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ScienceDirect
EJSO 36 (2010) 244–250
EJSO the Journal of Cancer Surgery
www.ejso.com

A phase II study of cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer

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Accepted 7 December 2009
Available online 29 December 2009

Abstract

Background: Neoadjuvant chemoradiotherapy (CRT) reduces local tumor recurrence in locally advanced rectal cancer (LARC). This phase II study assessed neoadjuvant cetuximab with capecitabine-based CRT in LARC.
Methods: Patients with stage II/III LARC received capecitabine 1250 mg/m^2 twice daily for 2 weeks followed by intravenous cetuximab 400 mg/m^2 at week 3, then weekly intravenous 250 mg/m^2 cetuximab plus CRT including capecitabine 825 mg/m^2 twice daily (including weekends during radiotherapy) with radiotherapy of 45 Gy (25 × 1.8 Gy), 5 days a week for 5 weeks. Total mesorectal excision was scheduled 4–6 weeks following completion of CRT. The primary endpoint was pathological complete response (pCR).
Results: Thirty-seven patients were eligible for safety and efficacy. TMN staging at baseline was: T4N2, 11%; T3N2, 40%; T2N2, 3%; T3N1, 35%; T2N1, 3% and T3N0 8%. The most common adverse events included, grade 1/2 acneiform skin rash (86%), and grade 3 radiodermatitis, (16%), diarrhea (11%) and hypersensitivity (5%). pCR was achieved in 3 patients (8%). Overall-, T- and N-downstaging rates were 73%, 57% and 81% respectively. Total sphincter preservation rate was 76%, and 53% in 17 patients whose tumors were located within 5 cm from the anal verge. Non-fatal perioperative complications occurred in 13 patients (35%) with delayed wound healing occurring in 6 patients (16%). One death was recorded due to sepsis following colonic necrosis.
Conclusion: Neoadjuvant cetuximab with capecitabine-based CRT is tolerable in patients with resectable LARC. Whilst the pCR rate was similar to recent reports, a high pathological downstaging rate was achieved.

Keywords: Rectal cancer; Neoadjuvant chemoradiotherapy; Capecitabine; Cetuximab

Introduction

Multimodal treatment strategies aim to reduce tumor recurrence rates and improve survival in patients with resectable locally advanced rectal cancer (LARC). Pre- and postoperative radiotherapy are reported to decrease the risk of local relapse in this setting.[1–3] Chemotherapy in combination with radiotherapy can act as a radiosensitizing agent, potentially eradicating micrometastases. The combination of postoperative 5-fluorouracil (5-FU)-based chemotherapy with radiation in the treatment of LARC is reported to improve patient disease-free survival (DFS) and overall survival.[4] Lower rates of local regional failure (13% vs. 6%) in patients receiving preoperative 5-FU-based chemoradiotherapy (CRT) compared with postoperative 5-FU-based CRT have also been demonstrated.[5] The addition of continuous infusion (CI) 5-FU-based chemotherapy concurrently to preoperative long-term fractionation radiation is now considered by many to be the standard of care for LARC patients in Europe, following data from prospective randomized studies.[6,7] However, whilst rates of pathological complete response (pCR) and local control were found to be higher in the CRT arms than radiotherapy alone arms, no significant improvements to DFS or overall survival were found, with the occurrence of metastatic disease remaining a problem.[6–8] Thus new combinations of chemotherapeutic agents for CRT in LARC patients are urgently sought.

Capecitabine (Xeloda, Hoffmann-La Roche Ltd, Basel Switzerland) an oral fluoropyrimidine prodrug is readily

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doi:10.1016/j.ejso.2009.12.002

absorbed into the gastrointestinal tract and activated primarily in tumor cells displaying high levels of thymidine phosphorylase.[9] Capecitabine has the same efficacy as CI 5-FU but with less of the associated toxic side effects,[9,10] and has demonstrated radiosensitizing properties *in vivo*.[11] Furthermore when capecitabine was administered concomitantly with radiotherapy to LARC patients in phase II studies, low toxicity profiles, tumor downstaging and pCR rates ranging from 4 to 31% were reported.[12,13]

