THE CHANGING LANDSCAPE OF SYSTEMIC THERAPY IN ADVANCED PANCREATIC CANCER

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Abstract

Pancreatic cancer is a highly lethal disease due to its late presentation and its innate resistance to treatment. Although much research has been conducted in order to discover and develop new therapeutic targets to combat this disease, the survival gains for patients have been modest. This review aims to synopsize the current literature which has framed the approach to first and second line therapy of advanced disease. We look at the evolution of targeted therapies and briefly discuss current trials evaluating the role of immunotherapy. Finally, we cover the future of pancreatic cancer, in particular the essential role that predictive and prognostic biomarkers need to take in order to change the way we approach clinical trial design and management of patients.

Pancreatic cancer is a major cause of cancer related morbidity in Australia. In 2011, 2748 patients were diagnosed with pancreatic cancer in Australia, making it the 5th most common cause of cancer related death.[1] Although survival rates for pancreatic cancer have increased over the past decade, they still remain disappointingly low, with the five year survival rate at around 5%.[1]

Surgery is the only treatment with a potential for cure, however 80% of patients with pancreatic cancer present with stage IV disease and are not amenable to surgical

resection.[2] Late diagnosis is a hallmark of this cancer as presenting symptoms are vague. Chemotherapy is an important treatment option for patients with metastatic pancreatic cancer. Gemcitabine has been the standard of care until recent two phase 3 trials showed a benefit of multi-drug regimens.[3,4] Although these trials represent a clear advance in the treatment of pancreatic cancer, the survival gains are modest.

The relative chemoresistance of this malignancy and data from explorative genome analyses suggest that pancreatic cancer is a genetically heterogeneous disease.[5] Efforts continue across the world to address this heterogeneity in an attempt to use clinical, pathological and/or genetic factors to predict responses to treatment in order to personalise therapy to improve outcomes for patients. This review aims to summarise the pivotal studies and the evolving landscape of systemic treatment for advanced pancreatic cancer and future directions of research into this devastating disease.

First line treatment

Unlike many other cancers, where increased understanding of the molecular biology has led to improvements in treatment and management, pancreatic cancer management has shown minimal progress over the past decade. Chemotherapy remains the mainstay of systemic treatment for advanced pancreatic cancer, with gradual improvements made over time and targeted therapies showing small, incremental survival benefits (figure 1).

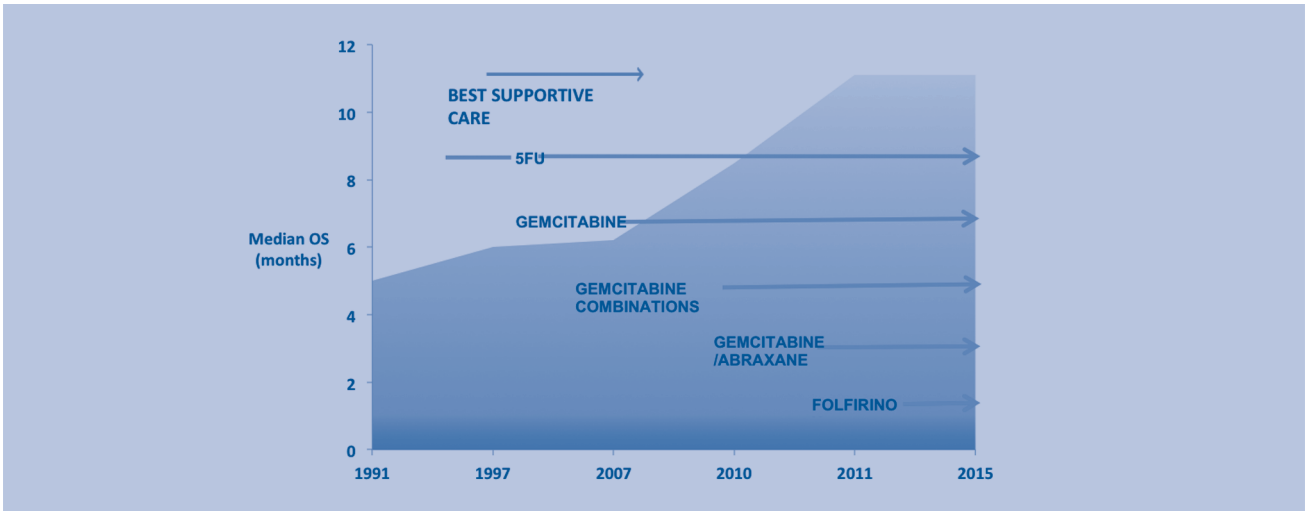
median overall survival (OS) was 6.2 months, however the overall response rate was only 7%. Alterations in dosing and frequencies have not resulted in a significant improvement in efficacy.[6,7,9]

