

Chemotherapy followed by chemoradiotherapy in locally advanced pancreatic cancer: A literature review and report of two cases

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Abstract. The optimal treatment of patients with locally advanced pancreatic cancer remains to be elucidated. Chemoradiotherapy is regarded as the treatment of choice, and studies have examined the sequential schedule of induction chemoradiotherapy followed by chemoradiotherapy, with favourable results. This study investigated the principal clinical trials of chemoradiotherapy treatment in locally advanced pancreatic cancer in 2 patients. The 2 patients received induction chemotherapy with gemcitabine 1000 mg/mq day on days 1 and 8 of a 21-day cycle for two cycles, followed by chemoradiotherapy with concurrent radiosensitizer bi-weekly gemcitabine 50 mg/mq for six weeks. Radiotherapy consisted of an external conformational 3D treatment administered to the pancreatic bed and locoregional nodes, with a total dose of 4500 Gy fractionated in 180 Gy/day, and a boost of 900 Gy to the neoplastic mass. Efficacy was evaluated four weeks after the end of treatment by a computed tomography (CT) scan and by fluorodeoxyglucose positron-emission tomography/CT. The patients underwent further treatment with periodical instrumental evaluation. A disease control rate was observed in the two patients following sequential treatment, enhanced by subsequent treatment. The two patients remained alive 23-24 months following the diagnosis. The sequential treatment schedule therefore was an effective option in our locally advanced pancreatic cancer patients. A phase III trial and further investigation are required to verify this option in clinical practice.

Introduction

Exocrine pancreatic adenocarcinoma is the fourth most common cause of cancer-related mortality in both genders in the US (1). Surgery is the only potentially curative option but is confined to patients with localized disease. Therapeutic options in patients not eligible for resection are limited to chemotherapy (CHT) or chemoradiotherapy (CRT). However, the prognosis is poor, ranging from 6 to 10 months in locally advanced stage disease.

Locally advanced pancreatic cancer (LAPC) is defined as a tumour localized in the pancreas, without metastatic spread, but directly encasing the adjacent arteries, such as the coeliac axis and superior mesenteric artery, or occluding the superior mesenteric vein, portal vein or mesenteric-portal vein confluence (2). The optimal treatment of LAPC remains to be elucidated. However, enhancement of clinical benefit, disease control rate (DCR) and survival, and an increase of the resectability rate in borderline resectable disease are crucial. Traditionally, CRT was considered to be the treatment of choice for LAPC. However, despite the known superiority of CRT compared to radiotherapy (RT) alone and best supportive care (3,4), no evidence is available to prove that the beneficial effect of CRT is superior to that of CHT alone (3-9). Although pancreatic tissue exhibits poor radiosensitivity, the addition of RT is designed to obtain local disease control and an early palliation of symptoms. Numerous studies have tested the sequential schedule of CRT as induction CHT followed by CRT, with favourable results (10-16). Thus, the association of various therapeutic techniques including CRT, surgery and locoregional treatment may be introduced in clinical practice to enhance the DCR in selected patients in multimodal treatment.

In this study, 2 patients with LAPC received a multimodal treatment starting with gemcitabine (GEM)-CHT followed by CRT, with concurrent radiosensitizer bi-weekly GEM, in order to prepare the patients for surgery.

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Patients and methods

Case 1. In August 2008, a 63-year-old male was diagnosed with locally advanced stage and poorly differentiated carcinoma originating from the head of the pancreas. The Eastern Cooperative Oncology Group (ECOG) performance status was 2. The tumour markers [carcinoembryonic antigen (CEA) and CA19.9] were negative. Since the patient was considered unfit for surgery, the tumour was treated medically. A sequential CHT followed by CRT was scheduled in September 2008. However, the treatment was discontinued due to toxicity, in the form of fever and nausea, during the induction CHT period. In February 2009, an abdominal computed tomography (CT) scan showed a significant reduction of the pancreatic tumour mass and a fluorodeoxyglucose positron-emission tomography/CT ($^{18}\text{CT-PET}$) revealed a complete metabolic response (Fig. 1). Consequently, the patient underwent surgery. Since the tumour involved the coeliac axis and superior mesenteric artery, surgery was confined to explorative laparotomy. In July 2009, a CT scan showed a further reduction of tumour size, and $^{18}\text{CT-PET}$ confirmed the complete metabolic response. The ECOG performance status was 0. In agreement with the patient, treatment involved the maintenance of GEM at 1000 mg/mq on days 1, 8 and 15 of a 28-day cycle from July 2009 to February 2010, when a single hepatic metastasis developed, 18 months following the LAPC diagnosis. A slight increase in CEA was found (6.7 ng/ml). Thus, CHT with gemcitabine and oxaliplatin (GEMOX schedule) commenced from March 2010. During treatment, a case of grade 3 neutropenia occurred.

