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Medical Therapy of Pancreatic Cancer: Current Status and Future Targets

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1. Introduction

Pancreatic cancer is a major cause of cancer-related mortality relative to its incidence. In the US alone, it is estimated that there were 43,140 new cases in 2010 with 36,800 deaths making it the fourth leading cause of cancer-related mortality.[1]

Typically patients come to clinical attention at an advanced stage of their disease with only 10-15% having potentially operable disease. Surgery is the only established method shown to cure pancreatic adenocarcinoma, yet the rate of cure amongst patients with resectable disease still remains low. Improvements in survival with the addition of chemotherapy or radiotherapy have only been relatively modest.

The medical management of pancreatic cancer in the adjuvant and advanced settings will be reviewed. The current standard of care in both settings is gemcitabine, with modest improvements in survival provided by the addition of erlotinib in the advanced setting. Despite arguably poor evidence for added survival benefit from combination cytotoxic regimens or other biological agents in the advanced setting, recent evidence for considering this in select patients will be discussed, along with a recent non-gemcitabine containing combination cytotoxic approach (FOLFIRINOX), that has challenged the traditional paradigm.

Some of the important molecular signaling pathways involved in pancreatic cancer growth, invasion, angiogenesis, metastasis, and drug resistance will also be summarised. It is hoped that in future, survival outcomes may be improved by better targeting of these pathways in the individual patient, aided by appropriate predictive and prognostic biomarkers.

2. Chemotherapy and chemoradiotherapy in resected pancreatic cancer

There is an established survival advantage with adjuvant systemic therapy in pancreatic cancer. Adjuvant systemic therapy can be delivered either solely, or in combination with

radiotherapy following pancreatic resection, however the role of the latter is more controversial, and will be briefly summarised. *A further discussion of radiotherapy and its role in the neoadjuvant and adjuvant setting is discussed elsewhere.*

2.1 Adjuvant chemoradiotherapy compared with surgery alone

A Gastrointestinal Study Group (GITSG) trial assessed the role of concurrent post-operative radiotherapy and radiosensitising bolus 5-fluorouracil (5-FU) compared with surgery alone.[2]

Patients were randomised to a split-course of radiotherapy in combination with bolus 5-FU compared with post-operative observation alone. Chemotherapy was given at 500mg/m² per day over the first three days of each course of radiotherapy. Patients were given 20 Gray (Gy) in 10 fractions followed by a 14 day break, then a further course of radiotherapy up to a dose of 40Gy. Although demonstrating a median overall survival of 21 months vs. 11 months (p=0.035) favouring the chemoradiotherapy group, criticisms include small patient numbers (43 patients), a slow patient accrual of 8 years, and selection bias where only a more prognostically favourable group of patients with microscopically clear (R0 resection) margins, were included in the study. A later GITSG analysis[3] of an additional 30 patients - all treated with adjuvant combined therapy - showed a median overall survival of 18 months.

The larger European Organization of Research and Treatment of Cancer (EORTC) 40891 study[4] however only showed a non-statistically significant trend towards an improved overall survival with chemoradiotherapy in a subgroup of 114 out of 218 patients with carcinoma of the pancreatic head. The median overall survival was 17.1 months vs. 12.6 months in the observation alone arm (p = 0.099). 5-FU delivery here was given as bolus daily doses at 25mg/kg up to 1,500mg/day, days 1-7 of each course of radiotherapy. There were two courses of radiotherapy given up to a total of 40Gy. EORTC 40891 included patients with T1 or T2 disease, and allowed patients with node-positive (N1) disease. 45% however had T1-3 periampullary disease. Shortcomings included the lack of maintenance chemotherapy, a significant (20%) of patients not proceeding with combination therapy and the large percentage of patients with periampullary cancers affecting the interpretation of outcome in pancreatic cancer.

The largest body of evidence has come from The European Study Group for Pancreatic Cancer (ESPAC) publishing the results the ESPAC-1 trial in 2004.[5] This study employing a 2x2 factorial design allowed a comparison between adjuvant radiotherapy or no radiotherapy, chemotherapy or no chemotherapy, and chemoradiotherapy vs. chemotherapy alone. Chemoradiotherapy was given as two courses of 20Gy separated by 14 days, combined with bolus 5-FU (500mg/m²) given for three days during each course. Following this, patients continued with a maintenance course of chemotherapy with 5FU/leucovorin (LV). Chemotherapy was given as bolus 5-FU (425mg/m²) with LV (20mg/m²) days 1-5 every 28 days, for a total of six cycles. 53% of patients had nodal involvement and 19% had involved margins. Patients who received chemotherapy compared with those who did not, survived a median of 20.6 months vs. 15.5 months (HR 0.71; 95% CI, 0.55-0.92 p=0.009). Patients who received chemoradiotherapy survived a median of only 15.9 months vs. 17.9 months in those who did not receive chemoradiotherapy (HR 1.28 ; 95% CI, 0.99-1.66 p=0.05). Notably, 2 and 5 year survival rates

of patients who received chemotherapy alone improved from 30 to 40% and 8 to 12% when compared to those who did not receive chemotherapy. Therefore in this analysis, patients did not benefit from a combined modality approach, and in fact their outcome appeared to be worse. Based on the results of ESPAC-1 it was difficult to justify the role of adjuvant chemoradiotherapy over chemotherapy with bolus 5-FU alone.

