Advances in Chemotherapy for Pancreatic Cancer

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Abstract Pancreatic cancer remains challenging to treat. Over the past decade, there have been some major improvements in systemic therapy. Gemcitabine remains the key drug for both early and advanced cancer but combination chemotherapy is emerging as a new paradigm for patients with good performance status. This review focuses on current chemotherapy status for patients with pancreatic cancer.

Keywords Pancreatic cancer · FOLFIRINOX · Gemcitabine · Nab-Paclitaxel

Introduction

The prognosis of pancreatic cancer remains poor despite clear advances in surgical technique, chemotherapy and targeted therapy. Most patients present with advanced disease and only 15 to 20 % of patients are candidates for pancreatectomy. Surgery remains the best and only curative option, with recent advances in surgical expertise and supportive care in the post op period, the 5 year survival of completely resected node negative pancreatic cancer approaches 40 % and overall 5 year

survival of 18 %. [1] For patients who underwent pancreatectomy, the reported stage predicted 5-year survival are stage IA, 31.4 %; IB, 27.2 %; IIA, 15.7 %; IIB, 7.7 %; III, 6.8 %; IV, 2.8 %. [2]

In advanced disease progress has been made with newer combination regimens with prolongation of survival but it still has not gone beyond a year. [3] Extensive research is ongoing into newer biological agents which are being combined with chemotherapy and markers of drug resistance like human equilibrative nucleoside transporter-1 (hENT1), [4] MMP-7 [5] and micro RNA21 (miR-21) [6] are being looked into so that treatment of each patient can be individualised. This review focuses on the current status of chemotherapy in all settings – neoadjuvant, adjuvant and metastatic for patients with pancreatic cancer.

Adjuvant Therapy

Complete surgical resection provides the only chance of cure. However even after complete (R0) resection long term survival remains poor. Most patients (>80 %) develop distant metastasis as first site of failure after surgery. Adjuvant approaches have included chemotherapy, radiotherapy and chemoradiotherapy. Adjuvant chemotherapy has demonstrated survival benefit and any additional benefit of combining radiotherapy to the treatment regimen has not been proven in this setting. [7]

Adjuvant chemotherapy is indicated for all patients (including T1N0 disease) with pancreatic adenocarcinoma following resection. [8] Persistent elevation or rising Ca 19.9 after resection is associated with extremely poor prognosis. [9] However strong data is not available so that one can guide treatment decisions based on the finding of a persistently elevated Ca 19.9. [10]

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The timing and duration of starting adjuvant chemotherapy was studied in an analysis from the patients enrolled in the ESPAC 3 study. This trial randomised 1,088 patients with resected pancreatic ductal adenocarcinoma to 6 months of postoperative adjuvant treatment with either gemcitabine or leucovorin modulated 5-FU. The primary outcome was overall survival. The time to starting chemotherapy did not influence overall survival (OS) rates for the full study population. The time to start chemotherapy (within 8 weeks of surgery versus later) was an important survival factor only for the subgroup of patients who did not complete all 6 months of therapy (and in this group, survival was better with later initiation of therapy). There seemed to be no difference in outcomes if chemotherapy was delayed for up to 12 weeks. The patients who completed the full six courses of treatment versus those who did not had a better OS (median survival 28 versus 15 months, hazard ratio [HR] for death 0.61, 95 % CI 0.44 to 0.60).[11]

Randomized controlled clinical trials and meta-analyses suggest a significant OS benefit from chemotherapy alone following resection of a pancreatic cancer.[5–19] Current standard of care is Gemcitabine alone for 6 months post-surgery given the interpretations from the ESPAC-3 study which showed that though there was not a survival advantage with Gemcitabine compared to 5-FU, toxicities were significantly less with Gemcitabine.[16]

Table 1 shows the key studies of adjuvant therapy in pancreatic cancer.

