PANCREATIC CANCER

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Abstract

Adenocarcinoma of the pancreas* takes the lives of 2500 Australians annually and because of the devastating effects of its diagnosis, has long been the poor cousin to other cancers. People with pancreatic cancer rarely survive to be champions of this disease. It has been noted to have the highest mortality to incidence ratio of any cancer and by 2020, will likely have the highest mortality of any cancer. Accordingly it is imperative that we drive awareness, research and treatment of this disease. Australia is privileged to have some of the best researchers in the world in the field of pancreatic cancer. This issue of *Cancer Forum* aims to take you through carcinogenesis, genomics and biology, and then into the clinical realms of epidemiology, diagnostics, treatment and palliation of pancreatic cancer. In each chapter we have asked Australian researchers and clinicians to review current knowledge, and then to inform us of their own practice.

Pancreatic cancer is a lethal disease with a five year survival of less than 5%.[1] The majority of patients present with locally advanced, or metastatic disease that is not amenable to surgical resection, which currently offers the only chance of cure. Of the 10-20% of patients who undergo resection the majority (~80%) still succumb with a median survival of less than two years.[2] Long-term survivors are rare and usually associated with those who undergo resection for small non-metastatic tumours with negative margins and clear lymph nodes.[3,4] This poor survival is partly responsible for the significant delay in understanding of pancreatic cancer when compared to commoner cancers with better survival.

Fortunately, recent advances in technology have accelerated our understanding of the biology of pancreatic cancer and tumour-host interactions. Recent initiatives such as the Australian Pancreatic Cancer Genome Initiative (APGI, pancreaticcancer.net.au/apgi) and the International Cancer Genome Consortium (ICGC, icgc.org) have seen major progress in the acquisition of high quality biospecimens for molecular studies in comprehensive cancer cohorts. Whole genome sequencing has facilitated identification of potentially actionable genomic changes with greater sensitivity and specificity.[5,6] Nic Waddell, a senior biostatistician on the APGI/ICGC project, summarises those findings for us.[7] As tissue requirements and costs for genome sequencing decrease, the potential to select treatments in a 'personalised' manner based on tumour biology moves closer to the clinic.[8]

Understanding biology underpins understanding cancer development and informs treatment

Andreia Pinho and colleagues review the mounting evidence that stromal factors may be crucially important not only in determining the development and behaviour of carcinoma, but in influencing treatment response and, ultimately, prognosis.[9] Stromal and epithelial cells may interact through direct cell-cell contact, or via paracrine signalling, and various non-cellular components in the stroma may influence either or both cell types. Many of these factors may contribute to cancer progression and metastasis through altered cell adhesion, epithelial-mesenchymal transition, matrix remodelling (facilitating tumour cell migration), and neovascularisation.

Models to recapitulate pancreatic cancer and inform future human therapies

In order to maximise benefit to patients, clinical trials should be conducted in populations based on molecular characteristics.[10] This highlights the importance of biomarker driven therapeutic development. Such trials are expensive, labour intensive and pose significant logistical difficulties, which in pancreatic cancer, are further compounded by the rapidity of clinical deterioration and the small percentage of patients who are well enough to receive more than one line of treatment. Anouschaka Akerman and her colleagues from the laboratory show us that useful animal models need to be orthotopic and model both stromal and tumour components together

to maximise the translational impact of modelling novel therapeutics.[11] Additionally, advances in nanoparticle technology are showing the way in dealing with previously 'undruggable targets', a key issue for pancreatic cancer, and intravital preclinical imaging of live tumours is providing new insight into the behaviour of the disease. It is hoped that these techniques will allow accelerated preclinical testing of new agents against newly discovered targets.

Pancreatic cancer diagnosis and screening

Pancreatic cancer evolves through non-invasive precursor lesions, the majority from microscopic ductal lesions known as pancreatic intraepithelial neoplasia, with a small percentage from cystic lesions - intraductal papillary mucinous neoplasms or mucinous cystic neoplasms.[12,13] Recent studies also estimate that a period of 10 to 20 years is required from the time of an initiating mutation, to the establishment of advanced disease, suggesting a prolonged period where intervention may be possible.[14] Early detection is essential to improve cure rates when cure relies on surgical resection. Vinh-An Phan and other gastroenterologists involved in research and development in this field take us through the processes for diagnosis of pancreatic cancer and illustrate that a pancreas protocol CT should be incorporated into diagnosis as well as an endoscopic biopsy.[15]