A meta-analysis of randomised control trials published in 2007, compared combination chemotherapy including 5-FU to best supportive care alone.[10] Six trials between 1980 and 2001 involving 385 patients were included and demonstrated that OS was significantly better in patients who received chemotherapy compared with patients who received best supportive care, with a relative risk reduction of 36% (HR 0.64).[11-15]

Gemcitabine became the new standard following the results of a study in 1997. Burris et al randomised 126 patients to either gemcitabine or 5-FU and demonstrated an improvement in median survival (5.6 months vs 4.4 months p=0.0025), as well as reduced toxicity in the gemcitabine arm.[17] Also, a rapid and sustained improvement in patient reported outcomes was seen, including pain, analgesic requirements and Karnofsky performances status in the gemcitabine arm.[17]

Over the next decade, multiple trials were conducted trying to improve the efficacy of gemcitabine, using it as a backbone to add novel chemotherapeutic agents and targeted therapies. A meta-analysis comparing gemcitabine combination therapy to gemcitabine alone demonstrated a small benefit with the addition of 5-FU to gemcitabine, with an improvement in OS (HR .89[0.81-0.97] p=0.008) and progression free survival (HR 0.78[0.7-0.87] p<0.00001.[18]

***Figure 1**: Overall Survival: progress over time. Demonstrates the gradual improvement of survival over time and the timing of when new treatment options became available, most recently with combination treatments including FOLFIRINOX or Gemcitabine/nab-paclitaxel.*



In the early 1990s, 5-fluorouracil (5-FU) was one of the first chemotherapeutic agents to be used in the management of solid tumours. In 1991 Decaprio et al conducted a single arm, phase 2 study looking at the efficacy of 5-FU in patients with metastatic pancreatic cancer.[6] A total of 43 patients were enrolled, and the

Two major advances in chemotherapy for advanced disease were made after 2010. Firstly, Conroy et al randomised 342 French patients to FOLFIRINOX (5-Fluorouracil/Irinotecan/Oxaliplatin) and gemcitabine.[20] The primary endpoint of OS was met with a median OS of 11.1 months reached with FOLFIRINOX treatment

compared to 6.8 months with gemcitabine (HR 0.57 p<0.001). Response rates were also higher at 31.6% vs 9.4%. Not surprisingly, toxicities were significantly higher in the FOLFIRINOX group, with a higher rate of febrile neutropenia, thrombocytopenia, diarrhoea and sensory neuropathy. Despite these increases in adverse events, quality of life at six months was superior in the FOLFIRINOX group, (66% vs 31% HR 0.47 p<0.001).[20] The second study performed by Von Hoff et al randomised 861 patients to either gemcitabine plus nab-paclitaxel or gemcitabine alone.[21] Median OS was 8.5 months compared to 6.7 months (HR 0.70 p<0.001), confirming the superiority of gemcitabine plus nab-paclitaxel.[21] Adverse effects including peripheral neuropathy were higher, as was the incidence of fatigue and neutropenia in the gemcitabine/nab-paclitaxel combination arm. Interestingly, despite the increased incidence of side-effects experienced by the patients receiving gemcitabine and nab-paclitaxel, this did not reduce the number of doses of chemotherapy received compared to the control arm. The peripheral neuropathy was rapidly reversible when the treatment was stopped or doses reduced.