The question of incorporating infusional 5-FU and gemcitabine into adjuvant radiotherapy has been addressed in the Radiation Therapy Oncology Group (RTOG) 9704 trial.[6] This was a phase III trial of 442 patients with pathological T1-4 and nodal stage N0-1 pancreatic cancer. Participants were randomised to either adjuvant chemotherapy with either weekly 5-FU or gemcitabine three weeks prior and for 12 weeks post chemoradiotherapy sandwiched in between. Radiotherapy was delivered at a dose of 50.4Gy (at 1.8 Gy/fraction/day) concurrent with continuous infusional 5-FU at 250mg/m²/day. Most patients (n= 381) had tumours confined to the pancreatic head. More patients with stage T3 and 4 disease received gemcitabine and more grade 4 haematologic toxicity was experienced in the gemcitabine arm (14% vs. 2%). Rates of treatment completion were comparable. Although no overall survival advantage of gemcitabine over 5-FU was seen if all pancreatic lesions were included, the subgroup of patients with pancreatic head tumours assigned to the gemcitabine group had a trend toward a more favourable survival (20.5 months vs. 16.9 months with a hazard ratio (HR) for death of 0.82; 95% CI, 0.65-1.03; p = 0.09). The 3-year rate of survival was also higher (31 vs. 21%) also favouring the gemcitabine group.

2.2 Adjuvant chemotherapy strategies

Older adjuvant cytotoxic regimes such as the triplet of doxorubicin, mitomycin and 5-fluorouracil (AMF) for six cycles to treat pancreatic and papillary cancers showed no overall survival advantage beyond two years, although there was a 1 and 2 year relapse-free survival advantage favouring chemotherapy over surgery alone.[7]

In addition to the survival advantage shown ESPAC-1, the Charité Onkologie (CONKO-001) study[8] published in 2007 demonstrated a survival benefit with adjuvant gemcitabine over surgery alone. Patients with R0 or R1 resections were assigned to observation alone or gemcitabine delivered at 1000mg/m²/week (days 1, 8 and 15 of a 28 day cycle) for a total of six cycles. There was a trend toward an improved median overall survival (22.8 vs. 20.2 months p=0.06) as well as a statistically significant improvement in disease-free survival (13.4 vs. 6.9 months p <0.001) over surgery alone. Importantly the rate of 5-year survival was significantly better in those patients receiving adjuvant gemcitabine over observation alone (21% vs. 9%).

In the largest adjuvant pancreatic trial to date, ESPAC-3[9-10] involved 1088 patients with R0- or R1 resected pancreatic adenocarcinoma, randomising patients into either observation alone, 5-FU/LV, or gemcitabine. Notably the 5-FU was delivered as five bolus doses (425mg/m² with leucovorin 20mg/m² days 1-5 of a 28 day cycle) rather than as an infusion. 551 patients received 5-FU and 537 received gemcitabine with treatment for a total of six months. The observational arm was discontinued after the outcome of the CONKO-001 trial was made available. At a median follow up of 34.2 months after 753 deaths, there was no advantage seen between the intervention arms (23.0 vs. 23.6 months p=0.39). 12 and 24 month survival was 78.5% and 48.1% respectively in those who received 5-FU with 80.1%

and 49.1% respectively in the gemcitabine arm. The side effect profile however favoured gemcitabine in terms of grade 3-4 toxicity and hospitalisation. Grade 3 and 4 mucositis was seen in 10% of patients who received 5-FU (compared with no patients on gemcitabine). Grade 3-4 diarrhoea was also significantly higher in the 5-FU group. The gemcitabine treated group did however experience higher rates of grade 3 and 4 thrombocytopenia, although the absolute risk of this remained small (1.5 vs. 0%) (p=0.003). Quality-of-life was also comparable.

Thus, survival outcomes were not significantly improved by gemcitabine over 5-FU group in ESPAC-3. This outcome differs to that seen in the advanced setting.[13] One reason could be that the 5-FU intensity was greater in ESPAC-3 than that seen in the Burris *et al*. trial.

2.3 Recommendations

Adjuvant chemotherapy in resected pancreatic cancer is the standard of care, yet the role of chemoradiotherapy remains controversial. Gemcitabine for six cycles is preferable over 5-FU based treatment due to its more favourable toxicity profile. Although modest improvements in median survival have been shown, progression-free and 5-year survival rates are improved.

3. Medical therapy of locally advanced and metastatic disease: First-line strategies

3.1 Single-agent chemotherapy

5-fluorouracil (5-FU), capecitabine, and gemcitabine

5-fluorouracil (5-FU) has been used for half a century in advanced pancreatic cancer.[11] As a single agent, objective responses rates have typically been less than 10% with some historical data reporting higher response rates probably based on cruder estimations of disease burden such as physical examination and ultrasound. Typically responses were usually for less than six months.

Capecitabine is an oral fluoropyrimidine prodrug which is metabolised to 5-FU. A small phase II study[12] in patients with locally advanced or metastatic pancreatic cancer was performed in 42 patients at a dose of $1,250mg/m^2$ given twice a day in 3-week cycles, with 2 weeks of treatment followed by a 1-week break. Disease response evaluation was based on either computerised tomography (CT) or physical examination. Of the 41 patients with evaluable disease the objective response rate (ORR) was 7.3% (3 patients), with 41% having stable disease. 38% had progressive disease within the first 7 weeks. Median survival was quoted at 182 days (95% CI, 85-274 days). 52% of patients developed hand-foot syndrome (HFS) (41% Grade 2-3) and 48 % had nausea (24% Grade 2-3). 12% had grades 2-3 mucositis.

The randomised trial leading to the acceptance of gemcitabine as standard therapy in advanced pancreatic cancer was published in 1997.[13] This study compared gemcitabine with bolus weekly 5-FU. Gemcitabine was favoured over 5-FU with a modest improvement in median survival (5.7 vs. 4.4 months, p=0.0025). More significantly, the rate of 1-yr survival was improved (18% vs. 2%), and importantly the rate of clinical symptom improvement (measured by at least four weeks of improvement in either pain, reduced analgesic use, improved weight loss or performance status) favoured the gemcitabine arm (24% vs. 5%).