European Study for Pancreatic Cancer (ESPAC)-1 trial reported the pooled analysis of 238 patients who received

adjuvant chemotherapy as compared with 235 who did not receive it and showed a survival benefit for adjuvant chemotherapy (median survival 19.7 versus 14 months, respectively), but no survival difference when the 175 patients receiving postoperative chemo radiotherapy were compared with the 178 who did not receive it (median overall survival 15.5 versus 16.1 months, respectively).[12] This trial was initially designed as a 2 × 2 factorial design with the following arms - observation, chemotherapy, chemoradiotherapy and chemoradiotherapy followed by chemotherapy. The trial later expanded to allow two further randomizations-chemotherapy versus no chemotherapy and chemoradiotherapy vs. no chemoradiotherapy. Intent to treat analysis was not used in the trial. The European Charité Onkologie (CONKO)-001 trial studied Gemcitabine in 368 patients with completely resected pancreatic ductal adenocarcinoma and reported improvement in OS that favoured Gemcitabine and persisted long term (5-year OS 21 versus 10 %; 10-year 12.2 versus 7.7 %).[13] The ESPAC 3 trial described earlier reported at a median follow-up of 34 months, median survival was similar in both the arms (23.6 versus 23 months with gemcitabine and fluoropyrimidine therapy, respectively). However, the patients assigned to FU/leucovorin had more grade 3 to 4 treatment-related toxicity including stomatitis (10 versus 0 %), diarrhea (13 versus 2 %), and more hospital admissions.[16] S-1 is an oral fluoropyrimidine that includes three different agents: florafur (tegafur), gimeracil (5-chloro-2,4 dihydropyridine, a potent inhibitor of DPD [dihydropyrimidine dehydrogenase]), and oteracil (potassium oxonate, which inhibits phosphorylation of intestinal FU, responsible for treatment-related

Table 1 Adjuvant therapy in pancreatic cancer

Author [ref];year	Trial arms	Patients	Median survival (mo.)	DFS (mo.)	OS (%)
Bakkevold [15];1993	Observation	31	11		5 y- 8
	Dox/5FU/Mito	30	24		5 y- 4
Takada [17];2002	Observation	77	13		5 y- 18
	5FU/Mito	81	13		5 y- 11.5
ESPAC-1 [18];2004	Observation	235	15.5		5 y- 8
	5FU	238	20.1		5 y- 21
Kosuge [19];2006	Observation	44	15.8		5 y- 14.9
	Cisplatin/5FU	45	12.5		5 y- 26.4
RTOG9704 [20];2011	5FU/CTRT	230	17.1		5 y- 18
	Gem/CTRT	221	20.5		5 y- 22
ESPAC3 [16]; 2010	5FU/FA	551	23.0	14.1	2 y- 48
	Gemcitabine	537	23.6	14.3	2 y- 49
JSAP02 [21]; 2009	Observation	60	18.4	5	5 y- 10.6
	Gemcitabine	58	22.3	11.4	5 y- 23.9
CONKO-001 [13];2013	Observation	175	20.2	6.7	5 y- 10.4
	Gemcitabine	179	22.8	13.4	5 y- 20.7
JASPAC-01 [14];2013	Gemcitabine	191	-	2 y- 29 %	2 y- 53
	S1	187	-	2 y-49 %	2 y- 70

5-FU 5-fluorouracil, Mito Mitomycin C, Dox doxorubicin, CTRT chemoradiotherapy, Gem Gemcitabine, FA folinic acid

diarrhea). S-1 (40 to 60 mg twice daily for 4 weeks and repeated every 6 weeks for four courses) was directly compared with Gemcitabine in a Japanese trial involving 378 patients. S-1 was found to be non-inferior to gemcitabine, and patients treated with S-1 actually had a lower mortality rate (hazard ratio for death [HR] 0.56, 95 % CI 0.42–0.74, 2-year survival 70 versus 53 %).^[14]

ESPAC-4 is currently randomising patients to Gemcitabine versus Gemcitabine plus capecitabine, hopefully this study will answer the key question whether a Gemcitabine doublet is superior to Gemcitabine alone. ^[22]

Does Chemoradiotherapy add Benefit to Chemotherapy Alone?

