Cisplatin-Modified De Gramont in Second-Line Therapy for Pancreatic Adenocarcinoma

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Objectives: In Belgium, combination chemotherapy of cisplatin and 5-fluorouracil + leucovorin (CFL) according to the modified de Gramont schedule is the treatment of choice in second line for metastatic pancreatic cancer. We retrospectively analyzed survival data in 2 Belgian centers in a nonselected population.

Methods: Between January 2004 and October 2011, 48 patients with histologically proven recurrent or unresectable pancreatic adenocarcinoma who had received CFL as second-line treatment were identified. We retrospectively analyzed the following parameters: progression-free survival (PFS1 and PFS2) for each line (after the start of first and second line), overall survival (OS), and growth modulation index.

Results: The median PFS1 was 5.4 months (95% confidence interval [CI], 4.1–6.6). The median PFS2 was 3.6 months (95% CI, 2–5.2). The median OS was 12 months (95% CI, 9.3–14.7). Twenty-three percent of patients had a growth modulation index >1.33.

Conclusion: We show an OS of 12 months with gemcitabine in first-line and CFL in second-line therapy for pancreatic cancer. Sequential therapy with good OS and good quality of life may be preferred to strong upfront therapy in an incurable disease such as pancreatic cancer.

Key Words: pancreatic cancer, pancreatic adenocarcinoma, second-line chemotherapy, cisplatin-modified de Gramont

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Pancreatic cancer (PC) is the fourth leading cause of cancer-related deaths in the United States with an expected incidence of 43,140 cases and 36,800 deaths in 2010.[1] It has a poor prognosis with a 5-year survival of less than 5%.[2] The median overall survival (OS) of patients receiving chemotherapy (CT) was less than 1 year in recent phase 3 trials.[3,4] Surgical resection is the only potentially curative approach. Unfortunately, less than 10% of patients with a diagnosis of PC actually can undergo resection. Even in this subset of patients, the 5-year survival rate remains low—approximately 20%—because of frequent relapse.[5]

For unresectable PC, gemcitabine has been considered a standard first-line CT since 1997 because a significant improvement in survival and clinical benefit over 5-fluorouracil (5FU) has been shown in a randomized phase 3 trial.[6] Since then, various combination regimens have been tested in clinical trials, but only one of them showed a benefit over gemcitabine alone. This recent multicenter randomized phase 2/3 trial compared gemcitabine with FOLFIRINOX (oxaliplatin, irinotecan, 5FU, and leucovorin) in 342 patients with metastatic PC (mPC). FOLFIRINOX showed to be superior both in response and survival (response rate [RR]: 31.6% vs 9.4%; $P < 0.001$; OS: 11.1 vs 6.8 months; $P < 0.001$; progression-free survival (PFS): 6.4 vs 3.3 mo; $P < 0.001$).[4,7–9] However, the safety of this regimen was less favorable with a very high toxicity (up to 45.7% had neutropenia). Moreover, there was a high percentage of patients with pancreatic tail tumors in this study (26.3%) that are less at risk for developing cholangitis. Therefore, this regimen may be less well tolerated outside clinical trials, and only a small number of patients with a very strict selected condition (age <76, good PS, no cardiac ischemia, and normal bilirubin level) could benefit from this regimen.

There is growing evidence supporting benefit of CT after gemcitabine failure. However, it is unclear which regimen should be used. A lot of centers use a combination regimen of cisplatin and 5FU. Single-agent cisplatin has shown promising activity in metastatic pancreatic carcinoma as first-line regimen.[10] Synergistic activity of cisplatin and 5FU has been reported in several tumor types.[11] A combination of these agents in various regimens with different toxicity profiles has been tested as first- and second-line treatments in both phase 2 and phase 3 trials with promising results.[11–15] In Belgium, a combination regimen of cisplatin and 5FU + leucovorin (CFL) according to modified de Gramont is often used as second-line treatment. In this study, we retrospectively analyzed the results of this combination therapy in 2 centers in a nonselected population.