3.2 Combination chemotherapy and epidermal growth factor receptor (EGFR) inhibition

Gemcitabine/erlotinib

Gemcitabine/other EGFR inhibitor combinations

Erlotinib, an oral tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR), has to date been the only EGFR inhibitor combined with a cytotoxic to show, an albeit modest, survival advantage in a phase III study. [14] It was evaluated with gemcitabine in patients with locally advanced or metastatic disease. Patients received either gemcitabine at 1000mg/m² (weekly for 7 out of 8 weeks) then continued with weekly treatment (in 3 out of 4 weeks), or the equivalent strategy combined with erlotinib at 100mg or 150mg per day. The latter dose was provided to a cohort of Canadian patients. Median overall survival improved with the combination approach of erlotinib with gemcitabine, compared with gemcitabine alone [(6.24 months versus 5.91 months; HR 0.82 (95% CI, 0.69 to 0.99; P = 0.038)]. The superiority of 150mg erlotinib over 100mg was not proven. One could argue that the benefit on overall survival is not economically justified, however with a 1-year survival rate improvement from 17 to 23% (95% CI, 18% to 28%, 95% CI, 12% to 21%, P = 0.023), this has become an acceptable standard of care in many centres.

Gefitinib, another EGFR inhibitor TKI has less evidence, but was evaluated in combination with gemcitabine in a phase II study[15] which reported either disease stability or response in 18/53 patients. The median progression-free survival was 4.1 months and median overall survival was 7.3 months. The reported 1-year survival rate was 27%.

Phase II and III studies combining other EGFR inhibitors such as cetuximab[16] or lapatinib (a dual HER2/EGFR inhibitor)[17] in combination with gemcitabine have not provided an additional survival advantage. Similarly a trial adding cetuximab to a gemcitabine/ cisplatin doublet did not progress beyond a phase II trial, as time to progression was equivalent at 5 months, despite a higher disease control rate.[18] Dual EGFR inhibition with erlotinib and panitumumab has recently been examined in a randomised phase II study, with a modest 3.3 vs. 2.0 month PFS advantage, though mature survival data and statistical significance has not been published to date[19].

The role of erlotinib incorporated into the management of patients with locally advanced disease is being evaluated in the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) LAP07 phase III trial.[20] Patients are randomised initially to either induction gemcitabine or gemcitabine/erlotinib. In those patients who do not progress after four months, there is a secondary randomisation into a chemotherapy (with either gemcitabine or gemcitabine/erlotinib), or a chemoradiotherapy arm (with concurrent capecitabine) until tumour progression.

3.3 Combination chemotherapy: Gemcitabine-containing regimens

Gemcitabine/fluoropyrimidine doublets

Gemcitabine/platinum doublets

A number of gemcitabine-containing combinations with either fluoropyrimidines or platinum agents have been attempted. Individually these trials have not provided

significant improvements in survival over gemcitabine alone. However subset-analyses of some of these trials, as well as a meta-analysis suggest that doublets may confer a meaningful survival improvement in the fittest patients with Karnofsky Performance Status (KPS) scores of 90% or above.[21]

Gemcitabine and 5-FU was examined in a phase III trial[22] which randomised 322 patients to a schedule of gemcitabine 1000mg/m² (three weeks out of four), with or without bolus 5FU 600mg/m²/week), however did not produce a statistically significant improvement in overall survival compared with gemcitabine alone (6.7 vs. 5.4 months respectively p=0.09).

Gemcitabine and capecitabine was also examined in a phase III trial comparing a gemcitabine/capecitabine doublet with gemcitabine with previously untreated locally advanced or metastatic disease.[23] It suggested a significantly higher objective response rate (ORR) of 19.1% vs. 12.4%; (P = 0.034), as well as an improvement in progression-free survival (HR 0.78 95% CI, 0.66 to 0.93; P=0.004) favouring the doublet. However it only demonstrated a trend toward an improved overall survival (HR 0.86; 95% CI, 0.72 to 1.02; P=0.08). Another study of this combination also showed no significant difference in the primary end-point of overall survival [(8.4 months with the combination arm vs. 7.2 months with gemcitabine alone (p= 0.234)]. However a post-hoc subgroup analysis did reveal evidence for more favourable survival in the combination arm if performance status was better. Patients with KPS of 90-100% receiving combination therapy had a median overall survival of 10.1 vs. 7.4 months compared with gemcitabine alone (p= 0.014).[24]

Combination gemcitabine and cisplatin was assessed in 195 patients enrolled in a phase III trial comparing gemcitabine 1000mg/m² (days 1, 8 and 15 of a 28 day cycle) with gemcitabine 1000mg/m2 and cisplatin 50mg/m² (days 1 and 15). Tumour responses were similar in the combination (10.2%) vs. standard treatment arms (8.2%), with an improved progression-free survival and equivalent toxicity. However, despite a trend toward an improvement in overall survival (the primary endpoint of this study) within the combination arm (7.5 vs. 6.0 months), this did not reach statistical significance (p=0.15).[25]

Louvet et al[26] compared a combination gemcitabine/oxaliplatin doublet (GEMOX) with gemcitabine. Patients received either treatment with gemcitabine 1000mg/m² and oxaliplatin 100mg/m² every 2 weeks compared with weekly gemcitabine 1000mg/m². The combination was shown to improve response rates (26.8 vs. 17.3% respectively, P=0.04), as well as progression-free survival (5.8 vs. 3.7 months P=0.04). However differences in median overall survival were not statistically significant (9.0 vs. 7.1 months P= 0.13). The combination arm was associated with greater rates of grade 3-4 thrombocytopenia, vomiting and sensory neuropathy. Some patients received radiotherapy for local control at the oncologists' discretion after they had completed 3 months of systemic therapy. The overall survival data may have been influenced by a proportion of gemcitabine patients receiving platinum-containing second-line therapy, once they had progressed and were off study.

