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Neoadjuvant chemotherapy in borderline resectable pancreatic cancer: A case report

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Abstract. Pancreatic cancer is the fourth leading cause of cancer mortality and is associated with a poor overall survival even when diagnosed early and considered resectable. Complete surgical removal with negative histological margins is an independent predictor of survival and remains the only potential curative treatment. In borderline resectable pancreatic adenocarcinoma (BRPAC), preoperative systemic therapy may increase resectability and margin-negative resection rate. There is no current consensus on the optimal chemotherapy regimen for BRPAC. The present case describes a patient with BRPAC who achieved a pathological complete response to neoadjuvant FOLFIRINOX (folinic acid, fluorouracil, irinotecan and oxaliplatin), but early relapse following a pancreaticoduodenectomy without vascular resection, with an uneventful postoperative course, except for a pulmonary embolism.

Introduction

Over the past decade, the incidence of pancreatic adenocarcinoma (PAC) has been increasing, and it accounts for 2.8% of new malignancies and 6.2% of all cancer mortalities, and is the fourth leading cause of cancer-associated mortality in the United States, according to the American Cancer Society (1,2). The 5-year relative overall survival (OS) rate is 6%, with a low level of improvement over the previous 3 decades compared to other types of tumors (1,2). Surgical resection is the only potential curative treatment. Poor prognosis is mainly associated with late diagnosis, low resection rate and aggressiveness of neoplasia. PAC presents as locally advanced (LAPAC) or metastatic in the majority of patients; thus, only 10-20% of patients are eligible for curative surgery (2).

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For many years, physicians have largely ignored the tumor node metastasis staging system (3) to categorize patients into three different groups: resectable, LA and metastatic PAC. At present, with improved imaging techniques and a renewed focus on surgical expertise, a fourth category has been proposed: borderline resectable (BRPAC). These patients must be identified *a priori*, as the goals of treatment differ from those in patients with truly unresectable PAC (4). Numerous anatomic definitions of BRPAC have been proposed, with the greatest points of contention revolving around the extent of involvement of the superior mesenteric vein (SMV) (5-7).

More effective systemic regimens, compared with single agent gemcitabine treatment, have emerged in the treatment of PAC. Large randomized trials of FOLFIRINOX (folinic acid, fluorouracil, irinotecan and oxaliplatin), or gemcitabine with nanoparticle albumin-bound (nab)-paclitaxel have revealed significantly improved overall survival (OS) and response rates (RRs) compared with those associated with single-agent gemcitabine (8,9). An increasing level of evidence supports the use of neoadjuvant strategies aiming to control micrometastatic disease, induce tumor shrinkage and achieve resection for cure/complete remission (R0).

Case report

In September 2014, a 58-year-old female patient was presented at the Lugano Regional Hospital (Lugano, Switzerland) with long-lasting diabetes, abdominal pain and weight loss. The Eastern Cooperative Oncology Group performance status was 1, and laboratory parameters were normal, with the exception of carbohydrate antigen (CA) 19-9, which was 149.2 U/ml (normal range: <35.4 U/ml), and carcinoembryonic antigen, which was 59.1 ng/ml (normal range <3.0 ng/ml). A computed tomography (CT) scan revealed a 3.7-cm mass in the pancreatic head, encasing the porto-mesenteric axis ≥180˚, with narrowing and almost complete short segment occlusion of the SMV, and superior mesenteric artery (SMA) abutment (Fig. 1A and B). There was no evidence of lymph node involvement or visceral metastatic spread. The result of an endoscopic ultrasound-guided fine needle biopsy was concordant with adenocarcinoma, and the patient was diagnosed with BRPAC.

