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Randomised, double-blind trial of carboplatin and paclitaxel with daily oral cediranib or placebo in patients with advanced non-small cell lung cancer: NCIC Clinical Trials Group study BR29 ☆

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Abstract ***Introduction:*** This randomised double-blind placebo-controlled study evaluated the addition of cediranib, an inhibitor of vascular endothelial growth factor receptors 1–3, to standard carboplatin/paclitaxel chemotherapy in advanced non-small cell lung cancer.
Methods: Eligible patients received paclitaxel (200 mg/m^2) and carboplatin (area under the concentration time curve 6) intravenously every 3 weeks. Daily oral cediranib/placebo 20 mg was commenced day 1 of cycle 1 and continued as monotherapy after completion of 4–6 cycles of chemotherapy. The primary end-point of the study was overall survival (OS). The trial would continue to full accrual if an interim analysis (IA) for progression-free survival (PFS), performed after 170 events of progression or death in the first 260 randomised patients, revealed a hazard ratio (HR) for PFS of $\leqslant$0.70.
Results: The trial was halted for futility at the IA (HR for PFS 0.89, 95% confidence interval [CI] 0.66–1.20, $p = 0.45$). A final analysis was performed on all 306 enrolled patients. The addition of cediranib increased response rate ([RR] 52% versus 34%, $p = 0.001$) but did not significantly improve PFS (HR 0.91, 95% CI 0.71–1.18, $p = 0.49$) or OS (HR 0.94, 95% CI 0.69–1.30, $p = 0.72$). Cediranib patients had more grade 3 hypertension, diarrhoea and anorexia.

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Conclusions: The addition of cediranib 20 mg daily to carboplatin/paclitaxel chemotherapy increased RR and toxicity, but not survival.

1. Introduction

Advanced non-small cell lung cancer (NSCLC) is the leading cause of cancer death world-wide. For patients without a known oncogenic driver, platinum-based combination chemotherapy is standard first-line treatment for advanced disease.

Angiogenesis is critical to the malignant phenotype [1] and the vascular endothelial growth factor (VEGF) pathway plays an important role. Cediranib (AZD2171, Recentin™, AstraZeneca, Macclesfield, United Kingdom (UK)) is a tyrosine kinase inhibitor (TKI) of all three VEGF receptors (VEGFR), in addition to c-Kit. In an NCIC Clinical Trials Group (CTG) phase I study, cediranib (45 or 30 mg daily) could be combined tolerably with carboplatin–paclitaxel (CP) [2]; 19 of 20 patients had tumour shrinkage (nine partial responses) without evidence of a dose–response relationship. BR24 was a randomised double-blind phase II/III trial of daily cediranib/placebo (initially 45 mg, but due to toxicity concerns, lowered to 30 mg) in combination with CP in advanced NSCLC [3]. Although the interim analysis (IA) for progression-free survival (PFS) met the threshold for proceeding to phase III (hazard ratio [HR] 0.77), and response rates (RRs) were improved (38% versus 16%, $p < 0.001$), the trial was halted due to an imbalance in fatal serious adverse events (deaths within 30 days of last dose of study drugs; 13% versus 0% for cediranib and placebo, respectively). The deaths were disparate, and in some cases, the investigator believed unrelated to protocol therapy. Severe toxicity was associated with hypoalbuminemia and advanced age. The highest accruing centres in Canada (which were also the phase I centres) had no fatal adverse events, suggesting patient selection and familiarity with the regimen improved tolerability.

Given the promising antitumour activity, the fact that trials in other cancers were proceeding at 20 mg, and lack of a clear dose–response relationship, the NCIC CTG felt further study was warranted. In conjunction with the Australasian Lung cancer Trials Group, this phase III randomised, double-blind trial (BR29) of cediranib/placebo 20 mg daily combined with CP was undertaken.

2. Methods

2.1. Patients

BR29 (NCT00795340) was conducted at 31 centres in Canada, Australia and Brazil. Eligible adult patients had advanced, incurable, pathologically-proven NSCLC (any histology), Eastern Cooperative Oncology Group Performance Status of 0–1, adequate organ function, and weight loss of <10% in the preceding 3 months (those with weight loss unknown or 5–10% required albumin of ⩾30 g/l). Measurable disease was required for patients enrolled prior to the IA. Permitted prior systemic therapies were adjuvant chemotherapy (>1 year before study entry) and epidermal growth factor receptor (EGFR) inhibitors (>21 days for monoclonal antibodies, >14 days for TKI).

Ineligibility criteria included: uncontrolled cardiovascular disease; QTc interval >480 ms; uncontrolled hypertension; untreated, symptomatic, cavitating or haemorrhagic brain metastases; appreciable central cavitation of the lung primary; overt bleeding (>30 ml within 3 months); pregnancy or lactation. Therapeutic anticoagulation was permitted.

This study was approved by the research ethics boards of the participating institutions. All patients provided written informed consent. The trial was conducted in accordance with Good Clinical Practice guidelines.

2.2. Protocol therapy and evaluations

Patients received P 200 mg/m^2 intravenously over 3 h and C (area under the concentration time curve 6) over 30 min, every 3 weeks for 4–6 cycles. Cediranib/placebo 20 mg orally daily, commenced day 1 cycle 1, and continued after the completion of CP in the absence of disease progression or unacceptable toxicity. Doses of all agents were adjusted for expected toxicities; one dose reduction to 15 mg of cediranib/placebo was permitted. Guidelines for management of diarrhoea and hypertension were provided.

Patients were assessed by the investigator every cycle. Blood pressure was recorded weekly for the first three cycles and, if normotensive, on day 1 of every subsequent cycle. Response was assessed every two cycles using the Response Evaluation Criteria in Solid Tumours version 1.1 [4] and toxicity graded using the Common Toxicity Criteria for Adverse Events version 3.0 [Bethesda, MD]. Quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire (QLQ-C30) [5], the lung cancer module (QLQ-LC13) [6] and two additional questions (hand–foot syndrome and headache) at baseline and every cycle.

Optional, limited paclitaxel pharmacokinetic analysis was performed on a subset of consenting patients. Plasma paclitaxel concentrations were determined using HPLC-tandem mass spectrometry [7].