Adjuvant chemotherapy in pancreatic cancer: state of the art and future perspectives

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Abstract

Purpose of the review:

The modalities of management of resectable pancreatic ductal adenocarcinoma (PDAC) have evolved in recent years with new practice guidelines on adjuvant chemotherapy and results of randomized phase III trials. The aim of this review is to describe the state of the art in this setting and to highlight future possible perspectives.

Recent findings:

Resectable PDAC is the tumor without vascular contact or a limited venous contact without vein irregularity. Several pathologic and biologic robust prognostic factors such as an R0 resection defined by a margin ≥ 1 mm have been validated. In phase III trials, the doublet gemcitabine-capecitabine provided a statistically significant, albeit modest overall survival benefit, but failed to show an improvement in relapse-free survival. Similarly, gemcitabine plus nab-paclitaxel did not increase disease-free survival. Modified FOLFIRINOX led to improved disease-free survival, overall survival, and metastasis-free survival, with acceptable toxicity. In the future, prognostic and/or predictive biomarkers could lead the optimization of therapeutic strategies and neoadjuvant treatment could become a standard of care in PDAC.

Summary:

After curative intent resection, modified FOLFIRINOX is the standard of care in adjuvant in fit PDAC patients. Others regimens (monotherapy or gemcitabine-based) are an option in unfit patients.

Key words:

Pancreatic ductal adenocarcinoma, definition, FOLFIRINOX, biomarker, neoadjuvant

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the second most common digestive cancer in Western countries [1,2] with a regularly increasing incidence and is projected to become the second cause of cancer-related death between 2020 and 2030.[3]

Many of the older studies included patients with both metastatic and locally advanced PDACs in the same cohorts. During the past decade, learned societies recommended carrying out studies dedicated to treatment of these two different group of patients.[4,5] Thereafter, locally advanced PDAC subgroup was divided into « true » locally advanced tumors with a low rate of secondary resection and borderline tumors for which secondary resection is possible after induction treatment (about two third of cases in recent studies).[6,7*] Most of the proposed classifications for borderline tumors are based on the degree of arterial and/or venous contact of the tumor, however an international consensus recently suggested adding an Eastern Cooperative Oncology Group performance status and biological factors aside from anatomical criteria.[8-12] Thus, at diagnosis, only 10%-15% of patients have a resectable PDAC.

To date, resection remains the only potentially curative-intent treatment and upfront surgery remains the standard of care for patients with resectable PDAC.[13,14] While the benefit of adjuvant chemoradiotherapy (CRT) is a matter of debate, adjuvant chemotherapy has been a standard for over a decade now.[13-17] Three chemotherapy regimens, gemcitabine plus erlotinib (Roche®, Bâle, Switzerland), modified FOLFIRINOX (5-fluorouracil, oxaliplatin, and irinotecan), and gemcitabine plus nab-paclitaxel (Celgene®, Summit, New Jersey, USA) were found to be significantly superior to gemcitabine monotherapy in advanced stage pancreatic cancer,[18-20] and have subsequently been assessed in the adjuvant setting.[21,22**,23**] Several adjuvant randomized phase III trials have been published until now.[15-17,21-25] Standard chemotherapy regimens and robust prognostic factors that are

used after upfront surgery are now validated and a number of promising biomarkers have been reported. In addition, new therapeutic strategies are currently being evaluated with the development of novel neoadjuvant strategies.

The aim of this review is to describe the state of the art in the adjuvant setting of PDAC and to highlight future possible perspectives.

Text of review

1. Resectable Tumor

Definition

Many expert consensus groups have proposed definitions of borderline PDAC tumors in order to further improve the criteria for resectability at diagnosis, with the primary objective being a margin-negative resection (R0). Currently, a resectable PDAC is defined by the absence of vascular tumor contact or ≤ 180° contact with the superior mesenteric vein (SMV) or portal vein (PV) without vein contour irregularity (stenosis, deformity).[14,26] For the tumors of the body and/or tail of the pancreas, invasion of splenic vessels (artery and/or vein) is not a contraindication to upfront surgery. The presence of peri-pancreatic lymph nodes on the imaging assessment likewise does not a resection. Contrarily, in patients with distant lymph node involvement surgery should not be considered.[27-29]

