European Journal of Cancer (2013) 49, 3609–3615

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: A phase II randomised trial

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Available online 27 July 2013

KEYWORDS
Anti-angiogenic therapy
Maintenance therapy
Metastatic disease
Pancreas
Pancreatic adenocarcinoma
Pancreatic cancer
Phase II trial
Randomised trial
Sunitinib

Abstract ***Background:*** New strategies to prolong disease control warrant investigation in patients with metastatic pancreatic adenocarcinoma. This open-label, randomised, multicentre phase II trial explored the role of maintenance sunitinib after first-line chemotherapy in this setting.

Methods: Patients with pathologic diagnosis of metastatic pancreatic adenocarcinoma, performance status >50%, no progression after 6 months of chemotherapy were centrally randomised by an independent contract research organisation, which was also responsible for data collection and monitoring, to observation (arm A) or sunitinib at 37.5 mg daily until progression or a maximum of 6 months (arm B). The primary outcome measure was the probability of being progression-free at 6 months (PFS-6) from randomisation. Assuming P0 = 10%; P1 = 30%, α .10; β .10, the target accrual was 26 patients per arm.

Results: 28 per arm were randomised. One arm B patient had kidney cancer and was excluded. Sunitinib was given for a median of 91 days (7–186). Main grade 3–4 toxicity was

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http://dx.doi.org/10.1016/j.ejca.2013.06.041

thrombocytopenia, neutropenia and hand–foot syndrome (12%), diarrhoea 8%. In arm A versus B, PFS-6 was 3.6% (95% confidence interval (CI): 0–10.6%) and 22.2% (95% CI: 6.2–38.2%; $P < 0.01$); 2y overall survival was 7.1% (95% CI: 0–16.8%) and 22.9% (95% CI: 5.8–40.0%; $P = 0.11$), stable disease 21.4% and 51.9% ($P = 0.02$).

Conclusion: This is the first randomised trial on maintenance therapy in metastatic pancreatic adenocarcinoma. The primary end-point was fulfilled and 2y overall survival was remarkably high, suggesting that maintenance sunitinib is promising and should be further explored in this patient population.

1. Introduction

More than half of patients with pancreatic adenocarcinoma present with metastatic disease at diagnosis and over 70% of them receive single agent gemcitabine as upfront therapy.[1] The most relevant therapeutic progress came from the combination of gemcitabine with nab-paclitaxel[2] or of multiple cytotoxic agents.[3,4]

Despite the outcome improvement, patients continue to fail and die of their disease and chemotherapy still remains a palliative approach whose efficacy has to be balanced with its toxicity. The optimal duration of chemotherapy is controversial because evidence of any additional benefit by continuing treatment until progression of disease (PD) is lacking. Conversely, the risk of cumulative toxicity is not negligible and a negative impact of relentless chemotherapy on patients' quality-of-life cannot be ruled out. Therefore, new strategies, such as maintenance therapy, aimed to prolong disease control warrant investigation.

Angiogenesis is a distinct and crucial step in the development and progression of cancer and vascular endothelial growth factor (VEGF) plays a pivotal role in the growth and metastasis of many tumours, being associated with prognosis.[5] Furthermore, inhibition of platelet-derived growth factor receptor (PDGFR) signalling, which is also implicated in the autocrine growth of tumour cells and in the recruitment and regulation of tumour fibroblasts, augments the antitumour and anti-angiogenic effects of VEGF receptor (VEGFR) inhibitors.[6] According to the Folkman's induced dormancy theory, angiogenesis inhibitors should prevent disease progression and maintain stable disease.[7] Consistently, maintenance therapy with sunitinib after radiotherapy, significantly prolonged tumour control in murine models.[8] Sunitinib (sunitinib malate; Sutent®; Pfizer Pharmaceuticals Group, New York, NY) is an orally bioavailable, multitargeted small molecule that inhibits several receptor tyrosine kinases, including VEGFR, PDGFR, kit and Flt-3 receptors[9–11] that are over-expressed in pancreatic cancer[12,13] and appears a suitable candidate for maintenance therapy in this disease.

The PACT-12 (Pancreatic AdenoCarcinoma Trials-12; ClinicalTrials.gov ID: NCT00967603) trial was undertaken to explore the hypothesis that sunitinib maintenance therapy is able to increase the rate of patients with metastatic pancreatic adenocarcinoma who are progression-free at 6 months from the end of first-line treatment.

2. Patients and methods

The PACT-12 was a multicenter, open-label, randomised, phase II trial. Patients were required to have pathologically confirmed metastatic pancreatic adenocarcinoma; absence of progressive disease after 6 months of first-line chemotherapy demonstrated with: (a) two consecutive computed tomography or magnetic resonance scans separated by at least 6 weeks and (b) normal or no carbohydrate antigen 19-9 (CA19-9) increase >20% during the last month; interval >3 and <8 weeks from last chemotherapy administration (>1 week in the case of 5-fluoruracil as continuous infusion or capecitabine); age >18 years; Karnofsky performance status (KPS) >50%; adequate bone marrow (granulocytes > 1500/μL, platelets > 100,000/μL, haemoglobin > 10 g/dL), hepatic (total bilirubin < 1.5 mg/dL, transaminases < 3 × upper limit of normal (ULN)), renal (creatinine < 1.5 mg/dL), coagulation (prothrombin time and partial thromboplastin time <1.5 ULN) and thyroid function. Measurable disease was not required. Patients who received prior adjuvant therapy; more than one line of chemotherapy for metastatic disease; or prior treatment with anti-angiogenic drugs were excluded. Patients could not have previous or concurrent malignancies at other sites with the exception of surgically cured carcinoma in-site of the cervix and basal or squamous cell carcinoma of the skin, and of other neoplasms without evidence of disease at least from 5 years. Other exclusion criteria included inability to take oral medications; tumour invasion of stomach, duodenum or intestine; major surgery within the preceding 30 days; clinically significant cardiovascular disease; pre-existing uncontrolled hypertension; QTc interval prolongation; pregnancy or lactation; current use of drugs with potential anti-arrhythmic activity or thrombolytic agents at therapeutic dose; current use or <7 days interval from withdrawal of drugs that are known CYP3A4 inhibitors; current use or <12 day interval from withdrawal of drugs that are known CYP3A4 inducers; concurrent treatment with other experimental drugs.