The ESPAC-1 was a multicenter European trial and randomly assigned 73 patients with resected pancreatic ductal adenocarcinoma to treatment with chemoradiotherapy alone (20 Gy over a 2-week period plus fluorouracil), 75 patients to chemotherapy alone (fluorouracil), 72 patients to both chemoradiotherapy and chemotherapy, and 69 patients to observation. The trial reported both the 2-year (40 versus 30 %) and 5-year (21 versus 8 %) survival rates were significantly greater among patients randomized to postoperative chemotherapy alone compared with those who did not receive it, despite the fact that 33 % of those assigned to adjuvant chemotherapy did not complete all six courses, and 17 % received no chemotherapy at all. Patient with complete (R0) resections derived greater benefit from adjuvant chemotherapy as compared to patients with R1 resections but in both groups the survival was increased with adjuvant chemotherapy. In contrast, there was no significant benefit for chemoradiotherapy in the two groups that received it, and in fact, the data suggested a trend toward worse survival for this group (2- and 5-year survival rates were 29 versus 41 %, and 10 versus 20 % for the chemoradiotherapy and no chemoradiotherapy groups, respectively). In this trial, radiation therapy quality assurance was not centrally audited; the radiation oncologists had the option of giving up to 60 Gy, although the allocated dose was 40 Gy. ^[18]

The only other trial to compare the relative benefits of adding chemoradiotherapy to systemic therapy versus systemic therapy alone was the EORTC 40,013/FFCD-9,203/GERCOR phase II feasibility study.^[23] 90 patients were randomly assigned to receive either four cycles of Gemcitabine (control arm) or Gemcitabine for two cycles followed by weekly Gemcitabine with concurrent radiation (50.4 Gy; CRT arm). In contrast to the results of the ESPAC-1 analysis, chemoradiotherapy was not deleterious; median DFS was 12 versus 11 months in the control group, and median overall survival was 24 months in both arms.

The benefits of chemoradiotherapy with and without chemotherapy were addressed in a 2013 network meta-analysis of nine randomized trials comparing six different adjuvant strategies (observation alone, FU alone, Gemcitabine alone, chemoradiotherapy alone, chemoradiotherapy followed by FU, and chemoradiotherapy followed by Gemcitabine).^[7] This meta-analysis could not show a statistically significant survival benefit for chemoradiotherapy. Compared with observation alone, the hazard ratios (HRs) for death were 0.91 (95 % CI 0.55–1.46) for chemoradiotherapy alone, 0.54 (95 % CI 0.15–1.80) for chemoradiotherapy plus FU, and 0.44 (95 % CI 0.10–1.81) for chemoradiotherapy plus Gemcitabine.

Resection Margins and Adjuvant Decision Making

ESPAC –1 showed that R0 resections did better with adjuvant chemotherapy rather than R1 resections but both need adjuvant chemotherapy. Currently, most adjuvant clinical trials for chemotherapy include R1 resections as an inclusion criteria (i.e., ESPAC-4). Both R1 and R2 resections warrant chemotherapy and not chemoradiotherapy.^[24] Through a surgical perspective – the surgeon is made more aware of margin positive resections by improved concepts in pathology,^[25] hence surgeons have also strived to improve techniques to achieve margin negative resections.^[26]

