Original Study

Disease Control, Survival, and Toxicity Outcome After Intensified Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer: A Single-Institution Experience

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Abstract

Development of distant metastasis remains high in locally advanced rectal cancer patients treated with a trimodal approach. We intensified the neoadjuvant treatment regimen by adding oxaliplatin to the standard 5-fluorouracil. Five-year follow-up data were encouraging, with excellent disease control rates and long-term survival. An oxaliplatin-based combination in the neoadjuvant setting could be a valid treatment option.

Purpose: To report the long-term follow-up data and determine the toxicity rate concerning patients with locally advanced rectal cancer (LARC) treated with an intensified neoadjuvant treatment regimen. **Patients and Methods:** Patients with histologically proven stage II to III adenocarcinoma of the rectum were included and treated with a trimodal approach. Intensified neoadjuvant treatment (chemoradiotherapy [CRT]) consisted of radiotherapy (total dose 50.4/54 Gy) and concomitant oxaliplatin (50 mg/m^2/week) and 5-fluorouracil (200 mg/m^2/5 daily continuous infusion). Surgery was planned 7 to 9 weeks after the end of CRT. Adjuvant chemotherapy was recommended in those patients with lymph node metastasis at diagnosis. **Results:** One hundred patients (median age, 64 years) were eligible. Overall, the 5-year overall survival and disease-free survival (DFS) were 76.4% and 74.5%, respectively. CRT was well tolerated, with only 17% grade 3/4 acute toxicity. Twenty-four patients (24%) had a pathologic complete response (pCR), and only 1 patient had perioperative metastasis. The 5-year DFS were 95.7% and 66.7% for pCR and no-pCR tumor histology, respectively ($P = .0275$). **Conclusion:** Although oxaliplatin is not considered to be a standard treatment, the high 5-year rate of overall survival and DFS, the low severe toxicity rates, and the effective benefit on pCR and perioperative metastasis support an intensified treatment regimen for LARC.

Clinical Colorectal Cancer, Vol. ■, No. ■, ■-■
Keywords: Neoadjuvant treatment, Oxaliplatin, pCR, Pre-operative treatment, Radiation

Introduction

Rectal cancer comprises approximately 2.4% of all human malignancies. More than 39,000 new cases of rectum cancer are estimated to have occurred in 2015 in the United States, and when combined with colon cancer, 132,700 individuals will be diagnosed, resulting in 49,700 deaths.[1]

In the past 40 years, survival rates have improved, and today in locally advanced rectal cancer (LARC) the standard of care is a trimodal approach combining surgery, radiotherapy (RT), and chemotherapy.[2] Frequent distant metastasis (30-40%) in this patient population has stimulated researchers to test more effective systemic cytotoxic therapy that could be provided in a neoadjuvant setting.[3]

Historically, 5-fluorouracil (5-FU) has represented the main radiation sensitizer, resulting in a pathologic complete response (pCR) rate of 5% to 20%, but it is not effective on distant metastasis.[4] Thus, the goal of further research was to intensify the therapy at the primary tumor site, regional pelvic lymph nodes, and distant

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Submitted: Nov 19, 2015; Revised: Dec 19, 2015; Accepted: Feb 3, 2016

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1533-0028/$ - see frontmatter
http://dx.doi.org/10.1016/j.clcc.2016.02.006

sites while minimizing the treatment and limiting toxic adverse effects.

There are several large phase 3 studies, including ACCORD 12/0405, CAO/ARO/AIO-04, NSABP R-04, and STAR-01, that have been completed and have evaluated the role of oxaliplatin (OXP) as novel radiation-sensitizing agent.[5-8] These trials showed more grade 3/4 toxicity when adding OXP to 5-FU concomitant treatment, but no significant difference was observed in surgical complications or the incidence of postoperative death within 60 days.[9] The best result was the large (1236 patients) German CAO/ARO/AIO-04 randomized trial, which convincingly showed an improved pCR rate, from 13% to 17% ($P = .038$), at the cost of higher grade 3/4 toxicity (23% vs. 20%).[6] Generally this significant effect on pCR was modestly confirmed in the meta-analysis of these studies (odds ratio, 1.20; 95% confidence interval [CI], 1.01-142; $P = .04$). Moreover, the OXP-5-FU regimen reduced the incidence of perioperative metastasis, supporting the hypothesis that it could improve systemic control.[9] But long-term results are currently maturing, and thus whether OXP in addition to 5-FU can improve treatment outcome and patient survival remains unknown.