MATERIALS AND METHODS

We performed a retrospective analysis of patients with a diagnosis of recurrent or unresectable PC who were treated with CFL as second-line therapy. This regimen consisted of cisplatin, 50 mg/m^2; leucovorin, 100 mg/m^2; and 5FU, 400 mg/m^2 (bolus), at day 1 and 5FU, 2400 mg/m^2 (46-hour infusion). Adjuvant treatment was considered as first-line therapy if the recurrence occurred during or shortly (<4 months) after adjuvant CT.

Patients' Characteristics

Between January 2004 and October 2011, 48 patients with histologically proven recurrent or unresectable PC were found to have been treated with CFL as second-line therapy in 2 centers (40 patients at Ghent University Hospital and 8 patients at Maria Middelares Hospital). The patients' characteristics are described as (Table 1):

Overall survival was measured from the start of treatment to death or to the last follow-up assessment. Progression-free

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TABLE 1. Patients' Characteristics

Characteristic	
No. patients	48
Age, mean ± SD (range), yrs	60 ± 11 y (32–82)
Sex	
M	27 (27/48 [56%])
F	21 (21/48 [44%])
Tumor localization	
Head	29 (29/48 [60%])
Body	10 (10/48 [22%])
Tail	5 (5/48 [10%])
Unknown	4 (4/48 [8])
Pathologic characteristics (grade: n = 18†)	
Well-differentiated ADK*	1 (1/18 [6%])
Moderately differentiated ADK*	9 (9/18 [50%])
Poorly differentiated ADK*	8 (8/18 [44%])
Performance status	0–1

*ADK = Adenocarcinoma.

†Pathological classification can only be performed correctly in resection specimen, not in biopsies.

survival was defined as the interval between the start of treatment and the occurrence of progressive disease, the last follow-up, or death. It was also divided into PFS1 for first-line treatment and PFS2 for CFL as second-line treatment.

Growth modulation index (GMI) was calculated to assess the efficacy of the second-line regimen. This parameter was first proposed by Von Hoff[16] in 1998 and was measured as the ratio PFS2/PFS1. Thus, a GMI greater than 1 means that PFS2 is longer than PFS1. It was stated that a GMI greater than 1.33 (an improvement of 33%) was necessary to conclude that the latter line of CT has a significant benefit.[3,16,17]

Survival distribution was estimated by the Kaplan-Meier method. Analyses were performed with the SPSS version 16.0.0 statistical software system (SPSS Inc, Chicago, IL).

RESULTS

All 48 patients received a gemcitabine-based regimen in first line. Thirteen patients underwent surgery followed by adjuvant treatment with gemcitabine and had recurrence during or shortly after the termination of the treatment. Thirty patients had distant metastases before the start of first-line treatment—metastatic disease was diagnosed in 28 patients, and 2 patients developed recurrence after surgery of the primary tumor before the initiation of adjuvant chemotherapy, 5 patients had locally advanced disease. Most patients received gemcitabine as a single agent (36/48 [75%]), 10 patients (10/48 [21%]) had combination therapy of gemcitabine with tarceva, whereas 1 patient (1/48 [2%]) received gemcitabine with triapine, and 1 patient (1/48 [2%]) radiochemotherapy (radiotherapy + gemcitabine).

The mean number of lines of treatment was 2.25. Thirty-eight patients received 2 lines, 8 patients received 3 lines, and 2 patients received 4 lines of CT (Table 2).

The median PFS1 was 5.4 months (95% confidence interval [CI], 4.1–6.6), and the median OS was 12 months (95% CI, 9.3–14.7). This is in agreement with what is mentioned in the literature. The median PFS2 was 3.6 months (95% CI, 2–5.2). The 2-year survival rate after the start of first line was 8% (4/48) and the 1-year survival rate was 50% (24/48). The 1-year and 6-month survival rates after the start of the second line were 19% (9/48) and 44% (21/48), respectively. Twenty-three percent (11/48) of the patients had a GMI greater than 1.33.