A thoraco-abdomino-pelvien multi-detector computed tomography with intravenous contrast injection and fine sections on pancreatic area is a key diagnostic technique, allowing the assessment of locoregional and distant extensions.[14,26] Recently, some studies have highlighted the potential of adding a magnetic resonance imaging (MRI) with diffusion-weighted to this exam. Such approach has been suggested to increase the diagnosis of undiscovered infracentimetric liver metastases by 10%-15%.[30] The recently published French clinical practice guidelines indicate that a liver MRI at diagnosis is an option in patients with localized PDAC.[31] Histological proof of PDAC is not usually required before surgery if the medical history, symptoms, and imagery data are concordant with the diagnosis. However, this confirmation has to be obtained in case of doubt about the diagnosis or when neoadjuvant treatment is planned.[14,26,31]

Data on adjuvant chemotherapy in PDAC discussed below apply to resectable tumors defined along these criteria.

Prognostic factors

Carbohydrate antigen (CA) 19-9, a sialylated Lewis A blood group antigen, is currently the only biomarker validated in PDAC. This factor was found to be useful for monitoring treatment efficacy and follow-up after curative intent surgery, but not for screening.[14,26,31] While the CA 19-9 can be elevated in case of biliary obstruction or others cancers, it is normal in patients with a Lewis-negative genotype, present in about 5%-10% of the white population.[32] In case of resectable PDAC tumors, the level of pre-operative CA 19-9 is highly prognostic and some authors have proposed various cut-off values to define the resectability (from 100 to 500 U/ml),[12,33] in the absence of vascular involvement. Until now, at the exception of the International Association of Pancreatology, there is no pre-operative cut-off point recommended by the oncologic societies guidelines.[12,14,26,31] The level of post-operative CA 19-9 is also highly prognostic.[24,25] Moreover, it is noteworthy that the latter was added as an inclusion criteria in two recent adjuvant randomized phase III trials (the cut-off of $\leq$ 180 U/ml in PRODIGE24 and of < 100 U/ml in APACT).[22,23] Patients undergoing SMV or PV resection has been reported to be have worse prognosis.[34] This finding has led to restriction of the resecability definition to the PDAC tumors with limited vein contact (< 180°) and without contour irregularity.[11,14,26,31] Such defined resection was of poor prognosis in the ESPAC4 and PRODIGE24 trials. [22,25] and venous resections have to be reported in future adjuvant trials.

Several studies have reported variety of robust pathologic prognostic factors including grade of tumoral differentiation, N and T stage (maximal tumor diameter), and the resection margin status of which.[15-17,22,24,25] Most of these factors have subsequently been validated. The

definitions of T and N categories have been modified in the 8th version of American Joint Committee on Cancer (AJCC) TNM classification,[35] that recommends to look at least 15 lymph nodes to distinguish the N stage.[36] Historically among patients with PDAC, no consensual precise definition of the R0 resection margin and the modalities of its assessment were defined. Therefore, the R1-resection rate differs between adjuvant randomized phase III trials, ranging from 16% reported in the ESPAC1 trial to 61% in the ESPAC4 study.[15-17,22-25] According to the British College of Pathologists guidelines that have been validated by the International Study Group of Pancreatic Surgery, a positive-R1 resection margin is currently defined as < 1 mm.[10,14,31] Different surgical margins (anterior, posterior, medial, or SMV groove, superior mesenteric artery, pancreatic transection, bile duct, and enteric) have to be clearly identify by surgeon, at best by inking them with different colors.[10,37] In most studies on adjuvant chemotherapy for PDAC, the efficacy of this treatment on survival was reported in all subgroups defined by the grade of differentiation, N stage, T stage and the resection margin status.[15-17,22-25] Although, adjuvant chemotherapy is indicated in all patients who undergo curative intent resection of PDAC, a recent retrospective analysis from the US National Cancer database has suggested that patients with infra-centimetric PDAC (T1aN0 or T1bN0) may not necessary require this treatment.[38*] Indication of adjuvant chemotherapy in PDAC patients with infra-centimetric tumor should be discussed during multidisciplinary team meeting.