The results of both these studies have provided two new options for patients. The best option remains unclear as there have not been any randomised trials comparing these regimens. The von Hoff study included patients more typically seen in community practice in Australia (median age 63) and included patients with an ECOG of 2 (8%).[21] In contrast, the Conroy study was run in France only, excluded patients older than 70 years of age and only patients with excellent ECOG performance status of 0-1 were eligible. The high toxicity rates described in this study limit its applicability for all patients with advanced pancreatic cancer.

Gemcitabine and nab-paclitaxel has now become a standard of care in Australia. There is currently a neoadjuvant study looking at the tumour response of combination gemcitabine and nab-paclitaxel pre-operatively in patients with localised, potentially resectable pancreatic cancer. (ClinicalTrials.gov Identifier: NCT01783054)

Targeted therapies

Targeted therapies have led to significant advances in other cancer types, most notably with trastuzumab in HER2 breast cancer, however to date this strategy has had limited benefit in advanced pancreatic cancer. A variety of targeted therapies, including antibodies to vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and KRAS have been assessed. The results of these trials have mostly been disappointing. The single positive study by Moore et al, published in 2007, assessed the addition of erlotinib to gemcitabine compared to gemcitabine alone.[19] A total of 569 patients were randomised and there was a small, but statistically significant OS benefit seen in the treatment arm (6.24 months vs 5.91 months (HR 0.82 p=0.038)).[19] Although this combination is approved in Australia, it is not currently funded by the Pharmaceutical Benefit Scheme due to the small clinical benefit and high cost. Importantly, no relevant biomarker has been identified to aid patient selection for this targeted therapy.[19]

Erlotinib was not the first targeted therapy to be studied in advanced pancreatic cancer. Among the first targeted agents studied in pancreatic cancer was celecoxib. Selective cyclooxygenase-2 (COX-2) inhibition was shown to be significantly upregulated in pancreatic cancer tissue compared with normal pancreatic tissue or benign lesions.[23] Furthermore, pre-clinical and clinical studies demonstrate that COX-2 inhibitors seem to work synergistically with 5-FU or cemcitabine.[23-25] A phase 2 study of 42 patients by Ferrari et al in 2006 using celecoxib and gemcitabine, showed a disease control rate of 71% (four patients had a partial response and 26 had stable disease). Median survival was 9.1 months.[25] Grade three neutropenia was the most common toxicity (19%) and no grade four toxicities were observed.[25] Although the survival seen looked promising, 38% of the patients had locally-advanced pancreatic cancer, which typically has a better prognosis than metastatic pancreatic cancer. Larger studies of this low toxicity and low cost therapy, especially in combination with the newer chemotherapy regimens, are warranted.

Oral EGFR receptor tyrosine kinase inhibitors (erlotinib and gefitinib) have also been investigated in the second line setting.[26] Combination erlotinib with capecitabine was studied in the advanced pancreatic cancer setting and published in 2007 by Kulke et al. Thirty patients with gemcitabine refractory advanced pancreatic cancer were included and a median OS of 6.5 months was observed.[27] To date, no correlation between EGFR expression, EGFR mutation or KRAS mutation and response to targeted therapies has been consistently seen.

