Understanding radiotherapy and its potential for use in novel combination trials

Pancreatic cancer

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UK incidence

UK incidence: 7,000 cases per annum.
UK mortality: 6,900 per annum.

Stage distribution at presentation and indications for radiotherapy

Early stage disease: 10–20% patients present with operable disease and are treated with surgery followed by adjuvant chemotherapy (Europe) or chemoradiation (CRT) (USA). Median and 5-year survival for patients undergoing curative therapy are approximately 20 months and 20–25%, respectively. The role of adjuvant chemoradiation is, at best, contentious. The ESPAC 1 trial reported significantly worse outcome with the use of CRT but has been criticised because of poor RT quality assurance [Neoptolemos, 2004]. A more recent trial of adjuvant chemotherapy versus CRT has shown equivalent survival with a trend towards improved local control in favour of CRT [Van Laethem]. A meta-analysis has suggested that CRT may be more effective and chemotherapy less so in patients with positive resection margins [Stocken, 2005].

Locally advanced non-metastatic pancreatic cancer [LANPC]: Forty percent of patients present with inoperable disease which is loco-regionally advanced without evidence of systemic spread. In the UK, the vast majority of these patients are treated with chemotherapy alone [Mukherjee, 2008] whereas in the US the standard of care is CRT (45–59.4 Gy in 25–33 fractions given with a fluoropyrimidine, but with a trend towards the use of gemcitabine as a radiosensitiser). The median survival using either gemcitabine-based chemotherapy alone or primary CRT is reported to be approximately 10 months. A strategy of induction chemotherapy followed by consolidation CRT is being increasingly adopted worldwide following a report [Huguet, 2007] which suggested its superiority over chemotherapy alone (15 versus 11.7 months, p=0.0009) – this is currently the subject of a phase III clinical trial [LAP07].

Neoadjuvant strategies: For patients undergoing surgery, R1 resection is associated with poor survival, comparable to unresected locally advanced disease. A proportion of patients with borderline resectable cancer may be down-staged by CRT to enable successful resection and survival of these patients is reported to be equivalent to those undergoing primary surgery [Snady, 2000]. It is therefore important to identify this category of patients at the regional multidisciplinary team meetings, who should then be considered for aggressive multimodality therapy rather than proceed straight to surgery or considered for palliative options only.

Stage 4: Metastatic disease at presentation is seen in about 50% of patients and a short course palliative radiotherapy [20 Gy in 5 fractions or 30 Gy in 10 fractions] is given if symptoms require it [Morganti, 2003]. The median survival for stage 4 disease treated with palliative chemotherapy is about 6 months. Stereotactic body radiotherapy has the potential for accurate delivery of hypofractionated palliative radiotherapy but requires further testing [Chang, 2009].

Current chemosensitisers

The standard of care for CRT is to combine a fluoropyrimidine with radiotherapy. This is conventionally 5-fluorouracil (5-FU) but capecitabine is increasingly being used. Gemcitabine-based CRT has been shown to be more effective than 5-FU-CRT in one small phase III trial but is generally considered more toxic [Li, 2003]. A randomised phase II study of gemcitabine- vs capecitabine-based CRT is currently under way in the UK (SCALOP). A recent meta-analysis comparing 5-FU-based with gemcitabine-based CRT in 229 patients described a statistically significant advantage for gemcitabine-based CRT for 12-month overall survival (RR 1.54, 95% CI 1.05-2.26, p=0.03) [Zhu et al. 2011]. The combination of full dose gemcitabine [1000 mg/m^2] with a conventional dose of radiation using a 3D conformal radiation technique to a small planning target volume (PTV) is feasible, has acceptable toxicity and promising efficacy [Murphy, 2007]. Radiation induces EGFR activation, leading to radioresistance and repopulation during radiotherapy. The combination of the anti-EGFR monoclonal antibody, cetuximab, with radiation is being currently assessed in two Phase II trials in the UK (PACER, PERU) [Czito, 2006].

Pancreatic cancer biology: Key considerations

Pancreatic ductal adenocarcinoma (PDA) has a high incidence of KRAS mutation (>80%) and there is evidence to suggest that KRAS, through the Ras/Raf/MEK/ERK signalling, activates the hedgehog pathway and plays an important role in progression of PDA and in radiation resistance [Brunner, 2005]. MEK1 and 2 are attractive therapeutic targets in pancreatic cancer due to their downstream position within this pathway, and a MEK 1/2 inhibitor, alone or in conjunction with conventional therapy, would be a rational therapeutic strategy for this condition. Another important survival pathway downstream of Ras signals is through PI3-kinase and Akt.