Gemcitabine in combination with irinotecan was assessed in a trial that randomised 360 patients to gemcitabine 1000mg/m² and irinotecan 100mg/m² on days 1 and 8 every 21 days or gemcitabine alone.[27] Rates of diarrhoea, nausea and vomiting were higher in the combination arm with no improvement in the overall survival.

3.4 Combination chemotherapy: Non-gemcitabine containing regimens

Irinotecan-docetaxel

FOLFIRINOX

An earlier non-gemcitabine containing regimen of irinotecan and docetaxel was examined in a phase II study randomising patients into two arms with or without cetuximab but response rates were 7 and 4.5% respectively. This did not meet a pre-determined goal to proceed to a phase III study.[28]

The recent French PRODIGE 4 (ACCORD 11) study[29] randomised 342 patients with metastatic pancreatic carcinoma, who had an Eastern Cooperative Oncology Group performance status score of 0 or 1, to either a regimen of gemcitabine ($1000mg/m^2$ weekly for 7 of 8 weeks followed by weekly treatment for 3 out of four weeks) or FOLFIRINOX. FOLFIRINOX patients received oxaliplatin ($85mg/m^2$), irinotecan ($180mg/m^2$), leucovorin ($400mg/m^2$), with bolus ($400mg/m^2$) then infusional ($2400mg/m^2$ over 46 hours) 5-FU. Treatment was delivered every two weeks. It is important to note that more patients in the FOLFIRINOX arm (42.5%) received granulocyte colony stimulating factor (G-CSF) support than those in the gemcitabine arm (5.3%).

Using overall survival as its primary end point, and with an intended treatment period of six months, FOLFIRINOX treated patients had an impressive median 11.1 month overall survival, compared with only 6.8 months in those treated with gemcitabine alone (HR for death, 0.57; 95% CI, 0.45 - 0.73; p<0.001). Progression-free survival was also superior (6.4 vs. 3.4 months (HR, 0.47; P <0.0001). Objective response rates were significantly higher in the FOLFIRINOX group (31.6%) compared with gemcitabine (9.4%) (p<0.001). This advantage was at the expense of higher rates of grade 3 or 4 neutropenia (febrile neutropenia of 5.4% vs. 0.6% P=0.0001), thrombocytopenia (9.1% vs. 2.4% p=0.008), neuropathy, diarrhoea and grade 2 alopecia. There was one toxicity-related death in each arm of the trial. Despite the increased toxicity, quality of life scores were more preserved at six months in the FOLFIRINOX-treated patients. This regimen is therefore being considered a suitable option for some patients, particularly those with a good performance status. A survey of US Oncologists recently revealed that 18% would now adopt FOLFIRINOX over a gemcitabine-erlotinib doublet in the first-line setting for patients with a performance status of ECOG 1.[30]

3.5 Recommendations

The standard of care in the first-line setting of advanced pancreatic cancer remains gemcitabine or gemcitabine with erlotinib for most patients. The alternative of 5-FU remains if gemcitabine is poorly tolerated. Those who are particularly fit with a performance status of ECOG 0-1, might be considered for a gemcitabine-platinum or a gemcitabine-capecitabine doublet (based on subset- and recent meta-analyses), or the non-gemcitabine regimen of FOLFIRINOX. Recent phase III evidence for the latter challenges the traditional paradigm of a gemcitabine-containing backbone, but it must be balanced with the higher risks of toxicity when recommending treatment. Enrolment in clinical trials should always be considered if possible.

4. Medical therapy of locally advanced and metastatic disease: Second-line strategies in gemcitabine-refractory disease

4.1 Oxaliplatin-based doublets

The strategy of continuing gemcitabine with the addition of oxaliplatin (GEMOX) was evaluated in patients who have progressed on gemcitabine alone in a phase II trial of 33 patients with locally advanced and metastatic disease.[31] A partial response was seen in 7 of the 31 patients with evaluable disease and stable disease for 2 months or more was seen in 11 patients. The median survival was 6 months.

Second-line combination oxaliplatin/5-FU was examined in the Charité Onkologie trial (CONKO-003).[32] This began as a phase III trial with the intention to compare a 5-FU-oxaliplatin doublet (the OFF regimen) with best supportive care (BSC).[33] The OFF regimen differs from FOLFOX being a 42-day cycle where infusional 5-FU ($2000mg/m^2$ over 24 hours) with bolus LV ($200mg/m^2$) is given days 1,8,15, and 22. Oxaliplatin ($85mg/m^2$) is given on days 8 and 22. The protocol was revised due to poor acceptance of the best supportive care arm and later altered to include a 5-FU/LV arm as the control. Despite this methodological alteration, the study when presented as an abstract, did show an improvement in overall survival from 13 to 26 weeks favouring the doublet arm.[33]

There is phase II evidence showing activity with a doublet of oxaliplatin and capecitabine in the gemcitabine-refractory setting.[34] In a study of 41 patients, capecitabine was given at $1000mg/m^2$ BD days 1-14 with oxaliplatin $130mg/m^2$ every 3 weeks (doses of $850mg/m^2$ and $110mg/m^2$ respectively were used in patients greater than 65). Reported median overall survival was 23 weeks (95% CI, 17.0-31.0) with a progression-free survival of 9.9 weeks (95% CI, 9.6-14.5 weeks). Six month and 1 year survival rates were 44% and 21% respectively (95% CI 31-62% and 11-38%). Another recent phase II study has also confirmed activity in a mixed cohort of patients with pancreatic and biliary tract carcinomas.[35]

4.2 Capecitabine/erlotinib

A phase II study of capecitabine ($1000mg/m^2$ BD days 1-14 of 21 day cycles) combined with erlotinib 150mg daily enrolled 32 patients.[36] The objective radiological response (ORR) was only 10% and median survival duration was 6.5months. 17% had CA 19-9 reductions of more than 50% of baseline. Diarrhoea, fatigue, rash and hand-foot syndrome were common toxicities. This has been suggested as an active first or second-line option, especially if gemcitabine is not tolerated.