FOLFIRINOX (oxaliplatin 85 Mg/m^2, leucovorin 400 Mg/m^2, irinotecan 180 Mg/m^2 and 5-FU 400 Mg/m^2 bolus

then 2,400 Mg/m^2 over 48 h, all on day 1, and then repeated every 2 weeks), was administered to the patient for 3 months. No severe side effects occurred except mild asthenia and no dose reductions were applied. The patient experienced symptom improvement, the tumor markers levels reduced to the normal levels and the follow-up CT scan revealed a marked tumor reduction. As porto-mesenteric infiltration was no longer observed (Fig. 2A and B), a surgical exploration was planned.

In February 2015, the patient underwent a pylorus-preserving cephalic duodenopancreatectomy without vascular resection, since neither visceral spread nor arterial infiltration were observed intra-operatively. No macroscopic evidence of tumor was observed. A fibrous-like tissue was observed and the entire specimen was sent for microscopic examination. Neither residual tumor cells nor metastases in 14 regional lymph nodes were detected, and the surgical margins were negative. These findings were consistent with a pathological complete response (pCR). Pulmonary embolism occurred postoperatively, but the patient fully recovered. Adjuvant chemotherapy was suggested, but the patient refused due to a general worsening of condition following surgery. In June 2015, the patient complained of abdominal discomfort, and a CT scan revealed multiple hepatic metastasis. Chemotherapy with gemcitabine and nab-paclitaxel was administered for 2 months, but the disease progressed and the patient succumbed to the disease in October 2015. The patient gave us oral and written informed consent prior submission of the manuscript.

Discussion

BRPAC is a novel entity characterized by the limited involvement of the superior mesenteric vessels (SMA and SMV), celiac axis and hepatic artery. Although skill-demanding, resection is technically feasible in BRPAC, but is associated with a high risk of positive margins and, consequently, of early recurrence (6). The present case describes a patient with BRPAC who achieved pCR subsequent to neoadjuvant FOLFIRINOX, but relapsed following surgery. The present case raises certain issues.

Firstly, a multidisciplinary approach is required to properly assess the resectability of the PAC. There are unresolved issues with respect to the definition of BRPAC, including how much of the SMV or major visceral arteries must be surrounded on CT scan to diagnose BR or LA unresectable, or whether or not the requirement to replace a segment of vein defines resectability. SMV, SMA, celiac artery and hepatic artery involvement have been identified as an anatomic point of contention, and numerous definitions have been proposed (5-7,10). The patient in the present case was classified as BRPAC based on porto-mesenteric involvement, segmental SMV occlusion and SMA abutment.

Modern imaging techniques allow accurate preoperative staging, although there is no definite consensus on the most preferable approach. CT scans are ~80% accurate with respect to predicting resectability and almost 90% accurate in assessing vascular invasion (11). In experienced hands, accuracy of endoscopic ultrasound is 75-95 and 74-87% in assessing T and N stages, respectively (12-14). Endoscopic ultrasound is particularly useful in identifying lesions <2 cm, and may characterize the presence of vascular invasion or venous thrombosis (12-14). There are limited data on the role of positron emission tomography (PET)/CT in the staging of potentially resectable tumors. In a retrospective series, PET/CT has been shown to change the management in 17% of patients with BRPAC and 7% with resectable PAC (P=0.019), ultimately preventing unnecessary surgery (15). The accuracy of imaging in determining resectability has also been evaluated in patients with BRPAC who underwent neoadjuvant therapy, and response evaluation criteria in solid tumors (RECIST) criteria resulted unreliable to select patients for surgery (16). Although only 0.8% of patients experienced downstaging to resectable status subsequent to receiving neoadjuvant therapy, 66% of patients underwent pancreatectomy. The OS for 129 patients was 22 months, whilst the OS of the patients who underwent pancreatectomy was 33 months and was not correlated with RECIST response (P=0.78) (16). In a different study, neoadjuvant FOLFIRINOX resulted in a significant decrease in tumor size, however 47% of patients with BRPAC or LAPAC remained classified as unresectable. However, 92% of the patients underwent an R0 resection, suggesting that traditional imaging no longer predicts unresectability (17). Thus, it may be speculated that hyperdensity surrounding the major vessels considered to be neoplastic becomes, or was initially, fibrotic, possibly explaining the absence of radiological changes.

