Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer

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Received 1 September 2011; revised 16 January 2012; accepted 31 January 2012

Background: Preoperative chemoradiation in patients with locally advanced rectal cancer has no impact on overall survival (OS) and distant recurrences. The aim of the study was to evaluate local downstaging, toxicity and long-term outcome in patients with locally advanced rectal cancer after induction therapy with capecitabine and oxaliplatin (CAPEOX) followed by radiotherapy concomitant with capecitabine [chemoradiotherapy (CRT)] before total mesorectal excision (TME).

Patients and methods: Patients with T4 tumors, all T3N+ tumors or T3 tumors involving or with a distance ≤1 mm to the mesorectal fascia were included. Patients were planned for two cycles of CAPEOX followed by radiotherapy concomitant with capecitabine. TME was carried out 6 weeks after the completion of CRT.

Results: Of 84 consecutively admitted patients starting induction CAPEOX, 77 patients underwent surgery. R0 resection was seen in 94% and T downstaging in 69%. In the intention-to-treat group, pathological complete response was seen in 23%. Five-year disease-free survival (DFS) and OS were 63% [95% confidence interval (CI), 52.2% to 73.7%] and 67% (95% CI, 56.1% to 77.3%), respectively. Grade 3/4 toxicity was seen in 18%, and four deaths occurred within 2 months of therapy.

Conclusion: Induction chemotherapy before CRT and surgery showed a high local control rate and promising long-term outcome as OS and DFS.

Key words: complete pathological response, induction chemotherapy, locally advanced rectal cancer, neoadjuvant, tumor regression grading

Introduction

Rectal cancer is a frequent and deadly malignant disease in the western world [1, 2]. Locally advanced rectal cancer (LARC) constitutes ~50% of all cases and includes nonresectable and borderline resectable tumors.

Total mesorectal excision (TME) surgery removes the rectal tumor, the surrounding rectal fat tissue including all local draining lymph nodes in one intact resection specimen [3–6]. One of the most important factors predicting local recurrence after TME is the relationship of the tumor to the circumferential resection margin (CRM). Tumor within 1 mm of the potential CRM strongly predicts local recurrence and poor survival [5, 7]. Magnetic resonance imaging (MRI) has been effective in preoperative staging to predict the likelihood of achieving a clear CRM by evaluating the relation of the tumor to the mesorectal fascia (MRF) [8, 9]. Other risk factors of importance are tumors located in the lower end of the rectum, vascular invasion, perineural growth and residual local tumor tissue [10, 11].

Preoperative radiotherapy (RT) has further reduced the risk of local recurrence compared with TME alone but without affecting survival [12]. To promote resectability and increase the likelihood of R0 resection, several randomized phase III studies have added 5-fluorouracil (5-FU) to preoperative RT. This has produced a higher rate of pathological complete response (pCR) and there is evidence for even better locoregional control [13, 14]. However, there is an almost constant rate of distant metastases occurring in 24%–28% of the cases and no overall survival (OS) benefit of local treatment has been demonstrated in single trials [13, 15, 16]. Nevertheless, 5-FU-based preoperative chemoradiotherapy (CRT) followed by TME is now considered the standard treatment of patients with LARC [13, 14, 17–19].
Aiming to reduce the risk of developing metastatic disease, a combination of oxaliplatin and capecitabine/5-FU as induction chemotherapy, before preoperative CRT, has been explored in rectal cancer [20–22].

In our institute, 84 consecutive admitted patients with LARC were treated with capecitabine and oxaliplatin (CAPEOX) followed by CRT and TME surgery. We evaluated the rates of T downstaging, toxicity, disease-free survival (DFS), OS and impact of Tumor Regression Grade (TRG) on survival.

patients and methods

patient selection

Patients with LARC, who were considered candidates for induction chemotherapy, had tumors invading surrounding structures or peritoneum (all T4 tumors), T3 tumors extending to within 1 mm of the MRF (threatened or involved MRF) or T3-4N+ tumors, as defined by MRI.

