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Original Research

Neoadjuvant radiotherapy combined with capecitabine and sorafenib in patients with advanced *KRAS*-mutated rectal cancer: A phase I/II trial (SAKK 41/08)

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KEYWORDS
Dose escalation;
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Abstract ***Background:*** *KRAS* mutation occurs in ~40% of locally advanced rectal cancers (LARCs). The multitarget tyrosine kinase inhibitor sorafenib has radiosensitising effects and might improve outcomes for standard preoperative chemoradiotherapy in patients with *KRAS*-mutated LARC.

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Tyrosine kinase inhibitor;
Safety

Methods: Adult patients with *KRAS*-mutated T3/4 and/or N1/2M0 LARC were included in this phase I/II study. The phase I dose-escalation study of capecitabine plus sorafenib and radiotherapy was followed by a phase II study assessing efficacy and safety. Primary endpoints were to: establish the maximum tolerated dose of the regimen in phase I; determine the pathologic complete response (pCR) rate in phase II defined as Dworak regression grade 3 and 4.

Results: Fifty-four patients were treated at 18 centres in Switzerland and Hungary; 40 patients were included in the single-arm phase II study. Recommended doses from phase I comprised radiotherapy (45 Gy in 25 fractions over 5 weeks) with capecitabine 825 mg/m^2 twice daily × 33 plus sorafenib 400 mg/d. Median daily dose intensity in phase II was radiotherapy 100%, capecitabine 98.6%, and sorafenib 100%. The pCR rate (Dworak 3/4) was 60% (95% CI, 43.3–75.1%) by central independent pathologic review. Sphincter preservation was achieved in 89.5%, R0 resection in 94.7%, and downstaging in 81.6%. The most common grade 3 toxicities during phase II included diarrhoea (15.0%), skin toxicity outside radiotherapy field (12.5%), pain (7.5%), skin toxicity in radiotherapy field, proctitis, fatigue and cardiac ischaemia (each 5%).

Conclusions: Combining sorafenib and standard chemoradiotherapy with capecitabine is highly active in patients with *KRAS*-mutated LARC with acceptable toxicity and deserves further investigation. www.clinicaltrials.gov: NCT00869570.

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1. Introduction

Neoadjuvant chemoradiotherapy is often used in patients with locally advanced rectal cancer (LARC) to downstage tumours for better resectability and to enhance locoregional control [1]. Capecitabine is a standard neoadjuvant chemotherapy in this setting and has efficacy comparable to 5-fluorouracil [2].

Selecting patients for treatment according to molecular markers is a standard approach in metastatic colorectal cancer nowadays. To date, chemotherapy combinations, e.g. oxaliplatin and irinotecan, or addition of biologic agents, e.g. bevacizumab, to standard chemoradiotherapy have not led to breakthrough increases in efficacy and sometimes have imposed a relevant increase in toxicity [3–5]. Phase II trials in the neoadjuvant setting selecting patients with LARC and *KRAS* wild-type tumours have been published, but the impact of adding epidermal growth factor receptor (EGFR) antibodies to chemoradiotherapy has been modest [3,6]. Despite the fact that *KRAS* mutations are detected in ~35–45% of patients with LARC, no trials have previously focused on this patient group.

Sorafenib is an oral multikinase inhibitor with effects on tumour proliferation and angiogenesis. We initially selected this molecule based on its inhibitory effect on the serine/threonine kinases RAF1 and wild-type BRAF—pivotal components of the RAS/RAF/MEK/ERK pathway. Inhibitory effects were subsequently demonstrated against the vascular endothelial growth factor (VEGF) receptor as well as the platelet-derived growth factor receptor, FLT-3, and c-Kit [7]. Furthermore, sorafenib is an excellent radiosensitiser, as RAS/RAF inhibition combined with VEGF inhibition leads to increased sensitivity to radiotherapy [8]. There is further evidence that inhibition of RAF1 can resensitise tumour cells that are resistant to radiotherapy or chemotherapy [9,10]. These facts provide a rationale for adding sorafenib to a standard chemotherapy (capecitabine) and radiotherapy combination as treatment for LARC in the neoadjuvant setting.

Phase I and II trials defined sorafenib 400 mg twice daily in combination with capecitabine 1700 mg/m^2 daily as a feasible regimen [11]. No impact of capecitabine on the pharmacokinetics of sorafenib was reported, but concomitant sorafenib moderately increases exposure to higher doses of capecitabine, so it was decided to start with a full dose of sorafenib and to escalate the capecitabine dose [11].

2. Patients and methods

2.1. Participants

Patients with locally advanced, not otherwise pretreated rectal cancer, cT3/4 and/or cN1/2cM0 (staged by magnetic resonance imaging), and *KRAS*-mutant tumour status were recruited from 19 centres in Switzerland and Hungary. Patients were aged ≥18 years and had adequate organ function and an Eastern Cooperative Oncology Group performance status of 0/1. Other inclusion criteria were identical to the Swiss Group for Clinical Cancer Research (SAKK) trial 41/07 [6], which was performed at the same time.

2.2. Trial design and statistics

The phase I dose-escalation study of capecitabine given with sorafenib and external-beam radiation therapy was

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