DISCUSSION

Today, second-line therapy for PC has not been clearly defined. Many single or combination agents have been tested in small trials and have shown a limited significant clinical benefit.

Three regimens have been compared to best supportive care (BSC) in phase 3 trials for second-line treatment in gemcitabine-refractory PC.[18–20] Only oxaliplatin combined with 5FU has shown a survival benefit over BSC (Table 3).[20]

Many phase 2 trials have reported a benefit with a cisplatin-5FU–based regimen both in first and second line (Table 4). Rougier et al,[11] Nicolson et al,[12] and Rothman et al[13] have shown promising results with a combination therapy of cisplatin and 5FU in continuous infusion in first line comparable with what had been seen with gemcitabine (median OS, 5.65 mo; and 1-year OS rate, 18%).[6] A randomized phase 2 study with cisplatin-5FU either with or without interferon in mPC showed similar survival data but lower RR.[21]

The toxicity of ciplatin-5FU depends mainly on the regimen used.[11,13,22] A phase 3 study compared the safety of cisplatin combined with continuous 5FU (5FU, 800 mg/m^2 per day, in continuous infusion for 5 days and cisplatin, 100 mg/m^2, on days 1 and 2) versus bolus 5FU and leucovorin (leucovorin, 100 mg/m^2 per day in bolus 5 days followed by 5FU, 350 mg/m^2 per day in 1-hour infusion for 5 days and cisplatin, 100 mg/m^2, on days 1 and 2). Neutropenia was similar (35.1% vs 33%, respectively), and mucositis was lower in the arm with leucovorin (4.5% vs 16.4%; $P < 0.009$).[23] The association of 5FU and

TABLE 2. Line of CT

No. Patients	First Line	Second Line (n = 38)	Third Line (n = 8)	Fourth Line (n = 2)
29	Gemcitabine	CFL		
8	Gemcitabine + tarceva or triapine	CFL		
1	RCT + gemcitabine	CFL		
3	Gemcitabine (+/- tarceva)	CFL	Mitomycin-modified de Gramont	
2	Gemcitabine	CFL	Gemox	
1	Gemcitabine	CFL	Gemcitabine + Tarceva	
2	Gemcitabine	CFL	5FU	
1	Gemcitabine	CFL	5FU	Study protocol
1	Gemcitabine + tarceva	CFL	5FU	Taxotere

RCT indicates radiochemotherapy.

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TABLE 3. Results of Phase 3 Trials in Second-Line Treatment in PC

Authors	CT Regimen	No. Patients	PFS	OS1	OS2
Jacobs et al[18]	Rubitecan vs BSC	198 vs 211	58 vs 48 d	108 vs 94 d	NA
Ciuleanu et al[19]	Glufosfamide vs BSC	148 vs 155	46 vs 43 d	105 vs 85 d	NA
Pelzer et al[20]	Oxa-5FU vs BSC	23 vs 23	NA	9.09 vs 7.90 mo	4.82 vs 2.30 mo
Dahan et al[15]	LV5FU2-CDDP followed by Gemcitabine vs gemcitabine followed by LV5FU2-CDDP	102 vs 100	For LV5FU2-CDDP: PFS1 = 2.6 mo PFS 2 = 8.8 mo For gemcitabine: PFS1 = 3.6 mo; PFS2 = 6.3 mo (In patients receiving second-line therapy only)	6.6 vs 8 mo	

d indicates days; LV5FU-CDDP, leucovorin, 5-fluorouracil and cisplatin; mo, months; NA, not available; OS1, overall survival after first line; OS2, OS after the start of second line; Oxa-5FU, oxaliplatin, 5-FU; PFS1, the interval between randomization and progression during first-line treatment; PFS2, the interval between randomization and progression or death (all cause) during second-line treatment.