Before treatment, all patients with rectal cancer were assessed by a multidisciplinary team comprising oncologists, pathologists, gastrointestinal surgeons and radiologists. The criteria for treatment were a World Health Organization performance status of zero to two, normal renal and liver function and no distant metastasis as evaluated by a computed tomography (CT) scan of the chest and abdomen.

treatment

Two cycles of induction chemotherapy with CAPEOX were planned. Capecitabine was administered orally twice a day at a dose of 2000 mg/m²/day for 14 days followed by 7 days of rest. Oxaliplatin was given every 3 weeks at a dose of 130 mg/m². RT was given with 54 Gy in 27 fractions (five fractions a week) to the tumor bed and 48.6 Gy in 27 fractions to the regional lymph nodes extending up to the lower end of the fifth lumbar spine.

In patients with T3 tumors, prophylactic RT was administered to the lymph nodes surrounding the internal iliac vessels. In patients with T4 tumors affecting the urogenital structures, additionally prophylactic RT was administered to the surrounding lymph nodes of the external iliac vessels.

RT was given concomitant with capecitabine 1650 mg/m² on treatment days. Dose adjustment was made in case of grade 3 or 4 toxicity according to National Cancer Institute—Common Toxicity Criteria version 2 [23].

TME surgery was planned 6 weeks after completion of CRT. The choice of surgical procedure was decided by the surgeons. Patients had a posttreatment follow-up every 6 months the first 24 months and an annual follow-up until 5 years after surgery.

evaluation of local control

All patients were evaluated at baseline using high-resolution thin slice (3-mm) MRI scans [24]. The local T and N stage, extramural venous tumor invasion, tumor measurements and MRF involvement were evaluated. All baseline MRI scans were reviewed by the same oncological radiologist (LR).

Comparison between baseline MRI scan and posttreatment histological assessment was used to evaluate T downstaging. The absence of any residual tumor cells detected in the resected specimen and lymph nodes was defined as pCR.

tumor regression grade

The histological sections were reviewed by the same pathologists (DL and JL) and the regression grade was quantified according to a five-point scale proposed by Dworak et al. [25]: TRG 0: no regression; TRG 1: dominant tumor mass with obvious fibrosis and/or vasculopathy; TRG 2: dominantly fibrotic changes with few tumor cells or groups (easy to find); TRG 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; TRG 4: no tumor cells, only a fibrotic mass (total regression or response).

statistics

DFS was calculated from the date of treatment start until disease relapse or death from any cause. OS was calculated from date of treatment start until death of any cause or censored at last follow-up. We calculated OS and DFS in the intention-to-treat (ITT) population. The Kaplan–Meier method was used to estimate DFS and OS [26] and differences tested using the log-rank test. Hazard ratios were estimated with a Cox proportional hazards regression model. End point data was updated on 11 April 2011.

results

Between January 2005 and January 2008, 88 consecutive admitted patients with locally advanced adenocarcinoma of the rectum were considered candidates for induction chemotherapy with CAPEOX before CRT. Four patients were excluded due to co morbidity (n = 1) and a performance status more than two (n = 3). Table 1 lists the baseline characteristics. Supplemental Figure S1 (available at Annals of Oncology online) shows the progress of all patients considered candidates for treatment.

Table 1. Baseline characteristics

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<th>All (%)</th>
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<td>6 (7)</td>
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MRF, Mesorectal fascia; MRI, magnetic resonance imaging.
Patients received a median of two cycles of CAPEOX (range 1–3). Of the 84 patients starting CAPEOX, 79 patients proceeded to CRT and 77 patients proceeded to surgery. Median time from end of RT to surgery was 6.8 weeks (range 2.4–9.7 weeks).

Of the patients who underwent surgery by TME, R0 resection was carried out in 72 patients (94%; 95% confidence interval [CI], 88% to 99%) and in 86% on an ITT basis.

Table 2 shows the comparison between baseline MRI and postoperative pathological assessment.