Case 2. In July 2008, a 63-year-old male was diagnosed with a locally advanced adenocarcinoma of the pancreatic body. The ECOG performance status was 2. The tumour marker CA19.9 was 143 U/ml. The patient was considered unfit for surgery. Consequently, the tumour was medically treated. From July to October 2008 a sequential CHT followed by CRT was performed without major toxicities. In November 2008, a CT scan revealed a slight reduction in tumour size (30 vs. 39 mm), but coeliac axis tumour involvement persisted. Since the CA19.9 value remained high, the patient was treated with CHT according to the GEMOX schedule from January to September 2009. Further tumour shrinkage (28 vs. 39 mm) and a complete metabolic response were noted. The CA19.9 value decreased to 29 U/ml. In November 2009, the patient underwent radiofrequency ablation (RFA) with a positive locoregional response and a normalization of CA19.9 serum values. In March 2010, the patient resumed CHT according to the GEMOX schedule due to an increase in CA19.9 (345 U/ml), despite negative a $^{18}\text{CT-PET}$ evaluation. CHT was discontinued in May 2010 and a CT scan revealed stable disease: serum CA19.9 levels had decreased to 135 U/ml and $^{18}\text{CT-PET}$ showed minimal pathological uptake of the tracer at the mesenteric node and in the lung nodules.

Results and Discussion

This study evaluated clinical cases of patients characterized by long-term DCR and metabolic tumour deactivation, as noted by a negative $^{18}\text{CT-PET}$, obtained first by the early sequential CRT schedule, and followed by further treatment modality

(Figs. 1 and 2). Patient 1 developed a single hepatic metastasis 18 months after LAPC diagnosis, following upfront sequential CRT and the first line CHT. The patient remained alive at 23 months and in good clinical condition. RFA appeared to prolong disease control in patient 2. This patient developed metastasis 24 months after the LAPC diagnosis. The two patients therefore experienced clinical benefits.

It is known that the optimal treatment of patients with LAPC has yet to be elucidated. CHT alone is the treatment of choice in the UK, whereas CRT is the standard modality in the USA. Numerous trials have confirmed the enhanced efficacy of the CRT, although the survival benefit of combination treatment appears to be moderate (Table I). Discrepancies in the results of two phase III studies were noted (8,9). Loehrer *et al* showed a slightly longer survival in patients treated with CRT with concurrent GEM vs. GEM alone (11 vs. 9.4 months, $p=0.044$) (8). On the other hand, the Fédération Francophone de Cancérologie digestive (FFCD) and the Société Francophone de Radiothérapie Oncologique (SFRO) study proved that GEM was more favourable than CRT with 5-fluorouracil and cisplatin followed by GEM (13 vs. 8.6 months, $p=0.03$) (9).

In the last decade, CHT and RT have been tested in a sequential modality comprising an upfront mono- or multi-chemotherapy, followed by CRT, or maintenance CHT (Table II). The most significant data on the efficacy of induction CHT, derived from two large retrospective analyses and a phase II trial, proved the superiority of the sequential regimen compared to CRT or CHT. Krishnan *et al* (11) showed increased overall survival (OS) in patients pretreated with GEM-based CHT and CRT compared to patients who received only CRT (OS: 11.9 vs. 8.5 months, $p<0.001$; PFS: 6.4 vs. 4.2 months, $p<0.001$). On the other hand, the GERCOR analysis showed an OS of 15 months in patients pretreated with various CHT regimens prior to CRT with concurrent fluoropyrimidine, whereas OS was only 11 months in the CHT-only arm ($p=0.0009$) (12). In a phase II trial, Hudson *et al* (15), confirmed the positive effect of upfront CHT prior to CRT, achieving an OS of 15.3 months compared to 9.2 months in frontline CRT ($p=0.005$).