4.3 Irinotecan – based therapy

Single agent irinotecan ($150mg/m^2$) given every 2 weeks has demonstrated activity in the second-line setting.[37] 33 patients were evaluated in a phase II study where 48% had either stable disease or a partial response. The median time to progression was 4 months. With combination 5-FU and irinotecan regimens, disease control rates of 44.3-50% with overall survivals of 6 months or more have been reported.[38] Some patients received this in the third-line setting. However, patients were highly selected and much of the data is retrospective.

Recently a nanoparticle liposomal encapsulated form of irinotecan (PEP02) was evaluated as a single agent in a phase II trial at 120mg/m² given every 2 weeks in 37 patients who had progressed on gemcitabine.[39] A 74% 3-month overall survival endpoint was reached with initial reports of a 52% disease control rate. However 31% and 25% of patients had grade 3 or more fatigue and neutropenia respectively. Further prospective randomised evidence is awaited.

4.4 Taxanes/nanoparticle – bound paclitaxel

There is phase II evidence of 18 patients utilising weekly paclitaxel monotherapy with good tolerability.[40] Five patients had stable disease with one patient who achieved a complete response lasting beyond one year. The reported median overall survival was 17.5 weeks. Treatment was well tolerated with only one patient developing grade 3 myelotoxicity. A further report described evidence for activity using single agent docetaxel, combination docetaxel-gemcitabine or capecitabine regimes, however this was a small heterogeneous group of patients and assessment was retrospective.[41]

SPARC (Secreted protein acidic and rich in cysteine) is frequently expressed by stromal fibroblasts adjacent to pancreatic adenocarcinoma cells, and immunohistochemical expression within the peritumoral stroma is an independent predictor for poorer survival, whereas expression by cancer cells is not. An analysis of 299 pancreaticoduodenectomy specimens showed that patients who expressed SPARC had a median survival of 15 months whereas patients who did not, had double the median survival of 30 months (p <0.001).[42] Nanoparticle albumin-bound (nab) paclitaxel (Abraxane®; Abraxis BioScience) is believed to allow better paclitaxel delivery by allowing albumin to bind to SPARC. It also has the advantages of avoiding the Cremophor® - related hypersensitivity reactions associated with standard paclitaxel, as well as delivery with a shorter infusion time.

In a phase I/II study, patients with metastatic pancreatic adenocarcinoma were given first-line nab-paclitaxel (100-150mg/m2) in combination with gemcitabine 1000mg/m2 (days 1,8 and 15 of a 28 day cycle).[43] Of the 63 patients in the study, 35 had tissue available for immunohistochemical analysis. 29% of patients were SPARC positive. If SPARC positive, this predicted a metabolic response on positron emission tomography (PET) in 75% of those patients as well as a progression-free survival advantage of 6.2 vs. 4.8 months. A further phase II study of single agent nab-paclitaxel in patients who had progressed on gemcitabine however was less impressive with 63% of patients progressing by RECIST criteria at their first response assessment.[44] These patients were not preselected based on SPARC status.

The question of whether incorporating nanoparticle bound-paclitaxel into first-line chemotherapy with gemcitabine leads to a clinically meaningful improvement in survival is yet to be answered by a prospective randomised clinical trial currently awaiting completion.[45] Although tissue analysis for SPARC is included in this trial, the interventional arm will not be enriched with SPARC positive patients.

4.5 Recommendations

To date there is no established standard of care in the second-line setting or beyond. Treatment must therefore be tailored to each patient but may include oxaliplatin,

fluoropyrimidine or taxane-based regimens, as outlined above. There is very limited evidence for irinotecan-based treatment. A 5-FU/oxaliplatin or capecitabine-erlotinib doublet is an option. Consideration for enrolment in a clinical trial should be given if available.

5. Future targets in pancreatic cancer

Because attempts at improving survival in pancreatic cancer with cytotoxic and biologic therapy have been modest at the most thus far, newer strategies of targeting the core signaling pathways implicated in pancreatic cancer are needed.

Previously, genetic mutations affecting genes such as TP53, KRAS, CDKN2A and SMAD4 were known to be associated, but a more recent genome-wide analysis has identified a broader range of aberrant pathways implicated in pancreatic cancer growth.[46] In most of the 24 cancers examined in this series, the majority of the genetic mutations were felt to be disrupting one or more of 12 core signaling pathways.

In pancreatic cancer, aberrations can occur in signal transduction and other pathways that promote cell survival and allow proliferation. These include KRAS,[47] PI3K/Akt/mTOR,[49-50] EGFR,[52] insulin-like growth factor (IGF-1) (which is co-expressed with Src),[52] hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF).[53] There are embryonic developmental signaling pathways that also lead to progression such as the Hedgehog, Notch, and Wnt pathways.[54-57] Matrix metalloproteinases (MMPs) also play a part in promoting neovascularisation and tumour invasion, and abnormalities in core pathways involved in DNA repair as well as apoptosis control such as p53, SMAD/TGF-β and p14 AFR/p16 are also seen.[58-59]

Finally there is also documented activity or upregulation of other factors such as cyclo-oxygenase,[60] focal adhesion kinase (FAK) (which in turn interacts with the IGF-1 receptor),[61] telomerase,[62] as well as cholecystokinin, gastrin and gastrin receptors.[63]