2. Adjuvant treatment

Adjuvant chemoradiotherapy

Adjuvant CRT was not associated with a clinical benefit in the ESPAC-1 trial and the results of this study actually suggested that it might even be harmful.[15] This trial had however

some limitations as neither the protocol of CRT used was optimal according to current standards and nor quality control for CRT was planned in this trial. In fact, the interest of adjuvant CRT is discussed and debated in the published literature with several studies reporting discordant results.[37,38] The meta-analysis of pooling patient data from five adjuvant randomized trials has suggested that patient with R1 resection could benefit from adjuvant CRT.[41] However, the R1 rate ranging from 17% to 82% across studies highlighted high heterogeneity in evaluation of the resection margin preventing any clear conclusions. Adjuvant CRT is not recommended by all oncologic guidelines.[14,26,31] The RTOG 0848 trial assessing the role of CRT after adjuvant gemcitabine (ClinicalTrials.gov identifier: NCT01013649) is ongoing and results are expected shortly. Patients without evidence of relapse after 5 cycles of gemcitabine are randomized between one more cycle of chemotherapy alone or one more cycle of chemotherapy followed by CRT.

Adjuvant monochemotherapy

The benefit of adjuvant chemotherapy has been demonstrated in the ESPAC-1 trial (5-fluorouracil [5FU] bolus; Mayo clinical FUFOL regimen for 6 months) and in the CONKO-001 trial (gemcitabine for 6 months).[15-17] These two regimens have been directly compared in the ESPAC-3 trial.[24] The oncological results obtained were strictly identical, but the safety profile was better with gemcitabine, positioning 5FU as an alternative treatment option. It should be noted that unlike for colorectal cancers, the LV5FU2 protocol (bolus 5FU then continuous 5FU over 46h) or capecitabine monotherapy were not evaluated as adjuvant treatment after resection of PDAC.

Summary of results from major phase III trials of adjuvant chemotherapy after curative resection of pancreatic ductal adenocarcinoma are presented in Table 1. Adjuvant gemcitabine monotherapy has been the standard of care for more than a decade.

Adjuvant gemcitabine-based chemotherapy

Several randomized clinical trials have evaluated the value of adding an additional drug to gemcitabine in the adjuvant setting following encouraging results from studies in metastatic PDAC.[18-20]

The erlotinib plus gemcitabine regimen was associated with increased overall survival (OS; HR=0.82, 95% CI 0.69-0.99; p=0.038) in comparison to gemcitabine alone in patients with advanced PDAC.[18] Although statistically significant, the OS benefit was not clinically relevant with an only 14-day median difference. Therefore, this protocol was not considered as a standard, but more as an option. Adding erlotinib to gemcitabine did not increase disease-free survival (DFS) or OS in the adjuvant CONKO-005 trial (Table 1)[21] and showed no benefit in the LAP07 trial of patients with locally advanced PDAC.[42]

Two randomized phase III trials reported an increase in progression-free survival (PFS), but not in OS by the addition of capecitabine to gemcitabine in patients with advanced PDAC.[43,44] Following these findings, the ESPAC-4 trial compared the gemcitabine plus capecitabine (GEMCAP) combination to gemcitabine monotherapy in the adjuvant setting.[25] This trial was positive for its main objective with a significant but modest increase in OS with the 5-year survival rate of 28.8% (vs 16.3%; Table 1). Nevertheless, these results have been criticized, in particular because of the absence of a significant relapse-free survival (RFS) difference between the two arms despite a trend in favor of the GEMCAP arm (the 3 and 5-year survival rate of 23.8% and 18.6% with GEMCAP and 20.9% and 11.9% with monotherapy, respectively). The GEMCAP protocol was also associated with a poorer safety profile (Table 2).

Finally, the gemcitabine plus nab-paclitaxel (GEMNAB) combination has been evaluated in adjuvant randomized phase III APACT trial.[19,23**] The study did not meet its main

objective, the DFS in centralized reviewing (GEMNAB 19.4 months vs gemcitabine 18.8 months [HR=0.88; p=0.182]). In per-investigator analysis, GEMNAB conferred a significant but modest benefit in DFS, (Table 1) and a significant increase in OS. The toxicity profiles corresponded to those expected with significantly more toxicities in the GEMNAB arm (Table 2).