No consensus exists on an ideal schedule for sequential treatment. We used GEM-based CHT in the systemic induction phase as compared to the CRT phase (10,11,13-16), whereas in the majority of studies the concurrent drug in the CRT phase was 5-fluorouracil or derivatives thereof (11-13,16). Although the survival improvement was poor, the tumour resectability rate was increased by RT with concurrent GEM vs 5-fluorouracil in LAPC (17). No certain dose of GEM with concurrent RT (8,10,11,14-16) was defined; during conventional radiation the safe weekly dose of GEM should remain at <400 mg/mq, whereas this dose is not effective for systemic disease control. Instead, certain studies tested a lower dosage of GEM twice weekly as a radiosensitizer enhancer with positive results. For the same purpose, we treated our patients with bi-weekly 50 mg/mq concurrent to RT (18).

The rationale of sequential CRT is based on the early metastatic spread of LAPC: patients with disease that is still localized are likely to complete treatment with CRT, whereas patients with disease progression during the induction CHT may benefit more from a different CHT regimen. Theoretically the first CHT phase is utilized to select patients on the basis of

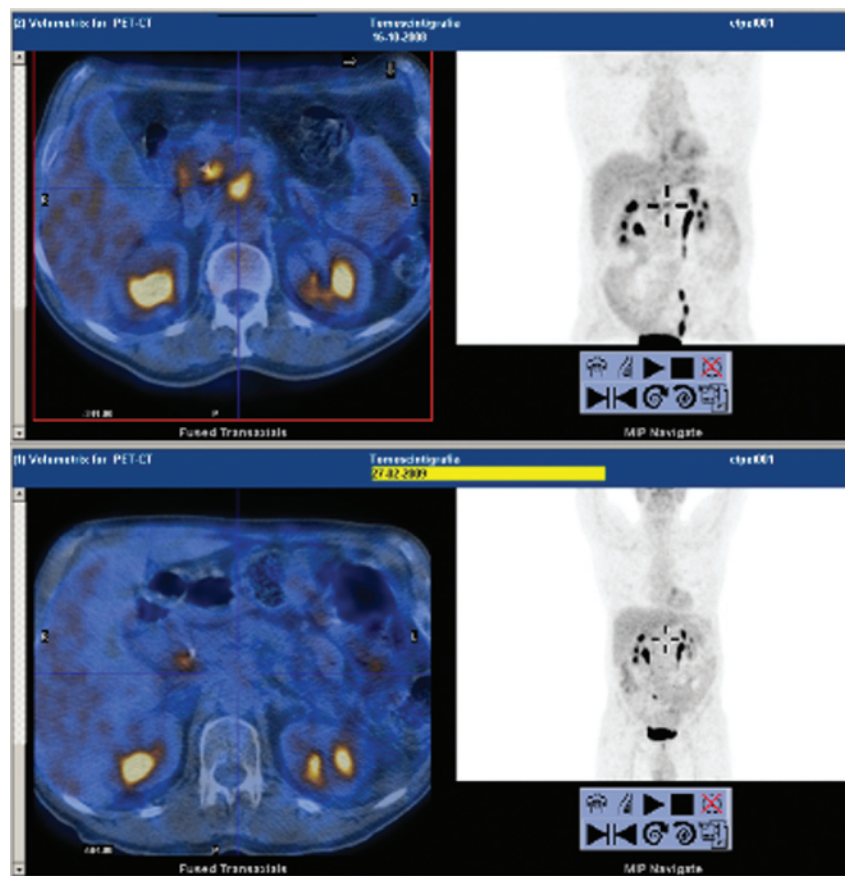


Figure 1. ^{18}F CT-PET evaluation prior to and following chemoradiotherapy treatment in patient 1.

