed by imaging every 6 months. An increase in the size of the primary and/or metastatic tumors, and/or the development of new regional or

Table 1. Patients demographics and baseline characteristics

Gender	
Male	31 (60.8%)
Female	20 (39.2)
Nationality	
Lebanese	40 (78.43)
Other	11 (21.57)
Smoker	
Never	27 (52.94)
Yes	24 (47.06)
Alcohol drinker	
No	42 (82.35)
Yes	9 (17.65)
Diabetes	
No	24 (47.06)
Yes	27 (52.94)
Hypertension	
No	40 (29.40)
Yes	11 (21.60)
Comorbidities	
More than one (kidney disease, liver disease, cardiac disease, thyroid disease, dyslipidemia, and hypertension)	12 (23.53)
One	39 (76.47)
Pancreatic tumor location	
Uncinate/head	20 (39.21)
Tail	13 (25.49)
Neck/Body	13 (25.49)
Body/Tail	5 (9.80)
Pancreatic tumor size	
3 cm	23 (45.10)
2 cm	15 (29.41)
1, 4, or 5 cm	13 (25.49)
Lymph node involvement	
None	21 (41.18)
One	16 (31.37)
Two	14 (27.45)
Distant metastasis	
No	21 (41.18)
Liver	17 (33.33)
Lungs	4 (7.84)
Peritoneum	1 (1.96)
More than one site	8 (15.69)
Stage	
IB	5 (9.80)
IIA	4 (7.84)
IIB	4 (7.84)
III	8 (15.69)
IV	30 (58.82)
Surgery	
Whipple	6 (11.76)
Distal pancreatectomy	1 (1.96)
None	44 (86.27)

Table 2. Distribution of "dose reduction" among the two arms

	Dose reduction ($P = 0.011$)			Total
	At cycle one inclusive	At subsequent cycles (after cycle one)	No dose reduction	
GTX	4 (26.7%)	0 (0.0%)	11 (73.3%)	15 (100%)
Gemcitabine nab-paclitaxel	1 (3.1%)	7 (21.9%)	24 (75.0%)	32 (100%)
Total	5	7	35	47

GTX: Combination of gemcitabine, docetaxel and capecitabine

distant metastasis was defined as progression. PFS was calculated at the patient level as the interval between the initiation of second-line treatment and disease progression. Progression of disease was defined as per RECIST guidelines. OS was calculated as the time from the second-line treatment until death from any cause or the last follow-up. Toxicity was evaluated by the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). All analyses were performed using SPSS statistical software (Chicago, IL, USA).

Results

Baseline characteristics

Table 1 presents the demographics and baseline characteristics of the patients. The majority of patients (88.2%) had pancreatic adenocarcinoma, while 11.8% had pancreatic adenocarcinoma with mucinous features. Of the patients, 20 (39.21%) had their tumor located at the uncinate/head of the pancreas, 13 (25.49%) had it at the pancreatic tail, 13 (25.49%) had it at the pancreatic neck/body, while 5 (9.80%) had their tumor located at the pancreatic body/tail. The tumor size was approximately 3 cm in 23 (45.1%) patients and 2 cm in 15 (29.4%) patients, while the remaining patients had a tumor of size 1, 4, or 5 cm. 21 patients (41.18%) had no lymph node involvement, 16 (31.37%) had one lymph node involvement, and 14 (27.45%) had 2 lymph node involvements. The majority of patients (58.8%) had metastasis, where 17 (33.33%) had metastasis to the liver, 4 (7.84%) had metastasis to the lungs, 1 (1.96%) had metastatic disease to the