Neoadjuvant Therapy

The low rate of resectability for lesions deemed operable on imaging, the suboptimal long-term outcomes following pancreaticoduodenectomy despite adjuvant therapy, and the fact that postoperative adjuvant therapy is delayed or not administered in about one-fourth of patients due to delayed recovery from surgery ^[27], have led to the investigation of neoadjuvant therapy. While neoadjuvant therapy is safe and does not increase peri-operative morbidity or mortality, no study has clearly demonstrated improved resectability or survival compared to patients treated with surgery alone in a randomised setting. Data is limited to small phase 2 studies.^[28, 29] Heinrich et al. studied 28 patients in whom after confirmation of resectability by contrast-enhanced computed tomography, positron emission tomography/CT, laparoscopy, and endoscopic ultrasound, patients received four biweekly cycles of gemcitabine 1,000 mg/m² (2) and cisplatin 50 mg/m² (2). Thereafter, staging was repeated and patients underwent surgery. 26 (93 %) had resectable cancer on restaging examinations, and the R0 resection rate was 80 %. On intention-to-treat analysis, overall survival was 9 months (95 % CI, 6.99 to 10.1 months) and 19.1 months (95 % CI, 15 to 23.1 months).^[28] Palmer et al. conducted a randomised phase 2 trial to study neoadjuvant chemotherapy in resectable

pancreatic ductal adenocarcinoma. 24 patients were randomized to Gemcitabine and 26 patients were randomized to Gemcitabine and Cisplatin. 27 (54 %) patients underwent pancreatic resection, 9 (38 %) in the Gemcitabine arm and 18 (70 %) in the combination arm, with no increase in surgical complications. 1 year survival for the Gemcitabine and combination groups was 42 and 62 % respectively.[29]

Borderline Resectable

Pancreatic lesions involving the major mesenteric vasculature to a limited extent, potentially resectable, but when an attempted resection may be compromised by positive surgical margins in the absence of either vascular resection or preoperative therapy are considered to be borderline resectable. In cases when there is no more than focal (less than one-half of the circumference) tumour abutment of the visceral arteries or short-segment occlusion or narrowing of the SMV or SMV/portal vein confluence they are considered to be borderline resectable.[30]. The NCCN criteria are widely accepted [31]

Neoadjuvant treatment strategy offers multiple theoretical advantages over an initial surgical approach such as (1) Immediate commencement of systemic therapy in a cancer in which micro metastatic disease is omnipresent, (2) Improve possibility of a complete (R0) resection, (3) Better tolerance and compliance due to better patient functional status at the time of therapy, (4) exclusion of patients with unfavourable cancer biology from a major surgery which is not likely to be beneficial and (5) Improved drug delivery for chemoradiotherapy due to better tumour oxygenation and, resulting in less treatment-related toxicity. The use of a neoadjuvant treatment strategy ensures that all patients who undergo surgery receive all components of multidisciplinary care. Furthermore, patients who do not undergo resection still receive active anti-cancer therapy.

Neoadjuvant therapy in this situation if effective can downstage the disease and therefore would improve the possibility of a complete resection and long-term survival. A 2011 meta-analysis of phase II trials looking at all the neoadjuvant strategies concluded that about one-third of tumours initially deemed borderline resectable were successfully resected after neoadjuvant treatment and that the median survival in this group was 22.3 months (range 18 to 26 months). In a large series which included 160 patients of borderline resectable disease from MD Anderson [32], 125 completed neoadjuvant therapy (induction chemotherapy in 82; chemoradiotherapy in 117) and were restaged. 79 underwent laparotomy; 66 were resected, 62 had R0 resection (38 %). The median survival durations for the unresectable and resectable cohorts were 13 and 40 months, respectively. Limited data with FOLFIRINOX is encouraging. Hosein et al. treated 18 patients with unresectable or borderline resectable LAPC were treated with neoadjuvant FOLFIRINOX. [33] 11 (61 %) had tumours in

the head of the pancreas and 9 (50 %) had biliary stents placed prior to chemotherapy. 7 (39 %) were converted to resectable lesions by radiological criteria; 5 had R0 resections, 1 had an R1 resection, and 1 had unresectable disease. Among the 11 patients who remained unresectable after FOLFIRINOX, 3 went on to have R0 resections after combined chemoradiotherapy, giving an overall R0 resection rate of 44 %. After a median follow-up of 13.4 months, the 1-year progression-free survival was 83 % and the 1-year overall survival was 100 %.

