Editorial

Intravenous and intraperitoneal paclitaxel with S-1: new hope for patients with pancreatic cancer and peritoneal metastases?

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Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis with a 5-year survival rate still below 7% (1) and is predicted to become the second leading cause of cancer-related mortality within the next two decades (2). Surgical resection in combination with systemic therapy offers the only chance of long-term survival or cure (3). However, at diagnosis only 10–20% of patients have resectable tumors, 30–40% have locally advanced borderline-resectable or unresectable tumors, and the majority of 50–60% of patients present with metastatic disease, frequently with peritoneal metastases (1). Patients with peritoneal metastases have an extremely poor prognosis with survival rates ranging from weeks to several months dependent on the extent of the disease, performance status, and therapy. Peritoneal metastases are frequently associated with severe complications such as intestinal obstruction, massive ascites, and malnutrition. These complications result in a poor performance status and hamper the administration of chemotherapy. Moreover, systemically administered chemotherapeutic drugs may not reach sufficient concentrations in the peritoneal cavity and in peritoneal nodules for effective treatment of peritoneal metastases. More effective treatment strategies for peritoneal metastases are, therefore, one of the most pressing needs in the fight against pancreatic cancer.

With this background and encouraged by remarkable results with a combination therapy of intravenous (i.v.) and intraperitoneal (i.p.) paclitaxel (PTX) and S-1 (an oral fluoropyrimidine derivative containing tegafur, gimestat, and otastat potassium) in gastric cancer with peritoneal metastases (4), Satoi *et al*. conducted a multicenter phase II study to evaluate the same regimen in patients with PDAC and peritoneal metastases. The primary endpoint of this study was 1-year overall survival rate, secondary endpoints were parameters of antitumor effect and safety. Eligibility criteria included histologically proven PDAC, macroscopic peritoneal dissemination or presence of cancer cells on peritoneal cytology in locally unresectable PDAC, chemotherapy-naïve tumors, and patients with ECOG performance status 0 and 1. Exclusion criteria were other distant organ metastases, positive peritoneal cytology without macroscopic dissemination in resectable or borderline-resectable PDAC, other active malignancies, and other severe medical conditions.

After a feasibility study in six patients (unpublished) a total of 33 patients with macroscopic peritoneal metastases (n=22) or locally unresectable PDAC and positive peritoneal cytology (n=11) were included in this study. A peritoneal port access was implanted during surgical exploration or staging laparoscopy. Patients received S-1 orally twice a day at a dosage of 80 mg/m^2/d for 14 consecutive days, followed by 7 days without treatment. On day 1 and 8 PTX was administered intravenously at 50 mg/m^2 and intraperitoneally at 20 mg/m^2 diluted in 1 L of normal saline over 1 hour. This treatment was repeated every 3 weeks for a median of 8.8 months until observation of unacceptable toxicity, disease progression, or conversion surgery. Criteria for conversion surgery were not predefined in the protocol but used upon consensus by the participating surgeons and were a combination of local tumor remission

on imaging, decreased tumor markers, disappearance of macroscopic peritoneal metastases upon staging laparoscopy or peritoneal cytology that turned negative.

Given the extremely poor prognosis of patients with PDAC and peritoneal metastases and the oncologic outcome observed with other treatments in the palliative setting (5-11), the outcome reported by Satoi *et al*. with i.v./i.p. PTX + S-1 is remarkable and very encouraging (*Table 1*). Satoi *et al*. observed a median survival time of 16.3 months, and 1- and 2-year survival rates of 62% and 23%, respectively. As further evidence of treatment efficacy, the objective response rate by RECIST criteria was 36%, the disease control rate was 82%, positive peritoneal cytology turned negative in 55%, malignant ascites disappeared in 60%, and CA 19-9 levels decreased in 51% and returned to normal levels in 35% of patients. Notably, 8 (24%) patients (5 with macroscopic peritoneal dissemination and 3 with unresectable tumors and positive peritoneal cytology) met the criteria for conversion surgery and underwent surgical resection. With extended resections including major artery and/or portal vein resections in 5 of 8 cases, an R0 status was achieved in 6 patients and an R1 resection in two patients. The overall median survival in patients with conversion surgery was 27.8 months and significantly longer than in patients who did not undergo resection (14.2 months). The toxicity of the regimen was acceptable. One patient died of a superior mesenteric artery thrombosis after the first treatment infusion, and this was regarded as treatment-related mortality.