Secondly, besides overall health status, the presence of significant comorbidities and nutritional deficiency (18), understanding tumor biology may assist clinicians in selecting patients for surgery. No validated prognostic biomarkers predict recurrence following resection. A study evaluated the association between CA 19-9 and surgical outcomes in BRPAC (19). Normalization of CA 19-9 following neoadjuvant therapy was associated with longer OS in resected (38 vs. 26 months, P=0.020) and unresected (15 vs. 11 months, P=0.022) patients. Conversely, failure of CA 19-9 to normalize was revealed to be an independent factor of shorter OS [hazard ratio (HR)=2.13; P=0.001].

Patients exhibiting wild-type SMAD family member 4 (SMAD4) gene were shown to display a lower propensity for metastases than those exhibiting the loss of SMAD4 (20). However, a different study failed to demonstrate an association between SMAD4 messenger RNA expression and OS (21). Secreted protein acidic and cysteine rich (SPARC) is a glycoprotein expressed by stromal cells surrounding the tumor, and is involved in cell migration and tissue remodeling (20). Patients who expressed SPARC in tumor stroma exhibited a significantly worse prognosis than those who did not (median OS, 15 vs. 30 months; P<0.001) (22), a result that has been supported by additional studies (23,24). SPARC is known to bind to albumin (25). By binding to SPARC inside the extracellular matrix, nab-paclitaxel successfully disrupts the organization of tumor cells and induces a marked alteration in tumor architecture, resulting in increased tumor softening and permeability (25). In human epidermal growth factor receptor 2-positive tumors, nab-paclitaxel was shown to be equivalent or even superior to polysorbate-based docetaxel in tumors with medium to high SPARC levels (26).

PAC cells overexpress epidermal growth factor receptor, and previous studies have demonstrated correlations between

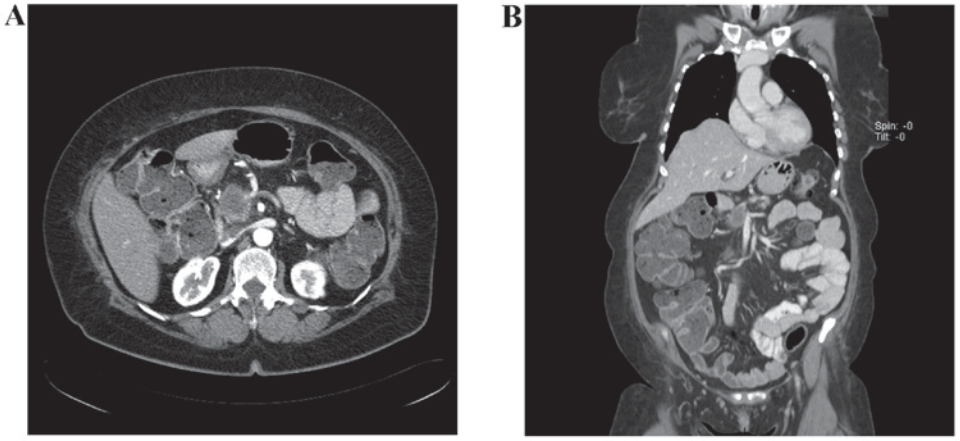

Figure 1. (A) Axial plane and (B) coronal plane computed tomography scan prior to neoadjuvant chemotherapy, showing radiological signs of a borderline resectable lesion: e.g. Encasement/short segment occlusion of the superior mesenteric vein and tumor abutment of the superior mesenteric artery.