Table 2 shows results of some key studies of neoadjuvant strategy in patients with pancreatic cancer [35–50]. The pragmatic trial from the Intergroup would throw light on how to manage these patients optimally- all patients with borderline resectable pancreatic cancer receive FOLFIRINOX for 4 cycles followed by chemoradiotherapy with capecitabine and if stable or responding, patients are taken for surgery 6–8 weeks post-completion of radiotherapy.[34]

Locally Advanced Unresectable Pancreatic Cancer (LAPC)

About 30 % of patients with LAPC do not respond to neoadjuvant treatment and develop distant metastasis within 3 months of treatment initiation.[51] Therefore for patients with locally advanced unresectable disease, an initial period of chemotherapy rather than radiation therapy (RT) or chemoradiotherapy is a reasonable approach, especially in resource limited settings. This strategy is being studied in ongoing trials. Patients who do not progress following initial chemotherapy, a standard approach would be to offer them external beam RT (EBRT) plus concomitant low-dose infusional FU (eg, 200 mg/m² daily) or Capecitabine.

In the same situation however it is unclear whether continuing chemotherapy alone would be inferior to chemoradiotherapy. There is no consensus on the superiority of chemotherapy versus chemoradiotherapy from the available information, with reports of increased toxicity especially with Gemcitabine with the use of chemoradiotherapy in the reported trials.[52]

Retrospective series have reported improved outcomes with median survival favouring chemoradiotherapy over chemotherapy (15 vs. 11.7 months) [53] Similar results were reported by the Eastern Cooperative Oncology Group 4,201 study [54] with Gemcitabine and chemoradiotherapy with Gemcitabine showing chemoradiotherapy was associated with significantly improved median survival from 9.2 months in the chemotherapy alone arm to 11.1 months .

Results of the LAP 07 trial were presented at the ASCO 2013 annual meeting, 442 patients with locally advanced pancreatic cancer were randomized to Gemcitabine or Gemcitabine with Erlotinib. Patients with stable disease or

Table 2 Neoadjuvant treatment in borderline resectable pancreatic cancer

Author, [ref] year	N	Neoadjuvant regimen (%)	No. Resected	R0 resections (%)	Survival
Christians KK, [35] 2014	18	FOLFIRINOX	12 (67 %)	12 (67 %)	Median 22 months
Leone F,[36] 2013	15	GEMOX then Gem-RT	9 (60)	NR	Median 28 months.
Takahashi H,[37] 2013	80	Gem-RT	43 (54)	42 (98)	5-y: 34 %
Kim E,[38] 2013	39	GEMOX-RT	24 (62)	NR	Median 18.4 months.
Motoi F,[39] 2013	16	Gem-S-1	NR	NR	2-y: 31.5 %
Kharofa J,[40] 2012	12	FOLFIRINOX then CRT	7 (58)	7 (100)	Median not reached at 13 months
Lee J,[41] 2012	18	Gem-Cape	11 (61)	9 (82)	NR
Kang C,[42] 2012	32	Gem +/- Cis-RT	32 (100)	28 (88)	NR
Chuong M,[43] 2011	14	GTX then CRT	14 (100)	12 (86)	NR
Barugola G,[44] 2012	27	Various	27 (100)	NR	NR
Stokes J,[45] 2011	40	Cape-RT	16 (40)	12 (75)	NR
Sahora K,[46] 2011	12	Gem-Tax	4 (33)	NR	NR
Chun Y,[47] 2010	74	Various	74 (100)	44 (60)	Median 21 month.
McClaine R,[48] 2010	29	Various	12 (41)	8 (75)	NR
Evans,[49] 2008	86	Gem-RT	64 (74)	NR	5-y: 36 %
Varadhachary,[50] 2008	90	GEM-Cis then Gem-RT	52 (57)	NR	Median 31 month.

better after 4 months ($n=269$) were then randomized to continued chemotherapy for 2 months versus Capecitabine-based chemoradiotherapy to 54 Gy. [55] The primary endpoint of the trial was OS, and the trial was stopped after a 3-year interim analysis demonstrated futility for superiority of chemoradiotherapy. There was no statistically significant difference between OS or PFS for the chemotherapy and chemoradiotherapy arms (OS: 16.4 vs. 15.2 months, respectively; PFS: 11.8 vs. 12.5 months, respectively).