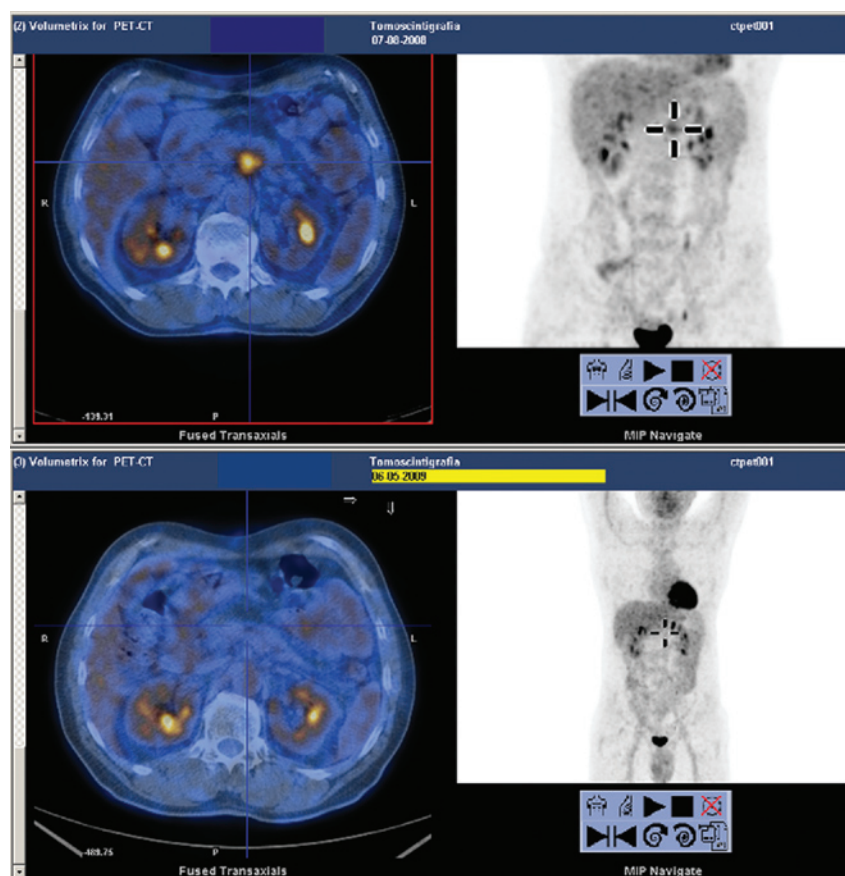


Figure 2. ^{18}F CT-PET evaluation prior to and following chemoradiotherapy treatment in patient 2.

Table I. Chemotherapy vs. chemoradiotherapy studies in locally advanced pancreatic cancer.

Authors	Refs.	Phase	Patients	Regimen	OS (mo)	p-value OS	PFS (mo)	p-value PFS	1 (ii) y OS rate
Hazel	(5)	III	30 (all)	CHT: 5FU 500mg/mq/wk bolus and methyl CCNU 100 mg/mq/6 wk until progression vs. CRT: 46 Gy and 5FU mg/mq/wk bolus followed by maintenance CHT	7.8 7.3				
Klaassen	(6)	III	47 44	CHT: 5FU 600 mg/mq/wk until disease progression vs. CRT: 4000 rad with concurrent 5FU 600 mg/mq the first three days followed by maintenance 5FU	8.2 8.3				
Gastrointestinal tumor study group	(7)	III	43 (all)	CHT: 5FU 600 mg/mq bolus on days 1, 8, 29 and 36 plus streptomycin 1 g/mq/8 wk plus MMC 10 mg/mq/8 wks vs. CRT: 54 Gy with concurrent 5FU 350 mg/mq bolus on days 1-3 and 36-38 followed by maintenance CHT	7.4 9.7				
Loehrer	(8)	III	74 (all)	CHT: GEM 1000 mg/mq/wk on days 1, 8 and 15 vs. CRT: 50.4 Gy with concurrent GEM 600 mg/mq/wk plus maintenance GEM 1000 mg/mq/wk on days 1, 8 and 15	9.2 11		6.1 6.3		
Chauffert	(9)	III	54 52	CHT: GEM 1000 mg/mq/wk for 7 wks vs. CRT: 60 Gy with concurrent 5FU 300 mg/mq/day days 1-5 for 6 wks and CDDP 20 mg/mq days 1-5 during wks 1 and 5	13 8.6			0.044 0.03	53% 32%

OS, overall survival; PFS, progression-free survival; mo, months; y, year; CHT, chemotherapy; CRT, chemoradiotherapy; 5FU, 5-fluorouracil; wk(s), week(s); CCNU, lomustine; MMC, mitomycin; GEM, gemcitabine; CDDP, cisplatin.

Table II. Induction chemotherapy followed by chemoradiotherapy studies in locally advanced pancreatic cancer.