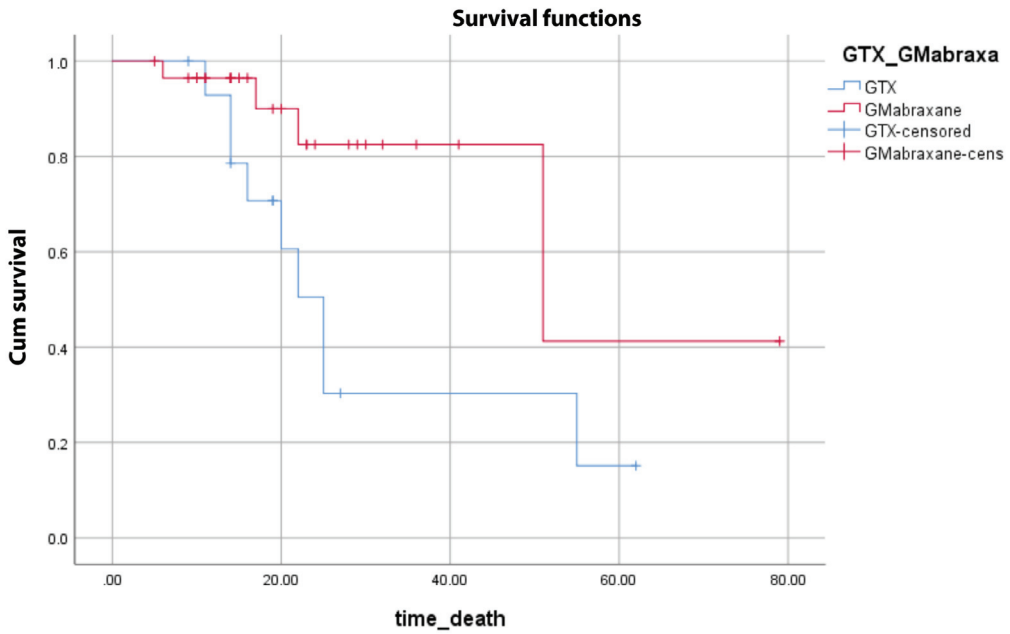

Figure 2. Kaplan-Meier survival curve for each of the two arms (GTX and GmAb)
Cum: Cumulative; GTX: Combination of gemcitabine, docetaxel and capecitabine; GmAb: Combination of gemcitabine and nab-paclitaxel

Table 3. Distribution of "anemia" among the two arms

	Anemia ($P = 0.047$)			Total
	No anemia	**CTCAE Grade I**	**CTCAE grade I**	
GTX	1 (6.7%)	14 (93.3%)	0 (0.0%)	15 (100%)
Gemcitabine nab-paclitaxel	12 (38.7%)	18 (58.1%)	1 (3.2%)	31 (100%)
Total	13	32	1	46

GTX: Combination of gemcitabine, docetaxel and capecitabine; CTCAE: Common Terminology Criteria for Adverse Events

peritoneum, and 8 (15.69%) had metastasis to more than one site. The majority of patients (58.82%) had stage IV at diagnosis. Six patients (11.76%) underwent the Whipple procedure, and 1 (1.96%) had a distal pancreatectomy. 32 patients (62.7%) did not receive radiation therapy, while 16 (31.4%) received radiation therapy.

The majority of patients (96.1%) received as the first-line regimen, 5-Fluorouracil, Irinotecan, and Oxaliplatin. Only 1 patient (2.0%) stopped this regimen due to neutropenia and mucositis, while the remaining patients stopped this regimen due to the progression of the disease. On progression, 39 patients (76.5%) had new distant metastasis; 22 of which (43.1%) had metastasis to the liver, while 6 (11.8%) had distant metastasis to the lungs.

Disease course in the whole patient population

15 patients (29.4%) received, GTX as a second-line regimen, while 34 (66.7%) received GmAb as a second-line therapy. The majority of patients (76.5%) did not require a dose reduction, while 5 (9.8%) had a dose reduction in cycle 1, and 7 (13.7%) had a dose reduction in subsequent cycles. 12 (23.5%) had their regimen changed due to the progression of the disease. 11 (21.6%) had stable disease after the second regimen, while 34 (66.7%) had disease progression. At the time of data review, 28 (54.9%) were alive, while 20 (39.2%) had died. Figure 1 shows the Kaplan-Meier survival curve for the entire patient population. The median OS for the whole patient population was approximately 24 months.