We await the formal publication of the LAP 07 trial, however as of now based on the results reported treatment decision for patients responding to chemotherapy should be continuation of chemotherapy. For patients with localized disease who have difficulty tolerating chemotherapy, patients experiencing symptoms from their primary tumour, or patients who may be considered for surgical exploration, consolidative chemoradiotherapy to optimize local tumour control and surgical resectability may be explored. Table 3 shows some studies of chemotherapy versus chemoradiotherapy in patients with LAPC [52, 54, 56–59].

Metastatic Disease – First Line Therapy

Gemcitabine has been the first line treatment of advanced pancreatic cancer since, Burris et al. compared Gemcitabine with 5-FU and showed a better OS (median 5.65 vs 4.41 months, $P=0.0025$ with 1-year survival of 18 vs. 2 % in favour of Gemcitabine).[60] Gemcitabine-Nab-Paclitaxel is emerging as the new standard of care due to the ease of administration and manageable toxicity profile.[61, 62]. For patients with excellent performance status FOLFIRINOX has

demonstrated the best efficacy in randomised controlled trials.[3] Previous studies have combined Gemcitabine with fluoropyrimidine (5-FU and capecitabine) [63], platinum (Gemcitabine and Cisplatin/Oxaliplatin) [64–66], Irinotecan [67], Docetaxel [68] and individually have not shown an OS benefit but there has been a benefit on disease progression in some studies.[69] A meta-analysis including almost 4,500 patients has shown that there is an improvement in OS when Gemcitabine is combined with a platinum (HR 0.84, $P=0.01$) or fluoropyrimidine (HR 0.90, $P=0.03$) but not with any other agent.[70] This meta-analysis also showed that ECOG performance status (PS) remains a crucial factor in deciding if patients should receive palliative chemotherapy, there is no benefit in patients with PS 2 or more.

Various targeted agents (bevacizumab, marimastat, tipifarnib, cetuximab) have been combined with Gemcitabine and compared to Gemcitabine alone in randomised setting and the only drug that has shown benefit has been the combination of Gemcitabine-erlotinib which showed that patients who were on the combination arm had a significantly better OS (median 6.24 vs 5.91 mo, $P=0.038$). [71, 72]

Two recent trials have been practice changing.[3, 61] The ACCORD/PRODIGE study showed that OS for FOLFIRINOX (infusional and bolus 5-FU, Gemcitabine, irinotecan given through a central line at 2 weekly intervals) is significantly superior compared to emcitabine alone and it was the first time that OS was closer to a year with the combination regimen. The downside of FOLFIRINOX is the significant toxicity and the use of growth factors which is mandatory for majority of patients. Our experience has been that majority of patients do not tolerate full dose and need a 25 % dose reduced regimen; recent studies are looking at

Table 3 Trials of chemotherapy vs. chemoradiotherapy followed or preceded by chemotherapy in LAPC