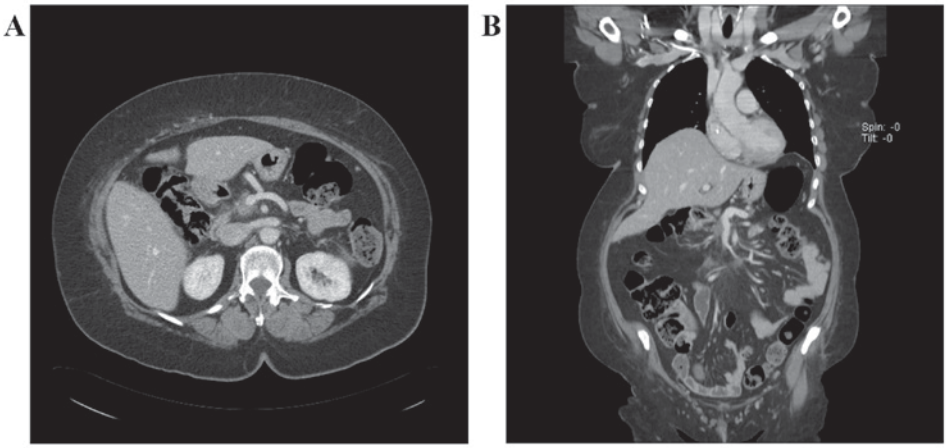

Figure 2. (A) Axial plane and (B) coronal plane computed tomography scan subsequent to neoadjuvant chemotherapy, showing radiological sings of the cancer's response to chemotherapy: e.g. Tumor shrinkage and recanalization of superior mesenteric vein.

receptor/ligand co-expression and larger tumors, advanced stage and decreased OS (27,28). Thymidylate synthase (TS) has been evaluated in 132 resected patients, and the median OS resulted improved in those with low TS expression compared with patients exhibiting high TS expression, which resulted in TS being an independent predictor of mortality at multivariate analysis (29). However, a similar study investigating TS expression reported conflicting results (30). Finally, non-coding RNAs have been observed to be deregulated in numerous types of human cancer. Studies have shown that non-coding RNAs affect the progression of PAC, and RNA profiling may assist the prediction of outcomes with high accuracy (31).

Thirdly, the present case reflects the growing recognition accorded to neoadjuvant strategies to improve OS in pancreatic cancer, a highly fatal disease. The main potential advantages of neoadjuvant strategies are: i) increased resectability and likelihood of margin-negative resection, which is relevant, as patients with BRPAC or LAPAC exhibit a similar prognosis to those with immediately resectable PAC if R0 resection can be achieved (10); ii) increased likelihood of completion of multimodal treatment, which is possibly the most effective way to improve the outcome of patients with BRPAC or LAPAC; iii) prevention of unnecessary surgery in aggressive, treatment-resistant disease; iv) evaluation of chemo-sensitivity and increased patient's compliance (32); v) minimization of pancreatic leak without increase of postoperative complications (33-37); and vi) cost-effectiveness (38).

With regards to chemotherapy, the optimal neoadjuvant regimen has not been established to date, as current evidence arises from small, single-institution, non-randomized trials. These studies are difficult to interpret, as they have used various definitions of BRPAC, different induction and post-resection regimens, and, if applied, incorporated varied radiation therapy plans (38-42). The most active regimens for advanced disease offer the best chance of achieving downstaging and systemic disease control. FOLFIRINOX regimen resulted in a statistically significant increase in OS (11.1 vs. 6.8 months; $P<0.001$) and RR (31.6 vs. 9.4%; $P<0.001$) compared with the results observed with gemcitabine in patients with metastatic disease (6). Thus, FOLFIRINOX has been incorporated in neoadjuvant trials for BRPAC and LAPAC (Table I), either alone or in combination with chemoradiation (43-59).

In a meta-analysis of 13 of the aforementioned studies involving 253 patients, resection rate and R0 resection were

Table I. Neoadjuvant clinical trials involving FOLFIRINOX (folinic acid, fluorouracil, irinotecan and oxaliplatin).