5.1 Current evidence and future strategies targeting specific pathways in pancreatic cancer

- K-ras
- Epidermal growth factor receptor (EGFR)
- Angiogenesis/matrix metalloproteinases (MMPs)/integrins
- PI3k/Akt/mTOR
- Nf-kβ
- Cyclo-oxygenase
- TGF-β, SMAD4, MET, and IGF-1
- Src
- Hedgehog/wnt pathways/Notch
- Gastrin/cholecystokinin receptors

5.1.1 The ras pathway

K-ras is part of the Ras group of genes, which code for GTP-binding proteins in the cellular membrane. Ras is important in cellular differentiation and proliferation, as well as adhesion

and the regulation of apoptosis. When activated by the associated EGFR, Ras leads to further downstream activation of Raf, MAP2K, MAPK and PI3K-Akt cascades. K-ras mutations lead to cell-cycle progression, and promote tumour cell survival. Mutated K-ras, seen in over 90% of pancreatic cancer is mostly identified in codon 12 but may also be seen in codons 13 and 61.[47]

There has been an attempt in an adjuvant phase II study to vaccinate against k-ras, in patients who harbour codon 12 k-ras mutations.[64] In 24 patients, this was felt to be safe, however less than half of patients had a detected immune response and the protective value of this strategy is unknown.

Another approach has been to inhibit the KRAS protein itself. This has been attempted through targeting its attachment to the cell membrane by inhibiting farnesyltransferase with tipifarnib - a farnysyltransferase inhibitor (FTI).[66] Inhibiting Ras-driven signal transduction and interfering with Ras-membrane binding with other small molecule drugs such a salirasib, or antisense/RNA inhibitors are early in clinical development.[65] Unfortunately to date the only strategy reaching a phase III study, combining tipifarnib with gemcitabine in advanced pancreatic carcinoma, did not provide any significant difference in either the clinical benefit rate, median progression-free, or overall survival.[66] This is likely due to alternate pathways that still allow the prenylation of Ras.

Downstream Ras pathway inhibition of mitogen-activated protein kinase (MAPK) with a MEK inhibitor has not shown any phase II activity.[67] This was despite preclinical evidence showing synergistic activity by dual inhibition with the EGFR TKI inhibitor gefitinib and the MAPK inhibitor CI-1040 (PD184532).[68]

5.1.2 The epidermal growth factor receptor (EGFR) pathway

Activation of this pathway leads to downstream signaling events through MAPK, PI3K-Akt and the STAT family of proteins. STAT proteins also have roles in cell proliferation, survival, motility, invasion and adhesion. Over-expression of this pathway and its ligands (EGF and TGF-α) are common in pancreatic cancer.[69-70] The clinical evidence for targeting the EGFR is outlined above. As previously mentioned, the addition of erlotinib or cetuximab to gemcitabine has resulted in only modest and no additional overall survival benefit respectively.

5.1.3 Angiogenesis, matrix metalloproteinases (MMPs) and integrins

VEGF overexpression is common in pancreatic adenocarcinoma and is associated with a poorer prognosis.[71] Despite this being an attractive target, multiple anti-angiogenic strategies added to a backbone of gemcitabine have been disappointing. Two phase III trials in advanced pancreatic adenocarcinoma, have shown no overall survival benefit with the addition of the VEGF monoclonal antibody bevacizumab[72] to either single-agent gemcitabine, or a doublet of gemcitabine with erlotinib.[73] The latter study did however demonstrate a difference in progression-free survival (HR, 0.73; 95% CI, 0.61 to 0.86; P = 0.0002).

Sorafenib is an oral multitargeted kinase inhibitor which inhibits the VEGF-receptor tyrosine kinase as well as Raf-1, the platelet-derived growth factor receptor (PDGFR), c-kit and FLT-

3. It has not shown any significant additive activity in a phase II study. [74] Similarly axitinib (a selective oral inhibitor of multiple VEGF receptors), has also failed to show improved efficacy when combined with gemcitabine in the phase III setting despite promise in an earlier phase II trial.[75-76] A phase III study randomised 546 patients with metastatic pancreatic cancer to gemcitabine with aflibercept (the VEGF 'trap') vs. gemcitabine with placebo (clinicaltrials.gov identifier NCT00574275). This was also terminated early due to no significant improvement in the primary or secondary end points of overall and progression-free survival.

Matrix metalloproteinases (MMPs) are enzymes that break down the extracellular matrix and are required for tumour spread and neovascularisation. However, randomised trials utilising the MMP inhibitor marimastat in metastatic disease did not show any added survival benefit over gemcitabine alone.[77-79] Whether there might be a role in the adjuvant setting remains unknown.

Volociximab is a monoclonal antibody that inhibits fibronectin binding to $\alpha5\beta1$-integrin, which promotes apoptosis in tumour endothelial cells. A small, phase II study combining this agent with gemcitabine in 20 patients showed activity with stable disease in half of patients and a partial response in one patient. The median time to progression (TTP) was 4.3 months with 37% of patients alive at 12 months. However there is no prospective randomised evidence to date.[80] Cilengitide is another agent that interferes with integrin binding leading to proliferative endothelial cell apoptosis, but it was not shown to be of added benefit when combined with gemcitabine.[81] There are other integrin inhibitors in preclinical and early clinical stages of evaluation.