Author;[ref] year	5-FU plus arms	n	RT dose	Outcome
Hazel J;[56] 1981	5-FU+methyl-CCNU	15	46 Gy	Median OS 7.8 versus 7.3 months
	RT+5-FU Post CRT: 5-FU+methyl-CCNU	15		
Klaassen D;[57] 1985	5-FU weekly	44	40 Gy	Median OS 8.2 versus 8.3 months
	RT+5-FU Post CRT: 5-FU weekly bolus	47		
GITSG;[58] 1988	5-FU+STZ+mitomycin	21	54 Gy	Median OS significantly better with CRT (42 versus 32 weeks)
	RT+5-FU. Post CRT: 5-FU+streptozocin+mitomycin	22		
Chauffert B;[59] 2008	Gemcitabine	60	60 Gy	Median OS significantly better with chemotherapy alone (14.3 versus 8.4 mo)
	RT+5-FU+cisplatin days 1–5 every week. Post CRT: Gemcitabine	59		
Loehrer P;[54] 2011	Gemcitabine	37	50.4 Gy	Median OS significantly better with CRT (11.1 versus 9.2 months)
	RT versus Gemcitabine	34		
Mukherjee S;[52] 2013, SCALOP	(12 weeks Gem-Cape) Gem –RT vs. Cape –RT	38 Gem-RT 36 Cape-RT	50.4Gy	Median OS significantly better with Cape-RT

dose-modified regimen [73] and it would be worth looking to see if long-term outcome remains the same. The second study was the MPACT study which randomised patients to Gemcitabine-Nab Gemcitabine and Gemcitabine alone and showed that patients in the combination arm had a significantly superior OS (median 8.5 vs 6.7 mo). There is some interest that SPARC (secreted protein rich in cysteine) testing may select patients who may benefit from Nab Paclitaxel. [62, 74]

Table 4 shows the results of some key studies in first-line metastatic pancreatic cancer [3, 60, 61, 66, 69, 72, 75, 76].

Metastatic Disease – Second Line

The only data to suggest a survival benefit for second-line treatment versus supportive care alone come from a trial in which 46 patients failing first-line Gemcitabine monotherapy were randomly assigned to best supportive care with or without Oxaliplatin and 5FU chemotherapy.[77] The trial was stopped prematurely because of insufficient accrual. However, the treated group had a significantly longer median survival from the start of treatment (4.8 versus 2.3 months) and longer

Table 4 Randomized clinical trials for unresectable or metastatic pancreatic cancer

Author [Year] [ref]	Regimen	n	Response (%)	Median OS (months)	%1-year survival
Burris [1997] [60]	Fluorouracil	63	0	4.41	2
	Gemcitabine	63	5.4	5.65	18
Moore [2007] [72]	Gemcitabine	284	6.9	5.9	17
	Gemcitabine/erlotinib	285	8.2	6.2	23
Cunningham [2009] [69]	Gemcitabine	266	12.4	6.2	22
	Gemcitabine/Cape	267	19.1	7.1	24
Colucci [2010] [66]	Gemcitabine	199	23	8.3	34
	Gemcitabine/Cisplatin	201	15	7.2	31
Bramhall [2002] [75]	Gemcitabine	119	11	5.4	18
	Gemcitabine/Marmistat	120	16	5.4	17
Conroy [2011] [3]	Gemcitabine	171	9.4	6.8	20.6
	FOLFIRINOX	171	31.6	11.1	48.4
Ueno [2013] [76]	Gemcitabine	277	13.3	8.8	35.4
	S-1	280	21.0	9.7	38.7
	Gemcitabine/S-1	275	29.3	10.1	40.7
Goldstein [2014] [61]	Gemcitabine	430	11 %	6.6	22
	Nab-paclitaxel+Gemcitabine	431	31 %	8.7	35

median survival from the start of emcitabine (9 versus 7.9 months, $p=0.031$).

Other active agents to which the patient was not exposed in the first line should be used either as single agent or as doublets if patient is fit for chemotherapy.