The majority of patients (70.6%) had anemia, while only 10 (19.6%) had neutropenia, and 14 (27.5%) had thrombocytopenia during their treatment. Only three patients (5.9%) had mucositis and oral thrush, 5 (9.8%) had nausea and vomiting, 3 (5.9%) had diarrhea, and 6 (11.8%) had fatigue. 45 (88.2%) did not have infections during their treatment course. Only two patients (3.9%) had liver toxicity, and one (2.0%) had neurological toxicity. Other adverse events included muscle spasm reported in one patient (2.0%), and abdominal pain and decreased appetite in 1 patient (2.0%).

The two arms

The variables and outcomes that showed statistically significant differences between the two arms were dose reduction, anemia, and death (Tables 2-4). The majority of patients who received either the GTX or GmAb regimens did not require dose reduction, with 73.3% and 75.0% of patients from each arm, respectively, not requiring dose modification. However, 26.7% of patients who received GTX required dose reduction starting from cycle one, while only 3.1% of those who received GmAb required dose reduction from cycle one. Instead, 21.9% of patients in the latter arm required dose reduction at subsequent cycles during the treatment course (Table 2, $P = 0.011$).

Of the patients who received GmAb, 38.7% did not have anemia throughout the course of treatment, 58.1% had CTCAE grade I anemia, and 3.2% had grade II anemia. On the other hand, the majority of patients who received GTX, 93.3%, had grade I anemia (Table 3, $P = 0.047$). 60% of patients who received GTX had died at the data cut-off time, while 84.4% of patients who received GmAb were still alive (Table 4, $P = 0.005$). The median follow-up was 24 months. Figure 2 shows the Kaplan-Meier survival curve for each of the two arms. The median OS for the

Table 4. Distribution of "death" among the two arms

	Death ($P = 0.005$)		Total
	Death	**No death**	
GTX	9 (60.0)	6 (40.0%)	15 (100%)
Gemcitabine nab-paclitaxel	5 (15.6%)	27 (84.4%)	32 (100%)
Total	14	33	47

GTX: Combination of gemcitabine, docetaxel and capecitabine

GmAb group was around 52 months, which was greater than that of the GTX group, which was 25 months ($P = 0.029$). Other variables did not show a statistically significant difference and are shown in table 5.

Discussion

There is currently no consensus regarding a standard approach in the second-line setting for advanced pancreatic cancer. This becomes particularly important with the increasing use of FOLFIRINOX in the first-line setting. There is considerable interest in the choice of second-line chemotherapy, especially gemcitabine-containing regimens. In this study, GmAb seemed to be a better second-line treatment option than GTX with better tolerance to the dose, less anemia, and a better survival profile. At the time of data review, 28 patients (54.9%) were alive, while 20 (39.2%) had died. The median OS for the GmAb group was around 52 months, which is greater than that of the GTX group, which was 25 months. 26.7% of patients who received GTX required a dose reduction starting from cycle one, while only 3.1% of those who received GmAb required a dose reduction from cycle one. 38.7% of patients who received GmAb did not have anemia throughout the course of treatment, while the majority of patients who received GTX, 93.3%, had grade I anemia.