Adjuvant modified FOLFIRINOX

In metastatic PDAC, the FOLFIRINOX protocol has demonstrated its superiority compared to gemcitabine.[20] This protocol was further evaluated in the PRODIGE24 trial in the adjuvant setting.[22**] To improve the tolerability, 5FU bolus was removed. The dose of irinotecan had to be reduced from 180 mg/m² to 150 mg/m² (modified FOLFIRINOX [mFOLFIRINOX]) due to a grade 3-4 diarrhea rate greater than 20% at the first planned interim analysis. The mFOLFIRINOX regimen was associated with a significant increase in DFS (the 3-year rate 39.7% vs 21.4%), OS (the 3-year rate 63.4% vs 48,6%), and metastasis-free survival (Table 1). The benefit of mFOLFIRINOX chemotherapy was found in all of the predefined subgroups with a statistically significant survival improvement in patients older than 65 years (n=201, 41%) and a trend in patients older than 70 years (n=101, 20%). There was no difference in neutropenia rates between the two arms, but 62% of patients in the mFOLFIRINOX arm had received granulocyte-colony stimulating factor. mFOLFIRINOX was associated with more mucositis, diarrhea, fatigue, vomiting, and neuropathy (Table 2), but these toxicities were manageable and no toxic deaths were reported. Diarrhea was most frequent in patients with a higher number of lymph nodes (≥20 vs <20; adjusted odds ratio, 2.4; 95% CI 1.3-4.4; p<0.001), which was expected given that extensive lymphadenectomy can be associated with more diarrhea in post-operative treatment but not with better oncologic outcomes.[36] Gemcitabine chemotherapy resulted in more thrombocytopenia and flu-like

illness. Overall, 66% of patients from the mFOLFIRINOX arm and 79% from the gemcitabine arm received all of the scheduled cycles.

Summary of adjuvant chemotherapy phase III trials

Considering the remarkable results of the PRODIGE24 trial, mFOLFIRINOX is now the standard adjuvant chemotherapy regimen in fit PDAC patients, while GEMCAP or mono-chemotherapies with gemcitabine or 5FU are validated treatment options in unfit patients. Gemcitabine monotherapy should be preferred over 5FU based on the better safety profile, while no consensus exists to favor GEMCAP over gemcitabine monotherapy. These regimens are proposed as equivalent updated options in the latest ASCO guidelines.[45] Although the APACT trial was negative for its primary objective, future indications of the GEMNAB regimen will need to be clarified in clinical guidelines given the positive per-investigator DFS and OS results.

3. Perspectives

Promising biomarkers

At least two major lines of research are currently underway to improve oncological results using biomarkers.

The first line of research has been undertaken in order to better define the optimal chemotherapy to use in the adjuvant setting for PDAC according to intra-tumoral expression of predictive biomarkers. Among these, the levels of intra-tumoral expression of human equilibrative nucleoside transporter 1 (hENT1) and deoxycytidine kinase (dCK) have proven to be the most promising potential biomarkers of the gemcitabine efficacy.[46-51] Nevertheless, discordant results have been reported due to the use of antibodies not equivalent

in activity.[46-53*] The level of dihydropyrimidine dehydrogenase (DPD) expression could also be predictive of the 5FU efficacy.[51*] Similarly, the recent molecular signatures (based on mRNA expression profiles) could also be predictive of chemotherapy efficacy, but there are no data in the adjuvant setting.[54*]

The second line of research has been undertaken to better define the patients with a resectable PDAC who will benefit the most from an upfront surgery. In fact, the risk of relapse remains very high after curative intent surgery, superior to 60%,[22] and PDAC is commonly considered as a systemic disease. The detection of circulating prognostic biomarkers could help to identify the patients who have the highest risk of early relapse after surgery and to propose them alternative therapeutic strategies (e.g. neoadjuvant chemotherapy). For instance, patients with detectable circulating tumor DNA before surgery do not seem benefit from upfront surgery.[55,56*] Others circulating biomarkers such as circulating tumor cells or exosomes are promising and could also be used as reliable markers of treatment efficacy.[57,58]

However, robust and reproducible methodologies to assess these biomarkers have to be developed and prospectively validated before any used in routine practice.