Surgery in Metastatic Disease in the era of Improved Chemotherapy

The presence of distant metastases in patients with pancreatic cancer is widely regarded as a terminal event in a disease where mortality nearly equals its incidence. However, since surgery currently remains the only treatment option with a chance of cure for localized disease, surgeons have attempted to treat even metastatic pancreatic cancer with curative intent. There have been reports and even some small series that have looked into this aggressive surgical treatment option.[78–81]

In a series of 29 patients of metastasectomies (M1 disease) in locally resectable pancreatic cancer,[82] reported a median survival of 13.8 months after R0/R1 surgery for advanced pancreatic cancer with M1 disease that was deemed as limited M1 disease on the operating table by the operating team. The 1-year survival in this series was 58.9 %. While the median survival following resection of liver and peritoneal metastases was comparatively low (11.4 months and 12.9 months respectively), the median survival following removal of inter-aortocaval lymph node metastases approached an acceptable figure of 27 months. The morbidity and mortality in their series was 24 and 0 % respectively and this was no different compared to outcomes after conventional R0 pancreatic resections without distant metastases.

In contrast to the above study, another study [83] observed no survival difference in patients who had resections for liver and peritoneal metastases compared to those who did not. However, in 48 patients who did undergo removal of the involved inter-aortocaval lymph nodes, survival appeared to be better than those not resected.[84]

In a systematic review on the subject of pancreatic resections in metastatic disease, Michalski et al. evaluated data from 3 case reports and 21 studies on liver resections for pancreatic cancer.[85] This review concluded that while such resections were technically feasible in highly selected patients the actual benefit could be determined only from larger randomized controlled trials. In summary, sufficient evidence does not exist to objectively determine the precise role of surgery in metastatic pancreatic cancer. Presently such a surgical option should be restricted to only well powered clinical trials that should be designed to answer a question that remains open to debate. Current standard of care remains palliative chemotherapy for patients with metastatic disease even if it is oligo-metastatic.

Future

Biomarkers which are prognostic and predictive are being explored. SMAD4, a tumour suppressor, was reported as a potential predictor of local versus distant progression. [86] Patients with intact SMAD4 were significantly more likely to present with locally destructive disease compared with patients with loss of SMAD4 immunostaining. This correlation between SMAD4 and pattern of disease spread has been validated independently.[87] In future SMAD4-intact disease may be identified as the one subgroup likely to benefit from locally aggressive therapy.[88]

Immunotherapy in pancreatic cancers is also being explored Le et al.[89] investigated the effect of administering CRS-207 with GVAX on overall survival in metastatic pancreatic cancer. GVAX consists of irradiated pancreatic cancer cells that have modified to elude granulocyte-macrophage colony-stimulating factor (GM-CSF) and produce an anti-tumour immune response. Immunogenicity is further enhanced with low dose cyclophosphamide, which inhibits regulatory T-cells. CRS-207 contains live-attenuated *Listeria monocytogenes* that is modified to produce mesothelin, a protein that is overexpressed on pancreatic cancer cells. When given in conjunction with GVAX and cyclophosphamide, CRS-207 was shown to be synergistic in mouse models and phase I studies in humans subjects. They randomly assigned 90 patients with metastatic pancreatic adenocarcinoma and ECOG performance status 0–1 to receive either 2 doses of GVAX/cyclophosphamide followed by 4 doses of CRS-207, or 6 doses of GVAX/cyclophosphamide. Survival was much improved in the arm receiving CRS-207, with median overall survival of 6.1 months compared with 3.9 months in the GVAX/cyclophosphamide only arm. This disparity was widened to 9.7 months versus 4.6 months when comparing only patients who received at least 3 doses of treatment. Toxicity from this therapy was minimal in both arms.

Other agents that are currently being looked at in pancreatic cancer are hedgehog inhibitors, Notch inhibitors (Demiczumab), and heat shock protein 90 inhibitors (Ganetespib).[90–92]

Conclusion

Pancreatic cancer remains a difficult disease to treat despite ongoing progress. Questions that remain unanswered are would adjuvant FOLFIRINOX in modified doses lead to better outcome? Whether delaying chemoradiotherapy in patients with LAPC is the right way forward? Whether neoadjuvant strategy for borderline resectable patients compared to upfront surgery is preferable? Would it be possible for us to personalise therapy according to drug resistance markers, targets and molecular biology of the tumour?

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