leucovorin combined with cisplatin has been studied by Taïeb et al[14] in 2 different regimens (leucovorin, 200 mg/m^2, as a 2-hour infusion; 5FU bolus, 400 mg/m^2, followed by 24-hour infusion of 5FU, 600 mg/m^2, on 2 consecutive days and cisplatin, 50 mg/m^2, vs bolus leucovorin, 40 mg/m^2, 5FU bolus, 400 mg/m^2, on day 1 followed by 5FU, 2400 mg/m^2, 48-hour infusion, and cisplatin, 50 mg/m^2, on day 2). The latter regimen is similar to our protocol. This study demonstrated no significant difference in toxicity between both arms, with grade 3 and grade 4 neutropenia in 17% and grade 3 mucositis and nausea/vomiting in less than 10%. No treatment-related deaths were reported.

These results were confirmed by a recent phase 3 trial (Fédération Francophone de Cancérologie Digestive 0301) comparing 5FU, folinic acid, and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in mPC.[15] This trial showed no significant difference in either median PFS or OS between the 2 treatment arms (3.4 vs 3.5 months and 6.7 vs 8.03 months, respectively) when all patients were counted. However, if only patients receiving 2 line treatments were considered, the gemcitabine followed by the LV5FU2-CDDP arm seemed to be better (PFS1 and PFS2 were 2.6 and 8.8 months vs 3.6 and 6.3 months for LV5FU2-CDDP and gemcitabine, respectively; Table 3). It is important to note that in this study, the definition of PFS2 was not the same as in our analysis. It was defined as the interval between randomization and progression or death during the second-line treatment. The OS and the 2-year

TABLE 4. Results of Phase II Trials in PC (1st and 2nd Line Treatment)

Authors	CT Regimen	No. Patients	RR, %	PFS	OS	1-Year OS, %
Rougier et al[11] (naive and pretreated patients)	Cis-5FU	38	26.5	NA	7 mo	29
Nicolson et al[12] (naive and pretreated patients)	Cis-5FU	63	16	6.6 mo	7.6 mo	33
Rothman et al[13] (naive and pretreated patients)	Cis-5FU	55	16	2.5 mo	5.8 mo	26
Taïeb et al[14] (naive and pretreated patients)	LV5FU2-P	35	29	4.5 mo	9 mo	25
Wagener et al[21] (first line)	Cis-5FU vs Cis-5FU-inf	18 vs 15	0 vs 13.3	5 mo vs 3 mo	6.5 mo vs 5 mo	NA
Evans et al[22] (first line)	ECF	35	17.3	NA	7.43 mo for LAPC 5.75 mo for mPC	NA
Tsavaris et al[24] (second line)	FOLFOX	30	23.3	22 w	25 w	NA
Gebbia et al[25] (second line)	FOLFOX4	42	14	4 mo	6.7 mo	NA
Yoo et al[26] (second line)	mFOLFOX vs mFOLFIRI	31 vs 30	NA	6 vs 8.3 w	47.1 vs 47.1 w and 14.9 vs 16.6 w after the start of 2nd line	NA
Mitry et al[27] (second line)	OXFU	18	0	0.9	4.9 mo and 1.3 mo after the start of 2nd line	NA
Xiong et al[28] (second line)	Xelox	39	2.6	9.9 w	23 w	21
Gasent Blesa[29] (second line)	Xelox	15	NA	124 d	163 d	NA

Cis-5FU indicates cisplatin and 5FU; Cis-5FU-inf, cisplatin, 5FU, and interferon; ECF, epirubicin, cisplatin with continuous infusional 5FU; FOLFOX, 5FU, leucovorin, and oxaliplatin; LAPC, locally advanced pancreatic cancer; LV5FU-P, leucovorin–5FU, and cisplatin; mFOLFIRI, modified 5FU, leucovorin, and irinotecan; mFOLFOX, modified FOLFOX; OXFU, oxaliplatin, 5FU; RR, response rate; W, weeks; Xelox, capecitabine and oxaliplatin.