Neoadjuvant strategies

Like for gastric or rectal cancers, development of neoadjuvant strategies could allow to improve oncologic outcomes of patients with resectable PDAC. After pancreatic resection, about one third of patients cannot receive an adjuvant treatment because of postoperative morbidity and mortality.[59,60] Moreover, the rate of relapse remains superior to 60% in adjuvant phase III trials in which only fit patients have been included.[22-25] Data from the recent studies of patients with borderline PDAC have shown that neoadjuvant/induction strategies (most often, chemotherapy follow or not by CRT) were well tolerated and did not

impair the morbidity and mortality after secondary pancreatic resection, and even reduced the rate of pancreatic fistula.[6,7*,59-61] Moreover, and like in others digestive cancers, the pathologic response is a prognostic factor after neoadjuvant/induction treatment.[61] Promising preliminary results of the PREOPANC-1 trial assessing a neoadjuvant/induction strategy coupling gemcitabine and CRT in patients with resectable and borderline PDAC have been presented,[66] and several randomized neoadjuvant phase II and III trials are currently ongoing.[63-66]

Conclusions

The definition of resectable PDAC has evolved in recent years, but upfront surgical resection remains the standard of care in this disease setting. The mFOLFIRINOX regimen is now the adjuvant standard in fit patients. Modified FOLFIRINOX, gemcitabine-based regimens (GEMNAB, GEMCAP), monotherapy with gemcitabine or with 5-fluorouracil are the alternative options in unfit PDAC patients. Several promising predictive or prognostic biomarkers have been proposed, but they still need prospective validation. Neoadjuvant treatment will likely shape the future in this setting and several randomized trials are currently ongoing.

Key points

- Resectable PDAC is defined as the tumor without vascular contact or ≤ 180° contact with the superior mesenteric vein (SMV), or portal vein (PV) without vein contour irregularity.

- Upfront surgery remains the standard of care for resectable PDAC and robust and validated biological and pathological factors coupled with the sound international guidelines are in place.

- In fit patients, the modified FOLFIRINOX regimen is now the standard treatment after curative intent surgery of PDAC, while the gemcitabine-base regimens (GEMCAP or GEMNAB) or monotherapies are an option in unfit patients.

- Prospective validation of methodologies used to assess promising predictive and/or prognostic biomarkers and of steps that lead to interest in a specific therapeutic strategy with their use are necessary before these are applied in routine clinical practice.

- Neoadjuvant treatment strategies are probably the future and several randomized trials are ongoing.

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Table 1: Major phase III trials of adjuvant chemotherapy after curative resection of pancreatic ductal adenocarcinoma [15-17, 21- 25]

Trial, Year	Arm of treatment	Number of patients	R1 resection rate	N+ rate	Venous resection	Disease-free survival months (95% CI)	HR (95% CI)	Overall survival months (95% CI)	HR (95% CI)
ESPAC-1, 2001	5FU bolus	147	19%	50%	ns	15.3 (10.5-19.2)	ns p=0.02	20.1 (16.5-22.7)	0.71 (0.55-0.92)
	Observation	142	16%	58%	ns	9.4 (8.4-15.2)		15.5 (13.0-17.7)	p=0.009
CONKO-001, 2007	Gem	179	19%	70%	ns	13.4 (11.6-15.3)	0.55 (0.44-0.69)	22.8 (18.5-27.2)	0.76 (0.61-0.95)
	Observation	175	15%	71%	ns	6.9 (6.0-7.5)	p<0.001	20.2 (17.7-22.8)	p=0.01
ESPAC-3, 2010	5FU bolus	551	35%	70%	16%	14.1 (12.5-15.3)	0.96 (0.84-1.10)	23.0 (21.1-25.0)	0.94 (0.81-1.08)
	Gem	537	35%	73%	13%	14.3 (13.5-15.6)	p=0.53	23.6 (21.4-26.4)	p=0.39
CONKO-005, 2017	Gem	217	0%	66%	ns	11.4 (9.2-13.6)	0.94 (0.76-1.15)	26.5 (22.4-30.6)	ns p=0.61
	Gem + Erlo	219	0%	64%	ns	11.4 (9.6-13.2)	p=0.26	24.5 (21.1-27.8)	
ESPAC-4, 2017	Gem	366	60%	82%	17%	13.1 (11.6-15.3)	0.86 (0.73-1.02)	25.5 (22.7-27.9)	0.82 (0.68-0.98)
	Gem + Cap	364	61%	79%	11%	13.9 (12.1-16.6)	p=0.082	28.0 (23.5-31.5)	p=0.032
PRODIGE 24, 2018	Gem	246	45%	75%	28%	12.8 (11.7-15.2)	0.58 (0.46-0.73) p<0.001	35.0 (28.7-43.9)	0.64 (0.48-0.86)
	FOLFIRINOX	247	40%	78%	22%	21.6 (17.7-27.6)		54.4 (41.8-nr)	p=0.003
APACT, 2019	Gem	434	23%	72%	ns	13.7	0.82* (0.69-0.95)	36.2	0.82 (0.68-0.99)
	Gem + Nab	432	24%	72%	ns	16.6	p=0.017	40.5	p=0.045