A pCR was observed in 19 (25%; 95% CI, 15% to 35%) of the 77 treated patients and 19 (23%; 95% CI, 14% to 32%) of the 84 patients on an ITT basis. Seven patients with MRI-defined T4 tumor and 12 patients with MRI-defined T3 tumor at baseline obtained a pCR. Fifteen of these patients were node positive at baseline. The T stage was downsized in 53 patients (69%) and unchanged in 23 patients (30%). Only one patient with an MRI-T3 stage progressed to a pT4 stage. This patient had peritoneal carcinomatosis at the time of surgery. Another two patients had liver metastases with an overall number of 11 patients who had distant recurrences to the lung (n = 7/9%), liver (n = 79%), both lung and liver (n = 3/4%), peritoneal cavity (n = 1/1%) and lymph nodes (n = 1/1%). Of the patients with distant recurrences, 10 patients had a baseline MRI T3 stage and 9 patients had T4 stage.

Figure 1 shows DFS and OS for all 84 patients who commenced therapy. The percentage of 5- and 6-year DFS was 63% (95% CI, 52.2% to 73.7%) and all cases of recurrent disease occurred within 3 years. The percentage of 5- and 6-year OS was 67% (95% CI, 56.6% to 77.3%).

Supplemental Figure S2 (available at Annals of Oncology online) shows the OS and DFS for patients with T3 stage and T4 stage based on their MRI scan before treatment. Recurrences occurred within 3 years in both groups.

Supplemental Figure S3 (available at Annals of Oncology online) shows DFS and OS for patients according to presence or absence of malignant lymph nodes in the TME specimen. Twenty-one patients (28%) had malignant lymph nodes in the resected specimen. For patients without malignant lymph nodes, the 5-year OS was 85% (95% CI, 75.3% to 94.9%) compared with 44% (95% CI, 20.7% to 66.7%) in patients with malignant lymph nodes and a hazard ratio of 4.5 (95% CI, 1.8–11.1) were seen. The 5-year DFS was 86% (95% CI, 75.9% to 95.1%) for patients without malignant lymph nodes compared with 29% (95% CI, 8.8% to 48.4%) in patients with malignant lymph nodes and the hazard ratio was 7.5 (95% CI, 3.1–18).

Figure 2 shows OS according to the TRG. TRG 4 was seen in 20 patients and TRG 1–3 in 56 patients (TRG 1, n = 9; TRG 2, n = 35; TRG 3, n = 12). No deaths, local or distant recurrences were seen in TRG 4 patients. When patients with persistent disease (TRG 1, TRG 2 and TRG 3) were analyzed after surgery, one patient aspirated contras substance before an X-ray examination and developed cardiac arrest and died.

The median follow-up time from treatment start was 56.5 months (range 0.5–71). No patient was lost to follow-up. Only 1 patient (1%) had local recurrence and 19 patients (25%) had distant recurrences to the lung (n = 7/9%), liver (n = 79%), both lung and liver (n = 3/4%), peritoneal cavity (n = 1/1%) and lymph nodes (n = 1/1%). Of the patients with distant recurrences, 10 patients had a baseline MRI T3 stage and 9 patients had T4 stage.

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separately, TRG grading did not have any prognostic value for OS and DFS ($P = 0.6$ and $0.8$).

**discussion**

Preoperative chemoradiation for rectal cancer has been shown to improve local control [18] but single studies with 5-FU-based preoperative CRT did not improve DFS and OS and had no impact on distant metastases [13, 14]. Recently, a pooled analysis of 2795 patients receiving preoperative RT did report a benefit in distant metastases and 5-year OS in patients who had concurrent CT [27]. The last study does provide support for the rationale of intensifying treatment with CT in order to improve the effect on distant recurrences, which is the predominant mode of failure. Induction CT with oxaliplatin and 5-FU in the combination with radiation has been studied.
previously [20–22]. With a median follow-up time of 55 months, distant metastases were seen in 25% of the patients in the ITT group and a 5-year OS of 75% [20, 21].