Strategies that facilitate the early detection of pancreatic cancer or its precursors during the broad window between early lesions and invasive cancer are extremely attractive. However, they show why screening of the general population is not feasible due to the low incidence of pancreatic cancer and the lack of a robust screening test. As a consequence, how the focus has shifted to individuals considered to be at high-risk is reviewed. Established risk factors for pancreatic cancer constitute both environmental and inherited influences and include age, ABO blood group, cigarette smoking, diabetes mellitus, obesity and a family history of pancreatic cancer.[16] It is thought that up to 10% of pancreatic cancer cases have a heritable component,[17] and there are screening trials available for at risk individuals. Skye McKay, a genetics counsellor who has led the Australian Familial Pancreatic Cancer program, has come together with other Australian experts in the field to update this topic for us.[18]

Pancreatic neuroendocrine tumours

Fortunately, a small but important proportion of pancreatic tumours have a much more positive outlook - the entire gastrointestinal neuroendocrine tumour family (also known as carcinoid tumours) share many commonalities. David Chan and colleagues, who are involved in research in this rare subtype of pancreas cancer, describe the unique features of this disease and recent developments in treatment.[19] Australia is leading the world in clinical trials that include peptide radionucleotide radiotherapy for this disease.

Treatment of pancreatic cancer from surgery to systemic therapies to radiotherapy and back again – an evolving continuum

Nick Butler and his surgical colleagues tell us that although surgery is the only treatment that can offer cure, the rates of cure are disappointing, even in the most experienced hands, and outline approaches to optimise the selection of appropriate candidates.[20] Australia has been at the forefront of research into the use of neoadjuvant chemotherapy and radiotherapy to improve outcomes from surgical resection of pancreatic cancer.[21] Chelsie O'Connor and her co-authors lead a discussion about the principles and application of radiotherapy,[22] and Alycea McGrath's team expands on the specific role in locally advanced disease where emerging data may resurrect its role.[23] Like other treatment modalities, the technology to deliver radiotherapy has improved and a more directed approach with less toxicity is now possible.

Very little progress has been made in the systemic treatment of advanced pancreatic cancer until the last five years. Recent advances are reviewed by Dhanusha Sabanathan and two other leading medical oncologists in the field.[24] Gemcitabine, a nucleoside analogue, became established as the standard therapy following the demonstration of improved survival and clinical benefit (pain, performance status and weight) against 5-fluorouracil.[25] This led to a fruitless decade of subsequent focus on combining other drugs with gemcitabine to test doublets against gemcitabine monotherapy. However, recent combination therapies, initially with 5-FU based approaches and more recently a novel nanotechnology compound (Abraxane), have for the first time shown improvement in overall survival times from about six months to 9-11 months. Most important has been the small numbers of longer term survivors and the potential for application in the adjuvant setting. A more personalised approach is also now being explored to try and improve on this.

Improving outcomes by optimising treatment accessibility

One obvious first step to improve outcomes overall is to ensure that all Australians with pancreatic cancer receive optimal treatment. Rachel Neale and Elizabeth Burmeister report the findings of the largest Australian pattern of care study for pancreatic cancer. They reveal that not all patients receive optimal treatment and that access to treatment depends on geographic and socio-demographic factors.[26]

Palliative care and psychosocial aspects of care of patients

Pancreatic cancer presents particular challenges in the relief of a complex constellation of symptoms. Wendy Muircroft and David Currow emphasise that referral to a palliative care service with a team-based approach including dietetics, gastroenterology, interventional pain expertise and liaison psychiatry is likely to deliver the best outcomes.[27] Ideally, this should include meaning-centred therapies that can help with reducing demoralisation and maintaining dignity of both patients and their carers and families. Helen Gooden and her team, which includes pancreatic cancer survivors, tell us about this most important aspect of care.[28]

We hope that this issue of *Cancer Forum* will show you the depth and breadth of Australian research into pancreatic cancer and give you cause for optimism for the future of this disease.

* Approximately 90% of pancreatic cancer is pancreatic ductal adenocarcinoma. Accordingly, unless otherwise stated, the term 'pancreatic cancer' used in this Forum refers predominantly and typically to this tumour type.

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