Abbreviations: 5FU, 5-fluorouracil; Gem, gemcitabine; Erlo, erlotinib; Cap, capecitabine; Nab, CA, adjuvant chemotherapy; ns, non-specified; nr, not reached

* per-investigator analysis

Details of adjuvant chemotherapy protocols:

- 5FU bolus: leucovorin 20 mg/m^2 bolus follow by 5-fluorouracil 425 mg/m^2/day bolus for 5 consecutive days, every 28 days, for a total of 6 cycles.
- Gem: gemcitabine 1000 mg/m^2 in 30 minutes intravenous (IV) at days 1, 8, and 15, one cycle every 28 days, for a total of 6 cycles.
- Gem + Erlo: gemcitabine 1000 mg/m^2 in 30 minutes IV at days 1, 8, and 15, plus erlotinib 100 mg/day from day 1 to day 28, one cycle every 28 days, for a total of 6 cycles.
- Gem + Cap: gemcitabine 1000 mg/m^2 in 30 minutes IV at days 1, 8, and 15, plus capecitabine 1660 mg/m^2/day from day 1 to day 21, one cycle every 28 days, for a total of 6 cycles.
- FOLFIRINOX: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 at day 1 follow by 5-fluorouracil 2400 mg/m^2 in 46h continuous infusion, one cycle every 14 days, for a total of 12 cycles.
- Gem + Nab: nab-paclitaxel 125 mg/m^2 in 30-40 minutes IV follow by gemcitabine 1000 mg/m^2 in 30 minutes IV at days 1, 8 and, 15, one cycle every 28 days, for a total of 6 cycles.

Table 2: Summary of main grade 3-4 adverse events reported in adjuvant randomized phase III trials [15-17, 21- 25]

Type of adverse events	Gemcitabine	5-fluorouracil (bolus)	Gemcitabine + erlotinib	Gemcitabine + capecitabine	Gemcitabine + nab-paclitaxel	mFOLFIRINOX*
Hematologic						
Neutropenia	22%-43%	22%	27%	38%	49%	34%
Febrile neutropenia	≤1%	ns	ns	ns	5%	4%
Anemia	1%-8%	ns	ns	2%	15%	3%
Thrombocytopenia	1%-6%	0%	5%	2%	ns	1%
Non-hematologic						
Fatigue	2%-6%	8%	5%	6%	10%	11%
Diarrhea	1%-4%	13%	5%	5%	5%	19%
Nausea	1%-2.5%	3.5%	ns	ns	ns	5.5%
Vomiting	1%-2%	3%	ns	ns	ns	5%
Stomatitis	0%	10%	ns	ns	ns	2.5%
Hand-foot syndrome	0%	ns	ns	7%		<1%
Peripheral neuropathy	0%	0%	0%	0%	15%	13%

Abbreviations: ns, not specified

*62.2% of patients received granulocyte-colony stimulating factor during adjuvant treatment