Patients in our study had a long median follow-up of 56.5 months and none of the patients were lost to follow-up. We found that 5-year OS was comparable with other CRC trials [13, 14] and close to the results from Chua et al. [20]. Local control has been convincing after the introduction of adjuvant CRT. We only had one patient with local recurrence and this person also had synchronous distant metastasis. Local control seems insufficient to improve OS and reduce the rate of distant recurrences.

A high rate of pCR of 23% in the ITT group was seen. Fifty-three patients had a downstaging and further 24 patients had stable disease according to T stage. Although one patient did progress locally during treatment, our results imply good local control, and hereby support the safety and rationale for preoperative treatment. Of the three patients with distant metastases at time of surgery, one had downstaging of primary tumor and one had stable disease locally.

We report that 25% of the patients, who had surgery, had distant metastasis in the follow-up period. However, four patients died early and could not contribute to the follow-up observation. This point must be taken into account when reporting the rate of distant metastases.

All disease recurrences were seen within 3 years and DFS remained stable hereafter. Patients still died after 4 years but may be due to other causes since we had relative high median age at time of inclusion and 23 patients had an age over 70 at start of treatment and among them 6 patients had an age over 80.

The data in our study was retrospectively assessed. The patients were however unselected and treated consecutively from January 2005 to January 2008. Of all 84 patients identified with LARC, only 4 patients were not eligible for induction chemotherapy before CRT and surgery. All baseline MRI scans were reassessed afterward by the same radiologist with oncological experience. Minor corrections compared with the initial scan were done, with no impact on choice of treatment. Only T3 tumors with involved or threatened MRF (<1 mm) or T3N+ tumors were included, indicating high-stage tumor and a worse prognosis. Thirty-one patients (65%) with T3 tumors had an involved MRF and 14 patients (17%) were accrued based on a positive lymph node from the baseline MRI. Difficulties in nodal staging by MRI have been reported in the literature and there is only a modest reproducibility in N-staging between radiologist [28]. This might be due to variability in experience and that lymph node size is not a reliable criterion for metastatic involvement [29]. N-staging criteria in our study was irregular borders and inhomogenous signal as proposed by Brown et al. [30].

The rates of toxicity and mortality were worrying but consistent to previously reported results [20, 31–33]. Diarrhea and cardiac/thromboembolic events were the most frequent toxic effects reported. Two of the thromboembolic events were strokes, which caused the two patients to stop treatment and never proceed to surgery. Three of the four deaths in our study were probably treatment related.

OS is the gold standard end point, but in trials with localized rectal cancer, this end point may require a long follow-up time. To overcome this drawback, surrogate end points have been proposed such as the pathological assessments TRG and pCR. A better outcome for rectal cancer patients with pCR has been suggested, but in randomized trials, the addition of chemotherapy produced higher rates of pCR but no impact on OS [13, 14] and the use of pCR as a surrogate end point for outcome has been controversial. Maas et al. [34] did a pooled analysis of 3105 patients with rectal cancer from 14 study datasets to explore the long-term outcome in patients with pCR after CRT. Most of the datasets were retrospective with different tumor stages and a wide range of treatment regimens. They suggested a better outcome and patients with pCR had a 5-year crude DFS of 83.3% compared with 65.6% in those patients without pCR [34]. A pooled analysis also supported a lower risk for metastatic disease in patients with pCR [27]. None of the 19 patients in our study with pCR had local or distant recurrences nor did any die during the follow-up period. This strongly supports a better outcome in the patients with pCR, but whether this should lead to a change in the intensity of follow-up needs to be addressed in a prospective study. It has also been suggested that small tumors under 5 cm are more prone to achieve pCR [35]. Of the 19 patients with pCR, 14 (24% of all large tumors) patients initially had a tumor size over 5 cm and 5 pCR patients with small tumor size (27% of all small tumors). The small difference between small and large tumor among pCR patients does not imply that the size of the tumor has a significant impact on the pCR rate when a cut-off value of 5 cm in tumor length was determined.

When all grades in the TRG were compared as planned, no association in OS and DFS was seen. TRG 4, which is the most favorable grade, represents all the patients with pCR except one. It did not give any prognostic information to look at TRG 1–3 separately.