As VEGF expression is frequent in this disease, it was hypothesised that VEGF inhibition would improve OS when added to standard line gemcitabine. Disappointingly, multiple studies of VEGF inhibition have shown a similar outcome to the other targeted therapies. A study by Kindler et al, comparing gemcitabine and bevacizumab in combination to gemcitabine alone, showed no survival benefit (5.8 vs 5.9 months) and increased rates of hypertension in the bevacizumab arm.[28] Similarly, aflibercept (a chimeric fusion protein of human VEGF receptor which competitively binds VEGF) was tested in combination with gemcitabine in a phase 3 trial conducted by Rougier et al, which was terminated for futility, demonstrating no survival benefit and significant adverse events, specifically hypertension in the aflibercept arm,[29] thus suggesting that targeting this pathway is an ineffective strategy in controlling this disease.

Overall, targeted therapies have not significantly impacted on the life expectancy of patients with advanced pancreatic cancer. Although erlotinib with gemcitabine has been shown to improve survival, its high cost and very limited benefit has resulted in minimal used of this therapy in Australia.

Second line therapy

Increasingly, clinicians are faced with patients who, after failing first line therapy, can be considered for second line chemotherapy. Without active treatment, it has been shown that the expected survival is likely to be poor. An observational study reported a median survival of 1.9 months after progressive disease following gemcitabine in 74 patients, the majority of whom received best supportive care (97%).[32]

Limitations of current evidence for second line therapy include the significant heterogeneity between small sample sized trials comparing chemotherapy to best supportive care, likely a reflection of the patients' poor performance status when at this stage of advanced pancreatic cancer, and their potential to deteriorate rapidly (table 1).

In 2011, Pelzer et al randomised 46 patients to 5-FU, leucovorin and oxaliplatin, or best supportive care. Although stopped prematurely, this study provided evidence of the benefit of this regimen as second line therapy (HR 0.50, p=0.031). Finally, based on the results of the CONKO-003 study, which randomised 160 patients to combination 5-FU and oxaliplatin, to 5-FU alone, showing a survival benefit of 2.6 months (5.9 vs 3.3 months (HR 0.66; p = .010),[33] this is the recommended second line treatment for advanced pancreatic cancer according to the National Cancer Care Network and European Society of Medical Oncology guidelines.[34,35] However, as FOLFORINOX is now being utilised as first line treatment, alternate second line agents are needed.

Multiple other agents have been investigated, predominantly in single arm phase 2 studies. Anti-mitotic agents including taxanes and topoisomerase inhibitors, demonstrate similar response rates and survival benefit.[37-41] Rubitecan, a convenient orally active topoisomerase I inhibitor studied in patients with advanced pancreatic cancer, demonstrated tumour growth control of 28% vs 13% with best supportive care only. Median progression free survival was also

***Table 1**: Selected second line studies in advanced pancreatic cancer.*

Study	Year	Study regimen	Number of patients	Median age	ECOG 0-1 (%)	Median PFS (mo)	Median OS (mo)
Rothenberg et al	1996	Gemcitabine 1000mg/m2 Week 1-7 q8weeks, then D1, D8, D15 q28days	63	62	27	2.53	3.9
Oettle et al	2000	Paclitaxel 50 mg/m2 weekly for 6 weeks with a 1 week break	18	59	NR	3.2	4
Jacobs et al	2004	Rubitecan 1.5mg/m2 D1-D5 q7days	198	NR	NR	1.9	3.6
Burris et al	2005	Rubitecan 1.5mg/m2 D1-5 q7days for 8 weeks	58	62.5	NR	1.9	3
Androulakis et al	2005	Oxaliplatin 130 mg/m2 q3weekly	18	61	75	NR	3.5
Demols et al	2006	Gemcitabine 1000 mg/m2 D1, Oxaliplatiin 100 mg/m2 D2 q14days	33	57	88	4.2	6
Stathopoulos et al	2006	Lipoplatin 25-125 mg/m2 D1, D15 and Gemcitabine 1000 mg/m2 D1, D15 q28days	24	66	50	NR	4
Kulke et al	2007	Capecitabine 1000mg/m2 BD D1-D14, Erlotinib 150 md daily q21days	32	60	100	3.4	6.5
Boeck et al	2007	Pemetrexed 500 mg/m2 q3weekly	52	62.5	94	1.6	4.6
Hosein et al	2013	nab-Paclitaxel 100 mg/m2 D1, D8, D15 q28days	19	61	79	1.7	7.3

significantly longer (58 vs 48 days; p=0.003), with minimal increase in the rate of adverse events.[37,38] Pemetrexed showed limited responses, but was shown to be safe to use in the second line setting.[41] Weekly paclitaxel demonstrated a 17.5 week median survival time with very rare grade 3-4 toxicities.[39,40]