5.1.4 The PI3k/Akt/mTOR pathway

The phosphoinositide 3'-kinase (PI3k)/Akt/mammalian target of rapamycin (mTOR) pathway which is regulated upstream by KRAS is important in pancreatic tumorigenesis and angiogenesis. Activation in pancreatic cancer is common, and is associated with loss of the tumour suppressor PTEN, and with poorer outcomes as well as gemcitabine resistance.[82] Despite this, the mTOR inhibitors everolimus and temsirolimus have shown no objective responses in phase II studies, and when the former was combined with erlotinib, also no objective responses were seen.[83-84] It is felt that they are unlikely to have a role - at least as a single agent strategy - in this disease. The PI3K and Akt inhibitors (BKM-120 and MK-2206) are in phase I development. RX-0201 (an Akt-1 mRNA antisense oligonucleotide) is being evaluated in a phase II trial in combination with gemcitabine.[82]

5.1.5 NFkβ

Nuclear factor kappa light-chain enhancer of activated β cells (NFkβ) is also activated by the PI3k/Akt/mTOR pathway. Curcumin (diferuloyl methane) - a component of the common Indian spice turmeric - has been shown to inhibit NFkβ. A phase II study using 8g of curcumin as a single agent daily for two months found that this agent was tolerable in 25 patients, two of which received prolonged (up to 12 month) periods of stable disease. One patient achieved a partial response.[85] A further phase II study of 17 patients with curcumin in combination with gemcitabine showed that 5 patients either had stable or partial responses but another 5 patients could not tolerate treatment due to abdominal discomfort,

and had to discontinue therapy.[86] A phase III trial of gemcitabine with or without a combination of curcumin and celecoxib (a cyclo-oxygenase-2 (COX-2) inhibitor) is currently in progress.[87]

5.1.6 Cyclo-oxygenase

The cyclo-oxygenase (COX) pathway is also important. Inhibition with celecoxib has been proven to suppress tumour proliferation as well as VEGF expression in pancreatic cancer.[88] However phase II trial responses in combination with gemcitabine have been mixed. The most favourable phase II study was performed in 42 patients (most with metastatic rather than locally advanced disease) who received gemcitabine 1000mg/m2 (on days 1 and 8 only of a 3-week cycle) in combination with celecoxib 400mg BD. The clinical benefit rate in 30 patients was reported as 71% [95% CI, 58-84%]), and the median overall survival was 9.1 months (95% CI, 7.5-10.6 months).[89] However another phase II study showed that despite a clinical benefit rate of 52% in 25 patients, the 12 month survival rate was 15%, which did not reach predetermined efficacy in order to proceed to a phase III trial.[90]

5.1.7 Transforming growth factor-β (TGF-β), SMAD4, MET, and IGF-1

TGF-β binds to cell receptors that lead to downstream activation of SMAD4 which in turn moves into the cell nucleus to activate gene transcription. TGF-β is also involved with activating other pathways including Ras, PI3K and MAPK. Although tumour suppressive in epithelial cells, it is also involved in mediating invasion and metastasis. In pancreatic cancer, mutations in SMAD4 are seen in 50% and up to 4% of TGFβ receptors.[91] Mutations of the former can lead to reduced TGF-β tumour suppression as well as increased tumour cell invasiveness. Exploitation of this pathway with inhibitors such as antisense oligonucleotides specific to the TGF receptor are in early phase clinical development in several solid malignancies including pancreatic cancer.[92]

Overexpression of the c-MET proto-oncogene which codes for MET (mesenchymal-epithelial transition factor) is common in a number of solid malignancies such as colon, gastric, lung, breast, ovarian, bladder and pancreatic cancer.[93] The resultant protein - hepatocyte transcription factor receptor (HGFR) is stimulated by HGF which is produced by fibroblasts in the stromal microenvironent. This in turn, leads to further tumour growth, angiogenesis, invasion, and metastasis formation. Similarly, the insulin-like growth factor (IGF-1) and focal adhesion kinase (FAK) pathways which are implicated in tumour growth and survival are overexpressed in pancreatic cancer. Inhibitors such as the selective cMET inhibitor tivatanib (ARQ 197) and anti IGF-1 receptor antibody cixutumumab are also early in clinical development.

5.1.8 Src

Src is a proto-oncogene which codes for a non-receptor tyrosine kinase (RTK). Src proteins are a family of kinases involved in cell adhesion, and fibroblast division. Expression has been documented in a variety of cancers including pancreatic cancer, where overexpression is seen in 70%.[94] Overexpressed Src can lead to upregulation of the IGF-1 receptor.[52] Phase I trials of the BCR/Abl, c-kit and Src family inhibitor dasatinib have been performed in patients in a variety of solid tumours but at present another dual Src and Abl tyrosine

kinase inhibitor SKI-606 (bosutinib) is undergoing phase I/II evaluation with gemcitabine as adjuvant therapy in the postoperative setting.[95]

5.1.9 Hedgehog/Wnt pathways/Notch

The hedgehog signaling pathway plays an important part in embryonic development but when aberrant, may be implicated in tumorigenesis. [96] Two transmembrane proteins work in tandem. Ptch (patched), which is tumour suppressing, inhibits the Smo (smoothened) protein which when activated by a Ptch mutation, allows hedgehog proteins to bind. This leads to downstream activation of GLI-1 which promotes nuclear transcription. One of the hedgehog proteins (Sonic Hedgehog - SHH) is expressed in 70% of pancreatic adenocarcinoma. Preclinical evidence points to the drug cyclopamine inhibiting Smo, but further trial evidence for hedgehog pathway inhibitors in pancreatic cancer patients is awaited.