While waiting for longer follow-up data from these trials, we here present our intensified neoadjuvant setting experience with OXP used as a radiosensitizer in addition to standard 5-FU in patients with LARC. The aim of the study was to report the toxicity rate, oncologic outcomes, and main prognostic factors that could influence treatment response and survival by adding OXP to a standard chemoradiotherapy (CRT) regimen.

Patients and Methods

Patient Selection

Patients originated from the Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome. The investigational protocol was reviewed and approved by the institutional review board and the scientific review committee. Written informed consent was obtained from all patients before the initiation of therapy. All patients underwent complete physical examination, transrectal ultrasound, and total-body contrast-enhanced computed tomography (CT). Magnetic resonance imaging (MRI) of the pelvis was performed in case of an uncertain diagnosis until January 2011 and routinely thereafter.[10] Histologic confirmation of adenocarcinoma of the rectum was available for all patients. Patients with histology other than adenocarcinoma were excluded from analysis. The main eligibility criteria were tumor (T) within 12 cm from the anal verge, staged T3-4 and/or with lymph nodes (N) positive at diagnosis, without any evidence of distant metastases. Patient exclusion criteria consisted of synchronous tumors, cardiovascular disease, history of neurologic or psychiatric disorders, or previous pelvic RT.

Treatment Plan

All patients were treated with an intensified neoadjuvant treatment. RT was delivered with a 3D-conformational multiple field technique at a total dose of 45 Gy (1.8 Gy per fraction) to the whole pelvis, plus 5.4 to 9 Gy (1.8 Gy per fraction) to the tumor volume, with 6 to 15 MV energy photons. Concomitant chemotherapy consisted of 2-hour OXP infusion 50 mg/m^2 on the first day of each week of RT and 5 daily continuous infusion of 5-FU 200 mg/m^2/day. Details of target volume delineation and the chemotherapy protocol were described in our previous study.[11]

Five weeks from the end of CRT, the assessment of local clinical response was performed by abdominal-pelvic CT and/or MRI (from 2011). The criteria used to determine objective tumor response for target lesions included complete response, partial response, progressive disease, and stable disease, according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[12]

Independent of clinical response, surgery was planned 7 to 9 weeks after the end of CRT. Adjuvant chemotherapy was recommended in those patients with lymph node metastasis at diagnosis. Type of surgical approach and adjuvant chemotherapy regimen were left to the surgeons' and oncologists' discretion, respectively. Toxicity scoring was performed using the Common Terminology Criteria for Adverse Events, Version 4.0.[13]

Follow-Up

After a curative-intent trimodal approach, posttreatment surveillance was performed by physical examination and transrectal ultrasound every 3 months for 2 years, then every 6 months thereafter. Colonoscopy was proposed at 1 year after surgery and then annually. To monitor the presence of potentially local recurrence and distant metastasis, both total body CT and pelvic MRI were recommended annually for up 5 years after CRT.

Statistical Analysis

Statistical analysis was carried out using R-Studio 0.98.1091 software.

Standard descriptive statistics were used to evaluate the distribution of each factor. Continuous variables were presented as medians and ranges, and dichotomous variables were presented as percentages.

Overall survival (OS) and disease-free survival (DFS) were calculated in months from the date of the end of CRT to the first event, including date of the last follow-up or death (OS) and/or relapse (DFS). pCR was defined as the absence of any residual tumor cells detected in the operative specimen, including the primary tumor area, the whole mesorectal fat, and the resected lymph nodes. Patient follow-up was updated to a minimum of at least 1 year.

OS and DFS were estimated by the Kaplan-Meier method, and survival curves were compared by the log-rank test. The following variables were investigated: age at diagnosis (< 65 years vs. ≥ 65 years), sex (male vs. female), tumor location (< 6 cm vs. 6-8 cm vs. > 8 cm from anal verge), clinical T classification (cT3 vs. cT4), clinical nodal status (negative vs. positive), pathologic T classification (pT0-2 vs. pT3), pathologic nodal status (negative vs. positive), pCR (yes vs. no), interval time between CRT and surgery (< 8 vs. 8-12 vs. > 12 weeks), cycles of OXP (< 5 vs. 5 vs. > 5), and CRT interruption (yes vs. no). Variables associated with a P value of $< .25$ were included in a multivariate survival Cox regression analysis. All reported P values are 2 sided, and P values lower than .05 were considered significant.

Results

Patient Characteristics

Between January 2007 and December 2014, a total of 100 patients received intensified neoadjuvant CRT. Table 1 lists the