Pancreatic cancer is characterised by intra-tumoural hypoxia and in animal models, selective killing of HIF-1 active pancreatic cancer cells or inhibition of HIF-1 alpha mRNA expression significantly reduced tumour progression [Kizaka-Kondo, 2009; Chen, 2009]. Hypoxia is associated with reduced

sensitivity to chemotherapy and ionising radiation, and hypoxic regions of the tumour may require higher doses of radiotherapy.

Radiotherapy contributes to desmoplasia, which is predominant in pancreatic carcinoma. Conventional imaging [e.g. CT scan] is a poor discriminator between tumour and fibrosis and novel imaging modalities [PET, dynamic contrast-enhanced (DCE)-MRI, endoscopic ultrasound elastography] should be investigated to evaluate their usefulness in assessing primary disease and response to CRT. Additionally, pancreatic stellate cells which are responsible for the desmoplastic reaction have recently been described to protect pancreatic cancer cells from the cytotoxic effect of radiotherapy [Mantoni , 2011].

Therapeutic opportunities with radiotherapy in pancreatic cancer

General principles

The practice of CRT for pancreatic cancer is not well established in the UK and only 16% of patients received combined modality treatment in one survey of UK-based clinical oncologists [Saleem, 2010]. There is a need to engender its use within the UK, to develop consensus guidelines on dose, radiosensitiser and treatment volumes and to develop a quality assurance programme to ensure that high-quality pancreatic RT can be delivered uniformly across the UK. As newer systemic therapies have consistently failed to make a significant impact on survival and disease control, radiation-based strategies merit evaluation in every stage of the disease. CRT to the pancreas is challenging because of tumour hypoxia and its proximity to several critical structures, which limits the possible radiation dose. Advanced radiotherapy planning (4D planning CT, incorporation of FDG-PET during radiotherapy planning) and radiotherapy delivery (intensity-modulated RT [IMRT], image-guided RT [IGRT]), the use of novel radiosensitisers (e.g. nelfinavir) and the role of advanced imaging modalities to assess treatment response (PET, DCE-MRI) needs to be evaluated through carefully conducted phase I–II trials. It may be useful to do some of these studies in the pre-operative setting so that both pre- and post-therapy tissues are available, to help us understand the biology of this disease and the impact of therapy.

Phase I/II trials

Radiotherapy dose escalation trials

Early studies should evaluate whether hypoxic tumours as imaged by miso-PET are resistant to CRT. Subsequent studies should aim to evaluate the effect of higher doses of radiation to hypoxic tumours and whether it is feasible to map regions of hypoxia within tumour and boost these areas selectively using IMRT. Alternatively, drugs reducing hypoxia before the start of CRT such as nelfinavir are currently being tested with the aim of enhancing its therapeutic effect [ARC-II] to overcome the limitations on dose-escalation.

The concept of individually dosed RT [IDRT] could be explored whereby rather than prescribing a fixed radiation dose to the tumour, the tumour dose is escalated in individual patients defined by pre-determined dose constraints to the surrounding organs at risk [Gwynne, 2009].

Radiosensitisation trials

It is essential that these studies attempt to address the basic biology of the disease rather than using agent/agents known for their general radiosensitising properties. Thus agents which retain activity in a ras mutant context should be prioritised. MEK inhibitors, PI3-kinase and hedgehog pathway inhibitors should be considered. Drugs aimed to reduce intra-tumoural hypoxia as mentioned above could reverse resistance to CRT; the conduct of such studies require careful evaluation of the tumour pre- and post treatment, using novel imaging to assess response to therapy.

The design of these studies should use a randomised phase II approach, building on the SCALOP trial, with either a fluoropyrimidine or gemcitabine as the control radiosensitising agent depending on the best arm of that study. Single arm studies are less likely to be informative in designing any subsequent phase III trials.

Imaging studies, novel radiotherapy techniques

Some of these have been highlighted above and could be run in conjunction with either RT dose escalation or radiosensitisation trials.

Phase III trials

Clinical oncologists in the UK need to demonstrate their commitment to developing pancreatic CRT and engage in recruiting successfully to the ongoing phase II trials before phase III trials should be considered. The two patient groups to be considered are those with surgically resectable tumours in whom the role of pre-operative CRT should be evaluated in a phase III setting [Brunner, 2007] and those with localised but unresectable disease.

Despite our best efforts to control local disease, the majority of patients succumb to metastatic disease; further understanding of tumour biology, its interaction with the host micro-environment and improvements in systemic therapy remain as key challenges in the battle against pancreatic cancer [Philip, 2009].

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