The Wnt pathways are also important in normal embryonic development and mutations are implicated in tumorigenesis. If the Wnt-β-catenin cascade pathway is aberrant (65% of pancreatic cancer), abnormal overactivation of β-catenin occurs which promotes abnormal nuclear transcription.[97] There is preclinical evidence that blocking this pathway can lead to pancreatic cell death, which may be a future potential target for treatment. It is thought that chemokine receptor 4 (CXCR4) is key in tumour angiogenesis and metastasis. Specific blockade of this chemokine receptor or its ligand SDF-1 may be a further potential future clinical strategy. It is thought that inhibiting both these pathways may have anti cancer stem cell effects.[97]

Notch genes code for proteins also responsible for tumour differentiation, proliferation and apoptosis and the pathway requires the enzyme gamma-secretase to be activated. Notch 3 is also expressed in most pancreatic cancers with preclinical evidence of a potential role using siRNA and secretase inhibitors in therapy.[98]

5.1.10 Gastrin and cholecystokinin receptors

Targeting gastrin And the cholecystokinin receptor CCK-BR, with the intravenous agent JB95008 (gastrozole) has been attempted in advanced pretreated pancreatic cancer but was found to be no better than 5-FU in terms of survival.[99]

Another novel oral gastrin inhibitor named Z-360 has been was examined in a phase Ib/IIa study and found to be active when given in combination with gemcitabine, with a future randomised controlled trial planned.[100-101]

6. Biomarkers in pancreatic cancer

In contrast to other solid tumour malignancies, there have been relatively modest or poor responses achieved with molecularly targeted agents to date in unselected patients with pancreatic cancer. There is an urgent need for a personalised approach to better define biomarkers in order to predict patients that are more likely to benefit from a particular cytotoxic or molecular targeted therapy.

The biomarker with the most preclinical and clinical evidence is human equilibrative nucleoside transporter 1 (hENT1). Gemcitabine requires transmembrane nucleoside

transport proteins to enter cells and to have a therapeutic effect. Both hENT1 and 2 allow this with hENT1 being more selective. A lack of hENT1 expression has been shown to interfere with gemcitabine influx, and is associated with reduced efficacy and decreased survival in patients.[102-105] However it is not yet clear whether immunohistochemical hENT1 expression or gene expression will be the most predictive measure, or whether there is a concordance between hENT1 expression in primary and metastatic disease.

Once gemcitabine is transported into the cell, it is phosphorylated by deoxycytidine kinase (dCK) to difluorodeoxycytidine. It is gemcitabine triphosphate's (dFdCTP) incorporation into DNA that leads to strand termination. DFdCTP is metabolised by cytidine deaminase (CDA). There is evidence of correlation between dCK and CDA levels, and also detected single nucleotide polymorphisms (SNPs) in genes that code for these and other proteins involved in gemcitabine transport and metabolism, and overall survival.[106] However, to date, attempts at increasing the effective intracellular concentration of gemcitabine and its metabolite dFdCTP have not translated into improved patient survival in the phase III trial setting. Fixed-dose rate (FDR) gemcitabine ($1,500mg/m^2$/150mins) only modestly improved overall survival (6.2 vs. 4.9 months, HR 0.83 stratified log-rank p = 0.04) compared with standard gemcitabine, and did not meet predetermined efficacy. It was also associated with greater haematological toxicity.[107]

A modified form of gemcitabine, CP-4126 (gemcitabine-5'-elaidic acid ester, Clavis Pharma) bypasses nucleoside transporters. It is undergoing phase II evaluation in patients with advanced pancreatic cancer, after a phase I study showed a good safety profile.[108-109]

Other promising predictive and prognostic biomarkers may include variations in cellular histone modification patterns.[110] Immunohistochemical analyses of histone H3 lysine 4 and 9, dimethylation and histone H3 lysine 18 acetylation were performed on tissue banks. Tissue was derived from patients with resected pancreatic tumours (including those in the RTOG 9704 study which compared adjuvant 5-FU and gemcitabine). Low levels of some histone modifications predicted a poorer disease-free survival if patients were treated with adjuvant 5-FU compared with gemcitabine.

DPC4 (SMAD4) gene expression has recently found to be prognostic and associated with local failure following adjuvant chemoradiotherapy, or with metastatic spread in locally advanced disease.[111-112] However prospective validation is still required, especially if therapeutic targeting of this pathway is a future therapeutic option. These, and other markers such as mismatch repair polymorphisms, are also yet to be prospectively validated.

7. Conclusion

Despite research into the medical management of pancreatic cancer, survival remains poor. Numerous agents and combinations have been attempted in early phase clinical trials, but to date, very modest improvements have been made in overall survival. Single agent gemcitabine still remains the standard of care for most patients in both the adjuvant and advanced settings with adjuvant chemoradiotherapy being more controversial. In the advanced settings, gemcitabine or gemcitabine with erlotinib are appropriate for most, but fit patients may benefit from gemcitabine-containing cytotoxic doublets. FOLFIRINOX is now considered an option in the fittest of patients, but its toxicity is significant. Although no

standard of care exists in the second-line setting, fluoropyrimidines, oxaliplatin, erlotinib and taxanes including nab-paclitaxel show activity, often in combination regimens.

Increased knowledge of the molecular pathogenesis of pancreatic cancer has allowed new targets and therapeutic strategies to emerge. However, true progress in the personalised management of this disease will only be likely with equally important research into the identification, and validation of appropriate predictive and prognostic biomarkers.

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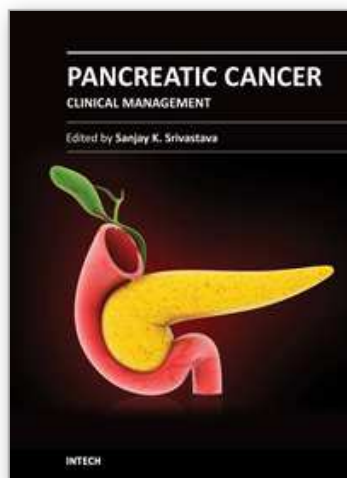
Pancreatic Cancer - Clinical Management

Edited by Prof. Sanjay Srivastava

This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic makers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

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