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Original Article

Oxaliplatin-containing Preoperative Therapy in Locally Advanced Rectal Cancer: Local Response, Toxicity and Long-term Outcome

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Abstract

Aims: This non-randomised study was undertaken to examine oxaliplatin as possibly an intensifying component of sequential neoadjuvant therapy in locally advanced rectal cancer for improved local and metastatic outcome.

Materials and methods: Ninety-seven patients (57 T2–3 cases, 40 T4 cases) received two cycles of the Nordic FLOX regimen (oxaliplatin 85 mg/m^2 day 1 and bolus 5-fluorouracil 500 mg/m^2 and folinic acid 100 mg days 1 and 2) before long-course chemoradiotherapy with concomitant oxaliplatin and capecitabine, followed by pelvic surgery. Treatment toxicity, local tumour response and long-term outcome were recorded.

Results: Good histologic tumour regression was obtained in 72% of patients. Implementing protocol-specific dose adjustments, tolerance was acceptable and 95% of patients received the total prescribed radiation dose. Estimated 5 year progression-free and overall survival were 61% and 83%, respectively. T4 stage was associated with an inferior local response rate, which again was highly associated with impaired long-term outcome.

Conclusions: In this cohort of rectal cancer patients dominated by T4 and advanced T3 cases given sequential oxaliplatin-containing preoperative therapy with acceptable toxicity, high tumour response rates and overall survival were obtained, consistent with both local and systemic effects. However, tumour response and long-term outcome remained inferior for a significant number of T4 cases, suggesting that the T4 entity is biologically heterogeneous with subgroups of patients eligible for further individualisation of therapy.

Key words: 5-fluorouracil; chemoradiotherapy; locally advanced rectal cancer; neoadjuvant chemotherapy; oxaliplatin

Introduction

In locally advanced rectal cancer (LARC), the 'non-individualised' standard of care is under debate. It is increasingly appreciated that the optimum sequence and combination of the various treatment modalities should be individualised in accordance with the patient's risk stratification. With local treatment of LARC currently comprising either short-course radiation or long-course fluoropyrimidine-based chemoradiotherapy (CRT) followed by resection of the residual tumour within its entire extension, local recurrence rates are reported well below 10% [1]. Refinement of high-precision radiation protocols as well as the use of cytotoxic or biologically targeted therapeutics as additional components of the preoperative regimen might further improve local control. Despite these efforts, development of metastatic disease remains the dominant cause of failure in rectal cancer patients, typically reported to be 30–40% of cases in recent clinical

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trials [2,3]. As such, there is increased interest in combining modalities in the treatment of LARC.

Generally in LARC, combined-modality chemotherapy and radiation have been shown to improve local control at the price of increased toxicity [4] but failed to have a significant effect on survival [5]. Treatment can be delivered sequentially or concurrently. Conceptually, combined-modality regimens may enhance the therapeutic effect on the local disease either through the additive killing of tumour cells by the two different modalities or through synergistic effects. A direct comparison of sequential and concurrent therapy has shown that the latter commonly is superior, and more toxic, reflecting radiosensitising properties of the systemic agent [6]. Additionally, a sequential regimen causes protraction of the total treatment time, which may add to inferiority. Because radiation has the ability to deliver cytotoxic effects in a focused tumour volume, it has been argued that a better systemic outcome may be achieved by intensifying these effects for improved elimination of the source that maintains the population of clonogenic cells [6]. By contrast, if the chemotherapy component of a sequential combined-modality strategy is effective, radiation will not influence survival when systemic relapse dominates the outcome.

Within this frame of reference, paying attention to the various concerns related to the combined-modality treatment option, we designed a prospective phase II, non-randomised LARC study composed of neoadjuvant chemotherapy (NACT) consisting of two cycles of the Nordic FLOX regimen (oxaliplatin 85 mg/m^2 day 1 and bolus 5-fluorouracil 500 mg/m^2 and folinic acid 100 mg days 1 and 2) before long-course CRT with concomitant oxaliplatin and capecitabine, followed by surgery and no further treatment (ClinicalTrials Identifier NCT00278694). The effect of oxaliplatin-containing chemotherapy is well documented in the adjuvant and palliative treatment of colorectal cancer, and its use has also recently been established in curative liver metastasis treatment [7,8]. However, the role of oxaliplatin in the context of LARC is controversial. During the conduct of our study, emerging data from randomised trials suggested no additional clinical benefit but significantly enhanced acute toxicity of adding oxaliplatin to fluoropyrimidine-based CRT [3,9–11], whereas another trial showed a significantly improved pathological complete response (pCR) rate and disease-free survival in the oxaliplatin-supplemented group [12,13].

Here we summarise the outcome data of local response, treatment toxicity and long-term survival for 97 study patients (57 T2-3 cases and 40 T4 cases) enrolled to receive sequential oxaliplatin-containing NACT and CRT followed by surgical resection.

Materials and Methods

Patients

Patients were enrolled onto the study between 5 October 2005 and 3 March 2010. Diagnostic evaluation, treatment and follow-up were carried out at Oslo University Hospital, while 11 patients received surgery and follow-up at Akershus University Hospital. Patient evaluation included a complete medical history, a physical evaluation, a digital rectal examination, endoscopy, a pelvic examination by magnetic resonance imaging (MRI) and computed tomography scans of the chest and abdomen. Eligibility criteria included histologically confirmed rectal adenocarcinoma that was either T4, T3 with mesorectal fascia margin of 3 mm or less (TNM version 5) or a tumour of any T stage with lymph node involvement assessed by MRI within 3 mm of this margin (as described in [14]), age 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and adequate haematological, hepatic, renal and cardiac function. Patients with potentially resectable synchronous liver or lung metastases were eligible for enrolment. The primary end point was pCR rate. The study protocol was approved by the Institutional Review Board and the Regional Committee for Medical and Health Research Ethics of South-Eastern Norway and is in accordance with the Helsinki Declaration. Written informed consent was required for participation.

Treatment

NACT was given as two cycles of Nordic FLOX (oxaliplatin 85 mg/m^2 day 1 and bolus 5-fluorouracil 500 mg/m^2 and folinic acid 100 mg days 1 and 2) [15] every second week. Radiation was delivered in daily 2 Gy fractions 5 days per week over a 5 week period; the initial 23 fractions to the macroscopic tumour volume and area at risk and the two final fractions restricted to the macroscopic tumour, as determined by computed tomography-based radiotherapy planning [16]. During the radiotherapy course, concomitant chemotherapy was given as oxaliplatin 50 mg/m^2 once weekly and capecitabine 825 mg/m^2 twice daily on days of radiotherapy. The CRT schedule was adjusted according to toxicity, as assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, by reducing doses of oxaliplatin, capecitabine or radiotherapy in that order of priority (and according to type of toxicity). Formal recording of CTCAE adverse events was carried out at baseline, at NACT and CRT completion and at evaluation of the preoperative treatment. Evaluation included repeat pelvic MRI, computed tomography scans of the chest and abdomen and rigid proctoscopy 4–6 weeks after the completion of preoperative treatment. Radical surgical resection (total mesorectal extension or an extended procedure if required) was planned 1–2 weeks after evaluation. Surgery with curative intent was carried out in 92 patients at Oslo University Hospital ($n = 81$) and Akershus University Hospital ($n = 11$). The latter group of patients did not receive protocol-specified evaluation of performance status and toxicity after the completion of preoperative treatment.

Histologic Evaluation

The study-specific evaluation was undertaken by an experienced rectal cancer pathologist (KKG) who was not

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