Author, year	Study	Patients (n)	Median age (years)	Stage BR/LA PAC	Schedule (median number of cycles)	Resection on (%)	R0 Resection (%)	ORR (%)_	Median OS (months)	(Refs.)
Ferrone *et al*, 2015	Retrospective	40	62	37/63	FOLFIRINOX (8)	100.0	92.0	90.0	>30.0	(17)
Mahaseth *et al*, 2013	Cohort	24	63	17 stage II/83 stage III	modified-FOLFIRINOX (3)	42.8	35.7	33.0	17.8	(43)
Boone *et al*, 2013	Retrospective	25	59	48/52	FOLFIRINOX (5)	43.0	33.0	NR	NR	(44)
Gunturu *et al*, 2013	Retrospective	16	60	0/100	FOLFIRINOX (11)	12.5	12.5	50.0	Not reached	(45)
Peddi *et al*, 2012	Retrospective	23	58	17/83	FOLFIRINOX (4)	34.7	34.7	33.4	NR	(46)
Hosein *et al*, 2012	Retrospective	18	57.5	23/77	FOLFIRINOX (6)	55.0	44.0	NR	Not reached	(47)
Tinchon *et al*, 2013	Cohort	12	NR	100/0	FOLFIRINOX (4)	83.0	NR	33.3	Not reached	(48)
Christians *et al*, 2014	Retrospective	18	59	100/0	FOLFIRINOX (4)	67.0	67.0	NR	Not reached	(49)
Faris *et al*, 2013	Retrospective	22	63	0/100	FOLFIRINOX (8)	22.7	22.7	36.4	Not reached	(50)
James *et al*, 2014	Prospective phase II	22	62	0/100	m-FOLFIRINOX (8)	46.0	NR	NR	NR	(51)
Hazariwala *et al*, 2013	Retrospective	14	NR	43/57	FOLFIRINOX (NR)	50.0	42.8	NR	NR	(52)
Vasile *et al*, 2013	Prospective phase II	32	60	100/0	m-FOLFIRINOX (6)	41.0	41.0	37.0	24.2	(53)
Kharofa *et al*, 2012	Retrospective	12	NR	100/0	FOLFIRINOX (4)	58.0	58.0	NR	Not reached	(54)
Lowery *et al*, 2012	Retrospective	19	58	0/100 stage III	FOLFIRINOX (6)	5.0	NR	21.0	13.7	(55)
Nanda *et al*, 2015	Retrospective	43	62.4	42/58	m-FOLFIRINOX (NR)	51.0	86.0	23.0	Not reached	(57)
Paniccia *et al*, 2014	Retrospective	29	60.3	0/100	m-FOLFIRINOX (4)	41.3	83.0	NR	18.6	(58)
Mellon *et al*, 2015	Retrospective	18	65	100/0	FOLFIRINOX (4)	94.4	100.0	41.2	Not reached	(59)
Petrelli *et al*, 2015	Retrospective	159	66	2/43	FOLFIRINOX (NR)	51.0	96.0	NR	34.2	(60)

BR, borderline resectable; LA, locally advanced; PAC, pancreatic adenocarcinoma; ORR, overall response rate; OS, overall survival; NR, not reported.

achieved in 43.0 and 39.4% of patients, respectively. R0 resection was possible in 63.5% of patients with BRPAC and 22.5% of patients with LAPAC (60). Three trials reported an OS between 13.7 and 24.2 months (60), compared with the OS of ~2 years of patients who complete adjuvant therapy subsequent to upfront surgery (61,62).