Our data on the second-line regimen in advanced pancreatic cancer are particularly important since randomized trials provide little evidence of greater benefit from second-line therapy compared with best supportive care alone and because there is no clear consensus regarding the best second-line treatment option.[7] There has been an increased use of second-line chemotherapy particularly over the past decade. The use of second-line regimens is mainly for patients who maintain a good performance status. There is a limited number of randomized clinical trials that evaluated the role of second-line chemotherapy in metastatic pancreatic cancer. The first German CONKO trial showed that the combination of oxaliplatin, Leucovorin (LV), and 5-FU (OFF) resulted in better OS (4.8 months) compared with best supportive care (2.3 months).[8] This trial was discontinued, however, due to low patient accrual. Moreover, Nal-IRI is a liposomal encapsulated form of irinotecan, which improves the therapeutic index and prolongs its half-life. The NAPOLI-1 trial, a study of MM-398 with or without 5-FU/LV, versus 5-FU/LV in patients with metastatic pancreatic cancer, was a phase III clinical trial that included patients with metastatic pancreatic cancer and good performance status following treatment with gemcitabine.[9] The median OS benefit was 6.1 months for the combination of nal-IRI and 5-FU/LV compared with 4.2 months for the control arm of 5-FU/LV.[9] These above-mentioned trials; however, did not address second-line chemotherapy following first-line treatment with FOLFIRINOX, and the majority focused on the role of oxaliplatin in the second-line setting. This is what makes our study of particular relevance, where we focused on second-line treatment regimens not involving oxaliplatin, specifically GTX and GmAb following first-line treatment with FOLFIRINOX. Our study introduces GmAb as a possibly better second-line treatment option than GTX, with better tolerance to the dose, less anemia, and a better survival profile.

Our patient population reported a median OS of 24 months. Despite advancements in

Table 5. Distribution of other variables among the two arms

	GTX	Gemcitabine nab-paclitaxel	Total	*P*-value
Gender				0.542
Male	10	18	28	
Female	5	14	19	
Smoking status				0.758
Non-smoker	8	19	27	
Smoker	7	13	20	
Alcohol drinking				0.404
No alcohol	14	26	40	
Drinks alcohol	1	6	7	
Diabetes				0.758
No diabetes	7	13	20	
Has diabetes	8	19	27	
Tumor site				0.472
Uncinate/Head	5	14	19	
Body	3	6	9	
Tail	3	9	12	
Body and tail	4	3	7	
Distant metastasis				0.542
No metastasis	5	14	19	
Has distant metastasis	10	18	28	
Stage at diagnosis				0.680
Stage I	1	4	5	
Stage II	3	5	8	
Stage III	1	7	8	
Stage IV	10	15	25	
Radiation therapy				0.062
Did not receive radiation	13	17	30	
Received radiation	2	14	16	
Thrombocytopenia				0.748
No thrombocytopenia	11	21	32	
Had thrombocytopenia	4	10	14	
Mucositis/oral thrush				0.690
None	13	29	42	
CTCAE grade I	2	1	3	
CTCAE grade III	0	1	1	
Nausea/vomiting				1.00
None	13	28	41	
CTCAE grade I	2	3	5	
Diarrhea				1.00
None	14	29	43	
CTCAE grade I	1	2	3	
Infections				0.656
None	14	27	41	
Had infections	1	4	5	
Fatigue				0.651
No fatigue	13	27	40	
CTCAE grade I	1	5	6	

GTX: Combination of gemcitabine, docetaxel and capecitabine; CTCAE: Common Terminology Criteria for Adverse Events

pancreatic cancer treatment, median OS remains around 1 year, as reported in the literature.[7]

When analyzing each of the two second-line chemotherapy regimens, GTX and GmAb, the median OS for the GmAb group was approximately 52 months, which was greater than that of the GTX group, 25 months ($P = 0.029$). The survival obtained in our population was

markedly greater than that published in the literature, particularly for the GmAb group. We checked our results several times to avoid possible errors and obtained the same results. Possible reasons for this high survival may be that our center is a major referral center in the Middle East and North Africa region where patient care may not be afforded by all socio-economic classes. As such, the patient population that seeks medical attention at our center reports the earliest symptoms, thus contributing to a generally earlier diagnosis and better prognosis even when metastatic disease is diagnosed.