Satoi *et al*. have to be commended for their nicely conducted and important study that holds high promise and may represent a milestone in the treatment of PDAC with peritoneal metastasis. However, as the authors discuss, even with its highly promising results, this study can only be hypothesis-generating due to its relatively small size and non-randomized design. Larger observational studies and intelligently designed randomized controlled trials are now warranted to answer open questions, to confirm the promising efficacy of i.v./i.p. PTX + S-1, and to compare this regimen with other treatments.

Several pieces of information that would have been of interest are not reported by Satoi *et al*.: did they observe differences in survival and efficacy between the subgroups of patients with macroscopic dissemination and positive cytology? While a large retrospective study in 462 patients treated between 1995 and 2005 showed no survival differences between patients who underwent resection with positive peritoneal cytology and of patients who had stage IV disease and were not resected (12), the impact of positive cytology versus macroscopic dissemination on survival may have changed with advances in systemic treatment. In the 22 patients with macroscopic peritoneal metastases the extent of dissemination using one of the available scoring systems for peritoneal surface cancers would have been of interest. Positive cytology versus macroscopic metastases, the extent of macroscopic dissemination, and other prognostic factors such as CA 19-9 levels will be important parameters to be used in future studies for patient stratification and to identify patient subgroups that benefit most from i.p. chemotherapy. It would also have been of interest to report the progression pattern (peritoneal or other organs) and the cause of death in the 23 patients who had died during the study. Finally, given the remarkable survival observed especially after conversion surgery, information on further cancer-directed therapy and disease status in this patient subgroup is of interest. Such information would certainly further stimulate and facilitate the design of future studies that are now necessary.

Based on randomized controlled trials the combination regimen FOLFIRINOX has been identified as highly effective in metastatic PDAC (10). Recently, several large observational studies and a patient-level meta-analysis found that FOLFIRINOX is also highly effective in locally advanced, unresectable PDAC (13-15). Of note, one of these studies also included 47.2% (59/125) patients who reached criteria for conversion surgery after FOLFIRINOX treatment for metastatic disease, 76 (60.8% of patients with FOLFIRINOX) underwent resection and the median survival was 16.0 months after resection (22.6 months after initiation of therapy) (14). Based on these data a randomized controlled trial of i.v./i.p. PTX + S-1 versus systemic FOLFIRINOX for PDAC with peritoneal metastases (and ECOG 0 and 1 status) may be one possible path forward.

But can the remarkable results observed with S-1 in Asian PDAC patients in randomized controlled trials in the palliative and adjuvant settings (16,17), and now in the study by Satoi *et al*., be extrapolated to patients of other ethnicities? The activity of cytochrome P-450 2A6, which is the key enzyme in converting Tegafur to 5-FU (18) is different between Japanese and Caucasians (19) and this fact may contribute to a higher gastrointestinal toxicity and lower tolerable doses of S1 in Caucasians (20). While S1 is commonly used in Asia, studies on its tolerability and efficacy in non-Asian populations are currently lacking. Therefore, the regimen used by Satoi *et al*. may not be applicable and may need to be modified in non-Asian

Table 1 Oncologic outcome of randomized controlled trials on palliative chemotherapy in PDAC and of Satoi *et al.*