The addition of platinum therapy to gemcitabine after progression on the latter has proved to be of benefit in a select group of patients. Two trials using gemcitabine in combination with oxaliplatin,[42,46] and three trials with cisplatin,[43] cisplatin/5-FU,[44] and cisplatin/5-FU/Irinotecan,[45] showed response rates of 8%-24% (median 23%) and a median PFS of four months (2.5-5 months) and OS of six months (4-10.3 months).[47] In a recent retrospective analysis of 20 patients who progressed on FOLFIRINOX, those who received gemcitabine had a median OS of 5.7 months. Although these results provide evidence of safety and tolerability in this setting, the lack of phase 3 data in the second line setting proves to be a challenging area warranting further research.

Immunotherapy

Cancer immunotherapy has recently emerged as a treatment modality in multiple advanced cancers including melanoma and non-small cell lung cancer. Over 20% of patients with metastatic melanoma show a sustained response of greater than two years when treated with agents targeting negative regulatory molecules on activated T cells, such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1).[48,49] However, the role of immunotherapy in pancreatic cancer is not yet clear. A phase 2 trial of ipilimumab (an anti-CTLA4 antibody) in an unselected population of patients with advanced pancreatic cancer as monotherapy revealed no responders, however one patient demonstrated a delayed response in Ca19.9. It is clear that predictive biomarkers are essential for appropriate patient selection for these therapies to be successful.[51] Similarly, studies have shown limited clinical response to vaccines.[50,51] This may be due to a combination of patient related immune factors or the inappropriate selection of tumour antigens.

The so far disappointing results with immunotherapy in advanced pancreatic cancer are currently in the process of being further investigated through the utilisation of combination treatment with existing immunotherapies, together with newer agents targeting different pathways. One of these trials, currently recruiting, is assessing the safety and tolerability of an anti-lymphocyte activation gene 3 antibody alone, and in combination with an anti PD1 monoclonal antibody in a phase 1 dose escalation study. (ClinicalTrials.gov Identifier: NCT01968109.)

Future directions

Initiatives including the Australian Pancreatic Cancer Genome Initiative continue to increase our understanding of the molecular and genomic alterations that lead to advanced pancreatic cancer and provide insights into reasons for the resistance to current therapies. As whole genome sequencing becomes faster and more affordable, identifying potentially actionable target mutations is closer to reality. Due to the rapidly progressive nature of pancreatic cancer, tests need to provide relevant information within a short timeframe to become useful in clinical practice.

Several potentially actionable mutations have already been identified and are currently being investigated to assist in directing treatment, including thymidylate synthase high intra-tumoral expression and topoisomerase expression.[52]

Identifying new therapies and new targets is vital for pancreatic cancer, but gaining a better understanding of the currently available treatments is also critical. Predictive biomarkers to select the most appropriate patient for treatment is an area of ongoing work. Currently there is mixed evidence for hENT1 expression being a positive predictive biomarker for adjuvant gemcitabine and evolving data to suggest there may be a relationship between markers of DNA damage repair and response to platinum agents.

Pancreatic cancer continues to be a devastating diagnosis. Despite decades of research into scores of novel therapies, most patients will die of their disease. What is clear is that pancreatic cancer is a heterogeneous disease and that genetic and molecular profiling must be expanded in order to stratify patients for clinical trials and ultimately to guide therapeutic choices.

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