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Capecitabine and streptozocin ± cisplatin in advanced gastroenteropancreatic neuroendocrine tumours

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Abstract ***Background:*** Cytotoxic chemotherapy is widely used for advanced, unresectable pancreatic and other gastrointestinal foregut neuroendocrine tumours (NETs) and the most commonly used regimen combines 5-fluorouracil with streptozocin. The NET01 trial was designed to investigate whether capecitabine combined with streptozocin was an acceptable regimen with or without adding cisplatin.

Methods: Patients with advanced, unresectable NETs of pancreatic, gastrointestinal foregut or unknown primary site were randomised to receive three-weekly capecitabine (Cap) 625 mg/m^2 twice daily orally, streptozocin (Strep) 1.0 g/m^2 intravenously on day 1, with or without cisplatin (Cis) 70 mg/m^2 intravenously on day 1. The primary outcome measure was objective response. Secondary outcome measures included progression-free and overall survival, quality of life, toxicity and biochemical response.

Results: 86 (44 CapStrep, 42 CapStrepCis) patients were randomised. Best objective response rate was 12% (95% confidence interval (CI) = 2–22%) with CapStrep and 16%

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(95% CI = 4–27%) with CapStrepCis. Disease-control rate was 80% with CapStrep and 74% with CapStrepCis. The estimated median progression-free and overall survival were 10.2 and 26.7 months for CapStrep and 9.7 and 27.5 months for CapStrepCis. 44% of CapStrep and 68% of CapStrepCis patients experienced grade ⩾3 adverse events.

Interpretation: The efficacies of the novel CapStrep ± Cis regimens were very similar. CapStrep was better tolerated than CapStrepCis.

The trial was registered as EudraCT: 2004-005202-71 and ISRCTN: 35124268.

1. Introduction

Cytotoxic chemotherapy is widely used for advanced, unresectable pancreatic and other gastrointestinal foregut neuroendocine tumours (NETs), although few randomised trials have been undertaken in this rare cancer [1–4]. The first of these trials [1] established streptozocin (Strep) and 5-fluorouracil (5-FU) as the standard of care for advanced pancreatic NETs. The remarkable 63% response rate [1] was based on combined clinical and biochemical response criteria in addition to radiological response. Subsequent studies using conventional WHO or RECIST response criteria reported lower response rates for Strep-based regimens ranging between 6 and 55% [5–12]. Cisplatin (Cis) was combined with Strep and 5-FU in a retrospective study of 49 patients with advanced pancreatic NETs and an objective partial response rate of 38% was reported [11]. However, no prospective trials of cisplatin-containing chemotherapy for NETs have previously been undertaken. Over the last 10 years, capecitabine (Cap) has been effectively substituted for 5-FU in many regimens used to treat gastrointestinal tract cancers [13–15]. Cap has reported activity as a single agent or in combination regimens for non-pancreatic NETs [16,17] as well as in combination with temozolomide for pancreatic NETs [18]. The NET01 trial was designed to investigate whether Cap combined with Strep was an acceptable regimen with or without adding cisplatin to treat advanced gastroenteropancreatic (foregut) NETs.

2. Patients and methods

2.1. Main eligibility

Patients with chemonaive, histologically confirmed, unresectable, advanced and/or metastatic NETs of the pancreas, other gastrointestinal foregut, or unknown primary site suggestive of abdominal foregut origin were eligible. Patients were required to have measurable disease by RECIST (version 1.0), Eastern Cooperative Oncology Group performance status (ECOG PS) ⩽2, adequate bone marrow, hepatic and renal function with creatinine clearance >60 ml/min. Radiological confirmation of progressing disease between consecutive imaging was not mandated. Ethics committee approval of the protocol and written informed consent from all patients were obtained. Paraffin-embedded (blocks/slides) or fresh-frozen biopsy material taken from the patient's tumour (primary/secondary) prior to treatment was collected for central pathology review and immunohistochemical assessment of Ki67 expression and mitotic index as previously described [19].

2.2. Treatment

Patients were randomised (1:1), using the stratified random block method, to receive six cycles of three-weekly CapStrep or CapStrepCis regimens. The stratification factors were functional tumour (yes versus no), previous treatment received (somatostatin analogues/interferon versus none) and primary tumour site (known versus unknown). The CapStrep regimen comprised capecitabine 625 mg/m^2 administered orally, twice daily on days 1–21, and streptozocin 1.0 g/m^2 (2-h infusion intravenously in normal saline) on day 1. The CapStrepCis regimen comprised CapStrep plus cisplatin 70 mg/m^2 (2-h infusion intravenously in normal saline with hydration) on day 1, directly after the Strep infusion. Patients could continue to receive the same treatment beyond six cycles if there was evidence of benefit.

2.3. Assessments

Patients were assessed for adverse events (AEs) every cycle, using the NCI CTC (version 3), and followed for disease progression and survival every 12 weeks. Tumour assessments with CT scans were performed at the baseline, every three cycles while on treatment and every 12 weeks until progression. Retrospective central radiology review was undertaken for objective tumour response assessments in 10% of randomly selected patients who completed at least three treatment cycles.

Biochemical measurements of 24 h urinary 5-hyroxyindoleacetic acid (5HIAA) and serum chromogranin A (CgA) were undertaken by radioimmunoassay prior to treatment and if above the normal range were repeated every three cycles while on treatment and at 12 weeks from the end of treatment. Patient quality of life (QoL) using the EORTC QLQ-C30 questionnaires was assessed before randomisation, after three