Trial	Inclusion criteria	Chemotherapy	N	Overall survival (median & survival rates)	Progression-free-survival (median & survival rates)	Response rates (RECIST)
Glimelius *et al.* 1996 (5)	Surgically non-curable pancreatic or biliary adenocarcinoma	5-FU, leucovorin, ± etoposide	47	6 months	NA	NA
		Best supportive care	43	2.5 months	NA	NA
Burris *et al.* 1997 (6)	Unresectable locally advanced or metastatic pancreatic cancer	5-FU	63	4.4 months; 1 YSR: 2%	0.9 months; 1 YSR: 5%	CR: 0%; PR: 0%; SD: 19%
		Gemcitabine	63	5.7 months; 1 YSR: 18%	2.3 months; 1 YSR: 9%	CR: 0%; PR: 5%; SD: 39%
Heinemann *et al.* 2006 (7)	Locally advanced or metastatic pancreatic cancer	Gemcitabine + cisplatin	98 (63 M1 HEP)	7.5 months (all); 10.3 months (locally advanced); 7.2 months (metastatic); 1 YSR: 25.3% (all)	5.3 months (all); 8.6 months (locally advanced); 4.2 months (metastatic)	CR: 0%; PR: 10%; SD: 60%; PD: 18%
		Gemcitabine	97 (68 M1 HEP)	6 months (all); 10.4 months (locally advanced); 4.7 months (metastatic); 1 YSR: 24.7% (all)	3.1 months (all); 3.2 months (locally advanced); 3.1 months (metastatic)	CR: 0%; PR: 8%; SD: 40%; PD: 43%
Moore *et al.* 2007 (8)	Locally advanced or metastatic pancreatic adenocarcinoma	Gemcitabine + erlotinib	285	6.2 months; 1 YSR: 23%	3.8 months	CR + PR: 8.6%; SD: 48.9%
		Gemcitabine	284	5.9 months; 1 YSR: 17%	3.6 months	CR + PR: 8%; SD: 41.2%
Colucci *et al.* 2010 (9)	Unresectable or metastatic pancreatic cancer	Gemcitabine + cisplatin	199	7.2 months; 1 YSR: 30.7%	3.8 months; 1 YSR: 14.5%	CR: 1.5%; PR: 11.4%
		Gemcitabine	201	8.3 months; 1 YSR: 34%	3.9 months; 1 YSR: 12.8%	CR: 1%; PR: 9%
Conroy *et al.* 2011 (10)	Metastatic pancreatic adenocarcinoma	FOLFIRINOX	171 (33 M1 PER)	11.1 months; 1 YSR: 48.4%	6.4 months; 1 YSR: 12.1%	CR: 0.6%; PR: 31%; SD: 38.6%; PD: 15.2%; NA: 14.6%
		Gemcitabine	171 (32 M1 PER)	6.8 months; 1 YSR: 20.6%	3.3 months; 1 YSR: 3.5%	CR: 0%; PR: 9.4%; SD: 41.5%; PD: 34.5%; NA: 14.6%

Table 1 *(continued)*

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Trial	Inclusion criteria	Chemotherapy	N	Overall survival (median & survival rates)	Progression-free-survival (median & survival rates)	Response rates (RECIST)
Von Hoff *et al*. 2013 (11)	Metastatic pancreatic adenocarcinoma	Nab-paclitaxel + gemcitabine	431 (19 M1 PER)	8.5 months; 1 YSR: 35%; 2YSR: 9%	5.5 months; 1 YSR: 16%	CR: 0.2%; PR: 23%; SD: 27%; PD: 20%; NA: 30%
		Gemcitabine	430 (10 M1 PER)	6.7 months; 1 YSR: 22%; 2 YSR: 4%	3.7 months; 1 YSR: 9%	CR: 0%; PR: 7%; SD: 28%; PD: 26%; NA: 39%
Satoi *et al*. 2016	Pancreatic cancer with peritoneal metastases or unresectable PDAC with positive peritoneal cytology	i.v./i.p. paclitaxel + S-1	33	16.3 months; 1 YSR: 62%; 2 YSR: 23%	NA	CR: 0%; PR: 36%; SD: 46%; PD: 6%; NA: 12%

PDAC, pancreatic ductal adenocarcinoma; NA, not available; YSR, year survival rate; CR, complete response; PR, partial response; SD, stable disease; M1, metastatic; HEP, liver; PD, progressive disease; PER: peritoneum.

patient populations.

Interdisciplinary treatment including surgical resection remains the only hope of long-term survival for patients with PDAC. With progress in both surgery and systemic therapy (3) the indications for surgical resection in high-volume centers have been extended towards extended resections in locally advanced PDAC (21,22) resection after neoadjuvant treatment for primarily unresectable PDAC (13-15,23), and re-resection for isolated local recurrence of PDAC (24). In highly selected patients even resections of hepatic oligometastatic PDAC are performed (25). With a rate of conversion surgery and resection of 24% in patients which initially presented with peritoneal metastases the study by Satoi *et al*. extends the possible indications for surgical resection even further. It is justified and necessary to test the concept of conversion surgery in patients exhibiting good treatment responses with remission to a resectable stage. However, the remarkable results observed by Satoi *et al*. after conversion surgical resection have to be interpreted with caution, because they may to a large extent be explained by selection of patients with favorable prognostic parameters for surgery. While the true impact of conversion surgery remains to be shown, Satoi *et al*. clearly demonstrate a promising efficacy of i.p. chemotherapy with respect to both overall survival and control of peritoneal metastases. This is highly relevant for effective palliation of patients with peritoneal metastases and may have a considerable impact on their quality of live and quality-adjusted survival, parameters that should be assessed in future studies.

In conclusion Satoi *et al*. have shown encouraging clinical efficacy of i.v./i.p. PTX + S1 in Asian patients with PDAC and peritoneal metastases. This study provides new hope for patients with PDAC and peritoneal dissemination and will hopefully trigger further studies to improve the treatment for these patients.

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Footnote

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