Authors	Refs.	Phase	Patients	Regimen	OS (mo)	p-value OS	PFS (mo)	p-value PFS	1 (ii) y OS rate
Epelbaum	(10)	II	20	CHT: GEM 1000 mg/mq/wk for 7 wks (i) followed by CRT 50.4 Gy with concurrent GEM 400 mg/mq for 2 cys (ii) followed by maintenance GEM (iii)	8 (median)				1y:30% (median)
Krishnan	(11)	Retrospective analysis	323	CHT: GEM based for 2.5 mo (i) followed by CRT 30 Gy with concurrent 5FU 300 mg/mq/day or CAPE 1600-1800 mg/mq/day or GEM 350 to 400 mg/mq/wk (ii)	9 (median) 11.9 (i+ii) 8.5 (ii)	<0.001	5 (median) 6.4 (i+ii) 4.2 (ii)	<0.001	2y:9% (median)
Huguet	(12)	Retrospective analysis	181	CHT: Various regimens for 3 mo (i) followed by CRT 55 Gy with concurrent 5-FU 250 mg/mq/day for 7 wks (ii); or followed by CHT (iii)	11.4 (median) 15 (i+ii) 11 (i+iii)	0.0009	6.3 (median) 10.8 (i+ii) 7.4 (i+iii)	0.005	46% (median) 65.3% (i+ii) 47.5% (i+iii)
Moureau-Zabotto GERCOR	(13)	II	59	CHT: GEMOX for 4 cys (i) followed by CRT 45 Gy over 5 wks plus 10 Gy boost with concurrent 5FU 250 mg/mq as continuous infusion and OHP 60 mg/mq/wk (ii)	12.2 (median) 12.6 (i+ii)		7.6 (median) 9.4 (i+ii)		1y:52.1% (median) 2y:20.8% (median)
Nakachi	(14)	II	20	CHT: GEM and S-1 for 4 cys (i) followed by CRT 30 Gy with concurrent GEM 250 mg/mq (ii) followed by maintenance GEM for 2 cys (iii)	14.4 (median)		8.1 (median)		54.2% (median)
Hudson	(15)	II	43	CHT: GEM or GEMCAPE for 3-4 cys (i) followed by CRT 45-50.4 Gy with concurrent GEM 300 mg/mq/wk (ii)	9.2 (median) 9.2 (i) 15.3 (i+ii)				34.1% (median) 30.8% (i) 74.5% (i+ii)
Reni	(16)	II	91	PEFG/PEXG or PDXG for 6 mo (i) followed by CRT 50-60 Gy with concurrent 5FU 250 mg/mq/day or CAPE 1250 mg/mq/day or GEM 150-200 mg/mq/wk (ii)	16.2 (median)	0.005	12.7 (i+ii) 9.9 (median)		

OS, overall survival; PFS, progression-free survival; y, year; mo, months; CRT, chemoradiotherapy; CHT, chemotherapy; cys, cycles; GEM, gemcitabine; FDR, fixed dose ratio; 5FU, 5-fluorouracil; wk, week; MMC, mitomycin; CDDP, cisplatin; CAPE, capecitabine; GEMOX, gemcitabine and oxaliplatin; OHP, oxaliplatin; GEMCAPE, gemcitabine and capecitabine; PEF, cisplatin, epirubicin, fluorouracil, gemcitabine; PEXG, cisplatin, epirubicin, capecitabine, gemcitabine; PDXG, cisplatin, docetaxel, capecitabine, gemcitabine.

their biological disease malignancy, and adopt the therapeutic strategy best tailored to the individual patient. The same rationale can be extended to the neo-adjuvant setting in that despite the failure of neo-adjuvant intent in our patients, certain authors promote the sequential schedule since it appears to enhance the selection of patients with borderline resectable LAPC (10,16,17). This promotion is crucial in increasing secondary resectability rate, when the bulk of the disease can be reduced, and avoiding surgery in patients becoming rapidly metastatic.

Conversely, induction CHT followed by CRT in our patients appeared to enhance the clinical benefit rate and DCR when combined with further treatment. In particular, the addition of RFA appeared to extend the metastasis-free survival time to 24 months in patient 2, although these data have yet to be elucidated in the available literature (19,20). To the best of our knowledge, the multimodal treatment may be considered in selected patients who obtain a protracted stable disease due to a number of treatment techniques employed at various stages of disease.

Our cases on sequential CHT and CRT may serve as a useful starting point for critical consideration. However, numerous issues have yet to be elucidated. These issues include which chemotherapeutic scheme is ideal in the induction phase and the amount of drugs to be administered; the length of time for which patients should receive frontline CHT to improve the selection for CRT; which drugs should be administered concurrently with radiotherapy; as well as the best dosage and purpose. Therefore, phase III studies are required to better define the role of sequential CHT and CRT in LAPC patients since patients with borderline resectable cancer may benefit from better selection for surgery, whereas patients with unresectable disease may experience enhanced DCR.

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