There was no statistically significant difference in baseline characteristics and other variables between the two treatment arms, which further suggests that patients who received GmAb may perform better than those who received GTX as second-line therapy after first-line FOLFIRINOX. In a retrospective analysis by Dakik et al., median OS was 22 weeks for patients who received GTX in the second-line setting. However, this analysis did not compare this regimen to other lines of therapy, and first-line therapy was Gemcitabine-based.[10] In a recently published study by Yildirim et al., there was no statistically significant difference between several second-line chemotherapy options, namely Xelox, GmAb, and other regimens (platinum-gemcitabine, FOLFIRINOX, Capecitabine, Xeliri, and FOLFOX), with PFS of 3.2 months, 3.7 months, and 3.5 months, respectively, and with OS of 5.9 months, 5.3 months, and 4.8 months, respectively.[3] Another study by Catalano et al. supported the use of fluoropyrimidine-based second-line chemotherapy for advanced pancreatic cancer, thus confirming the effectiveness and safety, to a greater extent compared with the FOLFIRI regimen, after progression to GmAb.[11] Interestingly, when comparing second-line FOLFIRI and FOLFIRINOX after first-line Gemcitabine-based therapy for locally advanced/metastatic pancreatic cancer at three Italian institutions, the FOLFIRINOX regimen had a favorable toxicity profile and better survival outcomes.[12] Therefore, our study can be considered the first to investigate non-oxaliplatin-containing second-line regimens after first-line FOLFIRINOX.

Furthermore, in our study population, the majority of patients who received either GTX or GmAb regimens did not require dose reduction, with 73.3% and 75.0% of patients from each arm, respectively, not requiring dose modification. However, 26.7% of patients who received GTX required dose reduction starting from cycle one, while only 3.1% of those who received GmAb required dose reduction from cycle one. Moreover, 38.7% of patients who received GmAb did not experience anemia throughout the course of treatment, while the majority of patients who received GTX, 93.3%, had grade I anemia. 60.0% of patients who received GTX had died at the data cut-off time, while 84.4% of patients who received GmAb were still alive. With similar baseline characteristics for both groups, these results support the consideration of GmAb as a better second-line treatment option than GTX, with better tolerance to dose, less anemia, and a better survival profile.

Our study has several strengths and limitations. To our knowledge, it is the first study to investigate non-oxaliplatin-containing second-line regimens after first-line FOLFIRINOX. While our results suggest that GmAb is a better second-line treatment option than GTX, there are several limitations.

Firstly, our sample size was small, which may have contributed to the population not being representative of the general population. Additionally, the retrospective study design is not ideal for assessing OS compared to prospective study designs. While this study design carries a few advantages, such as being suitable for rare diseases like pancreatic cancer progressing on FOLFIRINOX and small patient populations, it has several drawbacks. Retrospective studies are susceptible to selection and memory bias. The study subjects may not be representative of the population, and reasons for non-selection may not be ascertainable. Also, as indicated above, data available in the charts were not collected for research purposes. Therefore, some data may be missing for some patients.

Lack of homogeneity is another concern in a retrospective design. Different people are involved at different times in patient care and data entry, especially when studies look at charts over several years like our study, which spanned 6 years. In addition, prescription bias can exist among our population. Prescriptions may have varied according to patients' risk profiles, and the exact reasons may not have been recorded. Moreover, we cannot determine incidence in a retrospective design, nor can we determine the reason behind loss to follow-up. Reasons for lost follow-ups often cannot be ascertained in retrospective studies and can potentially bias the results.

Conclusion

Our study is one of the few that compare second-line regimens for pancreatic cancer. We have introduced GmAb as a potentially superior second-line treatment option to GTX, with better dose tolerance, less anemia, and a better survival profile. However, larger studies with a prospective design and a larger sample size are needed to confirm this possible difference between the two regimens. In the meantime, we recommend an individualized patient-based approach where either regimen can be considered, taking into account the first-line chemotherapy regimen and performance status. Larger prospective studies are required to better evaluate the differences in outcome and response between the two regimens.

Conflict of Interest

None declared.

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