In the single-arm pilot study Alliance A021101, 22 patients with BRPAC were treated with 4 cycles of modified FOLFIRINOX (FOLFIRINOX without fluorouracil bolus) followed by chemoradiation prior to pancreatectomy, and an additional 2 cycles of adjuvant gemcitabine. In total, 68% of patients underwent pancreatectomy, and of those patients, R0 resection was achieved for 93% while pCR was observed in 9% (63). The single-arm phase IIa Pancreatic Resectability in Cancers with Known Limited Extension trial is currently ongoing, and evaluates gemcitabine and nab-paclitaxel in a neoadjuvant setting (64). FOLFIRINOX exhibits a relatively complex toxicity profile, which may be a limitation of applicability. In a neoadjuvant setting, grade 3-4 adverse events were consistent with those reported in the original publication (8), mainly neutropenia (3-20%, with a low rate of febrile neutropenia using granulocyte stimulating factors) and diarrhea (≤18%) (60).

Pancreatoduodenectomy is associated with a high morbidity rate (30-60%), and neoadjuvant therapy may put patients at a higher risk of complications such as wound infections, anastomotic leaks, intra-abdominal abscesses and mortality. The morbidity and mortality rates described in neoadjuvant studies are similar to those reported upon pancreatoduodenectomy in high-volume centers, suggesting that surgery subsequent to neoadjuvant chemotherapy is safe (33,34,65). In particular, no fistulae, a major complication of PAC resection, were reported (17,49). Although neoadjuvant therapy may allow resection in patients with an initially unresectable disease, the high incidence of recurrence, as in the present case, emphasizes the systemic behavior of the disease. This raises the question if palliative systemic chemotherapy and/or chemoradiation may achieve the same outcome, avoiding the morbidity and potential mortality of surgery (66). In the future, biomarkers may assist clinicians in decisional processes. For example, the DCP4 gene was revealed to be highly correlated with the presence of widespread metastasis but not with locally advanced tumors (67). In addition, in a series of 106 patients who underwent radical surgery, all of the 6 patients that achieved a 5-year survival exhibited intact SMAD4/DPC4 (68).

Finally, careful evaluation of histological changes subsequent to preoperative therapy is important to accurately assess treatment efficacy. Several variables of tumor response to neoadjuvant therapy have been proposed, including the number of severe degenerative cancer cells (SDCC), percentage of viable cells, degree of fibrosis or presence of necrosis (69,70). In a trial using SDCC to evaluate response to preoperative therapy, no advantage in terms of OS was observed in 13/26 patients who achieved a major response, defined as >80% SDCC (66). In trials where the percentage of remaining viable cells was evaluated, the patients whose tumors demonstrated minimal pathologic response exhibited more than twice the risk of mortality compared with patients who achieved a partial response or pCR (HR=2.74; P=0.01); although significant, this finding should be interpreted with caution, due to the small sample size (37,39). In total, two trials correlated survival with the degree of fibrosis following neoadjuvant therapy, with conflicting results (71,72). However, when the presence of tumor necrosis and fibrosis were analyzed, only tumor necrosis was observed to be an adverse prognostic factor (70). The College of American Pathologists has proposed a grading system for tumor response subsequent to neoadjuvant therapy: 0) Complete response, no viable cells; i) moderate response, single or small groups of cells; ii) minimal response, residual cancer outgrown by fibrosis; and iii) poor response, extensive residual cancer (67).

The significance and prognostic impact of pCR subsequent to neoadjuvant therapy for PAC is unclear. In malignancies such as rectal, esophageal and breast cancer, pCR has been associated with improved disease-free survival and OS (73-83). In PAC, a number of studies reported pathologic outcomes following neoadjuvant chemotherapy with or without fractionated radiotherapy or stereotactic body radiotherapy, and the pCR rate ranges between 2.4 and 32.0% (41,84-94). Two of these studies reported a significantly improved OS for patients who achieved pCR compared with that of patients who did not (88,89), although this finding was not confirmed by a different study (90). In the aforementioned studies involving neoadjuvant FOLFIRINOX, no specific survival data were reported in patients who achieved pCR.

In conclusion, the present case considers certain current issues of neoadjuvant approaches for patients with BRPAC and LAPAC. Well-designed trials with standardized diagnostic, surgical and pathologic procedures are required to define the optimal treatment and the real clinical impact.

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