The presence of malignant lymph nodes in patients with colorectal cancer has been associated with poor prognosis [36, 37] and a recent study found shorter OS and time to local recurrence in patients with lymph node-positive rectal cancer receiving neoadjuvant CRT [38]. Cancer cells in the removed lymph nodes were a strong predictor for recurrent disease and death and patients in our study with malignant lymph nodes had a worse prognosis than patients without malignant lymph nodes. Adjuvant treatment with combination chemotherapy after surgery might have a positive effect on risk of recurrence and OS in this subgroup of patients, even though these patients are heavily treated.

Our results and others show that induction CAPEOX is feasible and does not comprise CRT and surgery and hereby local control. The long-term outcome in our data is promising and we await the results of ongoing phase III trials, to see if they support a positive effect of induction chemotherapy in order to reduce the risk of distant metastases and improve OS.

Despite the promising long-term outcome, the potential treatment-related deaths are worrying and this regimen may be restricted to patients inside clinical studies with far advanced disease.
In conclusion, induction chemotherapy with CAPEOX before CRT and surgery is a feasible regimen. High rates of local downstaging and pCR were seen and a long follow-up period showed good local control and promising rates of OS and DFS. Nodal status was an important prognostic factor for recurrent disease and death but TRG did not predict long-term recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011; 29: 3163–3172.


references
An initial watch and wait approach is a valid strategy for selected patients with newly diagnosed metastatic colorectal cancer

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Received 7 March 2012; revised 30 April 2012; accepted 7 May 2012

Background: A range of treatments are available for patients with metastatic colorectal cancer (mCRC). An initial period without active treatment, a ‘watch and wait approach’, is variably employed in routine practice; however, there is no data to support this approach.

Patients and methods: We prospectively collected data regarding clinician treatment recommendations for patients with newly diagnosed mCRC in addition to subsequent treatment and outcomes. Follow-up and management was according to standard protocols.

Results: Seven hundred and thirty-six patients (59.1% male, 40.9% female) with mCRC (January 2003–December 2010) were analysed; the median age was 67.9 years (range 26.2–95.5). Three hundred and seventy-seven patients (51.2%) received immediate chemotherapy. For 133 (18.1%), treatment was considered inappropriate. 34 patients (4.6%) declined therapy. For 192 (26.1%), a watch and wait policy was adopted and 168 (87.5%) of these received treatment, at a median of 3.7 months (range 2–35 months) from diagnosis. Compared with patients immediately treated, the number receiving all active chemotherapy agents (30.4 versus 39.3%) was similar and median survival (27 versus 17 months, \(P = 0.0008\)) was superior.

Conclusions: Our study demonstrates that a substantial minority of patients underwent an initial watch and wait approach. Ultimately, they received a similar treatment exposure to patients treated immediately and the survival outcomes were not compromised.

Key words: delayed treatment, metastatic colorectal cancer, watch and wait

introduction

Colorectal cancer is one of the most common cancers diagnosed worldwide [1, 2]. About 40% of patients present with either advanced disease or develop recurrence after initial treatment of early-stage tumours [3]. A broad range of treatment options are now available, with current guidelines [4] recommending initial chemotherapy for all patients, either single agent or combination treatment, according to patient’s status.

Where treatment is not initiated when metastatic disease is diagnosed, specific concerns are that patients may miss a window of opportunity and thereby never receive treatment, or may receive treatment at a time point where, due to deteriorating Eastern Cooperative Oncology Group Performance Status (ECOG PS) or increasing disease bulk, it is less effective. Delaying treatment may also potentially compromise survival by reducing the opportunity to be exposed to treatment with all active agents [5]. However in routine practice, clinicians may consider the option of watchful waiting before initiating active therapy for selected patients, specifically those with asymptomatic, low volume and surgically incurable disease.

No previously reported series describes how frequently a watch and wait strategy is pursued in routine practice, or the outcome. Here, we present data from a multisite series where initial clinician decision-making was prospectively documented, and comprehensive clinical details, treatment received and survival outcomes were analysed.