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and 1-year OS rates were 8.03 months, 4.1%, and 32.7%, respectively, when LV5FU2-CDDP was used as second-line treatment. The authors stated that LV5FU2-CDDP was not suitable as first-line treatment owing to its toxic effects; but apparently, less adverse events were noted when LV5FU2-CDDP was used in second line.

Our results are better than what was seen in the Fédération Francophone de Cancérologie Digestive 0301 trial,[15] with a 1-year survival rate of 50%, a 2-year survival rate of 8%, and a median OS approaching 12 months. These results are also slightly better than what was seen with FOLFIRINOX in first line.[4] Moreover, in mPC, a disease in which cure is impossible, the goal is to prolong survival and retain good quality of life. The high RR with FOLFIRINOX translates in a higher OS in first line but not in an OS that is higher than what is seen by using sequential therapy. In mPC, it may be more interesting to use sequential therapy with different treatment lines that are not too toxic.

The GMI is an interesting and easy-to-use parameter to assess the benefit of second-line treatment in clinical trials. As stated previously, this parameter, suggested by Von Hoff, is the ratio PFS2/PFS1.[16] A GMI greater than 1 means that the PFS2 is longer than PFS1, suggesting that the second-line therapy has a modulating effect on tumor growth because it has changed the natural history of the disease. It has been stated that a GMI greater than 1.33 is necessary to suggest a real clinically significant benefit for the latter line of CT.[3,16,17] However, this value is arbitrary. Futhermore, in other metastatic cancers, therapies in further lines do not necessarily have to lead to a PFS better than or comparable with PFS in first line to be regarded as clinically meaningful treatments. However, the good OS figures in our study could have been the result of a selection bias, with only patients with an excellent performance status and good control on first-line therapy being treated in second line. This is not the case: in our study, 11 patients had a GMI greater than 1.33. Thus, these patients had progressed more rapidly on gemcitabine, whereas treatment with CFL most definitely changed the course of their disease.

Oxaliplatin has also shown promising results in PC in different combination regimens in phase 2 trials in gemcitabine-pretreated advanced PC.[24–26] However, disappointing results have also been noted in other trials.[27–29] In a randomized phase 3 trial, oxaliplatin combined with a 5FU regimen as second-line treatment has also shown a significant increase in OS compared with BSC.[20]

These results of oxaliplatin and 5FU–based regimens seem to be comparable to the cisplatin and 5FU–based regimens. However, cisplatin cannot simply be replaced by oxaliplatin in mPC. In a review of second-line therapy in PC, the use of oxaliplatin or cisplatin was compared by Reni et al,[30] and cisplatin was noted to be associated with longer survival compared with oxaliplatin ($P = 0.03$).

As stated previously, the toxicity of a cisplatinum-based regimen depends on the combination given. The toxicity with cisplatinum-modified de Gramont-like treatments in the study of Taïeb et al[14] resembles that reported by Gebbia et al[25] with FOLFOX with grade 3 and grade 4 neutropenia in 17% of patients, nemia in 14%, and most of the nonhematological symptoms less than grade 3.

CONCLUSION

There is growing evidence supporting the benefit of second-line CT after gemcitabine failure in PC. We show an OS close to 12 months with CFL in second-line therapy in a retrospective analysis, an OS that is higher than what has been described before. This good result was not due to selection of a patient population that responds well to CT, as 23% of the patients showed a longer PFS in second line than in first line. These results are in agreement with what is found in the literature: both combination therapy with oxaliplatin or cisplatin show promising results in PC. Oxaliplatin may be preferred because of its lower toxicity, but a recent meta-analysis shows more efficacy for cisplatin. Sequential therapy with good OS and good quality of life may be preferred to strong upfront therapy in an incurable disease such as PC.

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