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Advances in management of adjuvant chemotherapy in rectal cancer: Consequences for clinical practice

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Summary More than half the patients with rectal cancer present with locally advanced rectal disease at diagnosis with a high risk of recurrence. Preoperative chemoradiotherapy and standardized radical surgery with total mesorectal excision have been established as the 'gold standard' for treating these patients. Pathological staging using the ypTNM classification system to decide on adjuvant chemotherapy (ACT) is widely used in clinical practice, but the delivery of ACT is still controversial, as many discrepancies persist in the conclusions of different trials, due to heterogeneity of the inclusion criteria between studies, lack of statistical power, and variations in preoperative and adjuvant regimens. In 2014, a meta-analysis of four randomized phase-III trials (EORTC 22921, I-CNR-RT, PROCTOR-SCRIPT, CHRONICLE) failed to demonstrate any statistical efficacy of fluorouracil (5FU)-based ACT. Three recent randomized trials aimed to compare 5FU with 5FU plus oxaliplatin-based chemotherapy. Two of them (ADORE, CAO/ARO/AIO-04) appeared to find a disease-free survival benefit for patients treated with the combination therapy. Thus, while awaiting new data, it can be said that, as of 2015, patients with yp stage I tumors or histological complete response derived no benefit from adjuvant therapy. On the other hand, the FOLFOX chemotherapy regimen should be proposed for

Abbreviations: CRC, colorectal cancer; LARC, locally advanced rectal cancer; MRI, magnetic resonance imaging; CRT, chemoradiotherapy; TME, total mesorectal excision; LRR, locoregional recurrences; MR, metastasis recurrence; OS, overall survival; NCCN, National Comprehensive Cancer Network; ACT, adjuvant chemotherapy; ESMO, European Society for Medical Oncology; DFS, disease-free survival.

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yp stage III patients, and may be considered for yp stage II tumors in fit patients with high-risk factors. Nevertheless, well-designed and sufficiently powered clinical trials dedicated to adjuvant treatments for rectal cancer remain justified in future to achieve a high level of proof in keeping with evidence-based medical standards.

Introduction

In Europe, colorectal cancer (CRC) represents the second most common cause of cancer, with 342,137 cases diagnosed in 2012 and 150,036 estimated deaths [1]. The proportion of rectal cancer cases ranges from 27% to 58% [2], and about 55% of patients with rectal cancer present with stage II or stage III disease at diagnosis [3], with a high risk of recurrence.

The management of rectal cancer located > 12 cm from the anal verge, because of the low risk of local recurrence and similar prognosis to colon cancer, is based on surgery, followed by adjuvant chemotherapy in stage III, and some stage II, patients. For stage II and III rectal cancer located < 12 cm from the anal verge, a specific preoperative treatment is recommended to reduce the risk of local recurrences. Over the past few decades, the management of locally advanced rectal cancer (LARC) has been improved by the use of magnetic resonance imaging (MRI) for initial staging of the tumor, introduction of preoperative chemoradiotherapy (CRT) with fluorouracil (5FU)-based chemotherapy, and standardized radical surgery with total mesorectal excision (TME). This treatment has been established as the 'gold standard', bringing a > 70% decrease in locoregional recurrences (LRRs). Unfortunately, however, it has failed to improve metastatic recurrences and overall survival (OS) [4].

The use of adjuvant chemotherapy (ACT) in these patients to theoretically decrease distant recurrences is still controversial. Over the past few years, several studies have attempted to demonstrate the efficacy of ACT in rectal cancer patients and to identify factors that help to define patients that might benefit from such treatment. Use of ypTNM (tumor node metastasis) classification for pathological staging to decide on the use of ACT could avoid the treatment in 47% of cases; the staging system has been widely recommended by international guidelines, and used in recent trials and clinical practice [5,6].

However, many discrepancies persist in the conclusions of the various trials available due to: heterogeneity of inclusion criteria (particularly the use of cTNM or ypTNM classification); inclusion of high rectal tumors; difficulties in trial recruitment, resulting in a lack of statistical power at the time of statistical analyses; and variations in both preoperative and adjuvant regimens.

The delivery of ACT with a 5FU regimen is recommended by the US National Comprehensive Cancer Network (NCCN) guidelines for all patients with LARC undergoing neoadjuvant RCT, regardless to the histopathological results after surgery [7]. The European Society for Medical Oncology (ESMO) suggests ACT for 'high-risk' stage II and III tumors, as in colon cancer treatment strategies [8]. In contrast, the French national guidelines (www.TNCD.org) recommend adjuvant treatment only for ypT1—4N+ and ypT4N0 tumors.

Recent data from three large randomized trials (PETACC6, ADORE, CAO/ARO/AIO-04) aimed to compare 5FU with 5FU plus oxaliplatin-based chemotherapy. Two of them (ADORE, CAO/ARO/AIO-04) apparently found a disease-free survival (DFS) benefit for patients treated with the combination compared with 5FU alone. The present review discusses the characteristics of the most important published trials of ACT for rectal cancer (Table 1), and has attempted to summarize their major results to determine the best patients to treat, or not (Table 2).

Adjuvant studies with no preoperative chemoradiotherapy

A Cochrane meta-analysis [9] published in 2012 pooled the results of 21 randomized trials (with a total of 16,215 colorectal cancers, including 785 rectal cancers). All the trials were relatively old, with the majority of colon cancer stage II patients not receiving preoperative radio(chemo)therapy (except for the Quasar trial) [10] and no standardized TME surgery. This meta-analysis favored fluoropyrimidine-based ACT, which appears to be associated with significant decreases in disease recurrence and cancer mortality.

However, almost all patients nowadays receive preoperative treatment with TME surgery, which makes these results less meaningful in our current clinical practice.

Fluoropyrimidine as adjuvant therapy vs. after (chemo)radiotherapy

In 2014, four more recent randomized phase-III trials were published, including patients with clinical or pathological LARC treated with radio(chemo)therapy followed by surgery. These trials all failed to demonstrate any statistical efficacy of 5FU-based ACT, but all had critical flaws.

EORTC 22921 trial

The 10-year results of this European Organisation for Research and Treatment of Cancer trial [11] included 1011 LARC, including high rectal tumors, divided into four randomized groups in different therapeutic arms: patients received preoperative radiotherapy or CRT, followed by ACT with FUFOL (5FU and leucovorin) for 3 months, or just observation. TME surgery was used from 1999 onwards. Patients were randomized using clinical data (cTNM), with pathological analysis using ypTNM for a subgroup with downstage tumors. This trial failed to demonstrate any potential

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