Cetuximab (Erbitux developed by Merck KGaA Darmstadt, Germany [under license from Imclone, NY, USA]) an immunoglobulin G1 monoclonal antibody specifically targets the epidermal growth factor receptor (EGFR), competitively inhibiting ligand binding and ligand-dependent downstream signaling.[14,15] Cetuximab in combination with chemotherapy has demonstrated improved efficacy in the first-line treatment of patients with EGFR expressing metastatic CRC (mCRC) compared with chemotherapy alone arms.[16,17] Furthermore cetuximab has been shown to be safely administered with radiotherapy, improving survival in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).[18]

EGFR expression has been associated with reduced DFS in patients with LARC following preoperative CRT.[19,20] Thus EGFR-targeted agents appear to be attractive candidates for use with CRT in this setting. Recent phase I/II studies have reported acceptable toxicity and tumor downstaging when cetuximab was administered in combination with fluoropyrimidine-based CRT in rectal cancer patients.[21,22] In the present study the addition of cetuximab to capecitabine-based CRT was investigated in the neoadjuvant treatment of resectable LARC patients.

Patients and methods

Study design

This was a prospective, open-label single center phase II study. The protocol was approved by the Ethical Committee of Slovenia, Agency for Medicinal Products and Medical Devices, Ministry of Health and by the Independent Ethical Committee of the Institute of Oncology, Ljubljana, Slovenia. The trial was registered at CinicalTrials.gov. (NCT00689702). The study was conducted in accordance with the principles of the Declaration of Helsinki and the note for guidance on good clinical practice.

Main eligibility criteria

Eligible patients had a histologically verified stage II or III adenocarcinoma of the rectum, (International Union against Cancer [UICC] TNM classification 2002). Other inclusion criteria were; $\geq$18 years of age at diagnosis; World Health Organization (WHO) performance status $\leq$2; adequate bone marrow, liver, renal and cardiac function (no history of ischemic heart disease); no prior radiotherapy and/or chemotherapy; signed informed consent. Exclusion criteria included; patients with a history of prior malignancy other than non-melanoma skin cancer or in situ carcinoma of the cervix; a known hypersensitivity to biological agents; pregnant or lactating patients.

Pretreatment evaluation

Patient pretreatment work-up comprised a complete history, physical examination, full blood count, serum biochemistry, carcinoembryonic antigen, chest radiography, ultrasonography (US) and/or a computed tomography (CT) scan of the whole abdomen and colonoscopy with biopsy. The extent of locoregional disease was determined by magnetic resonance imaging (MRI) of the pelvis (100%); 56% of patients also had endoscopic US and 7% had a CT scan of the pelvis.

Patient treatment

A summary of the study treatment is shown in Fig. 1. Patients received capecitabine 1250 mg/m^2 twice daily for 2 weeks. Cetuximab 400 mg/m^2 was intravenously administered on week 3, followed by 250 mg/m^2/week during radiotherapy. Radiotherapy started on week 4 and was delivered once a day using 15 MV photon beams and a four-field box technique, 5 days a week. The small pelvis received 45 Gy in 25 fractions of 1.8 Gy over 5 weeks. Three-dimensional conformal CT-based treatment planning was performed. The clinical target volume (CTV) encompassed the primary tumor, entire mesorectal tissue, and internal iliac and presacral lymph nodes up to the L5/S1 junction and 5 cm distal to the primary tumor. An additional 1 cm in all directions was added to the CTV to obtain the planning target volume (PTV). During irradiation, patients were treated in the prone position, with a full bladder, and a belly-board immobilization device was used. A multileaf collimator was used for shaping the fields and for the protection of normal tissues. Chemotherapy was administered concomitantly with radiotherapy and consisted of capecitabine administered orally at a daily dose of 1650 mg/m^2, divided into two equal doses given 12 h apart, one administered an hour prior to irradiation. Chemotherapy was started on the first day and finished on the last day of radiotherapy (including weekends).

Patient and tumor assessments

During treatment, patients were evaluated weekly. Clinical examinations and complete blood counts were performed and body weight was measured. Toxic side effects were assessed according to National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0).

Following re-evaluation of the primary tumor with pelvic MRI and an assessment of tumor response as defined by RECIST criteria, definitive surgery was scheduled for