

Neoadjuvant chemoradiotherapy for locally advanced rectal cancer: The debate continues

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association with radiation therapy. The addition of oxaliplatin to the neo-adjuvant treatment has been shown to improve disease-free survival from 71.2% to 75.9% ($P = 0.03$). This editorial was planned to clarify the optimal treatment in patients with locally advanced rectal cancer, considering the results from CAO/ARO/AIO-04 study.

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Core tip: This editorial was planned to clarify the optimal treatment in patients with locally advanced rectal cancer, considering the results from CAO/ARO/AIO-04 trial.

Abstract

Rectal carcinoma represents the 30% of all colorectal cancers, with about 40000 new cases/years. In the past two decades, the management of rectal cancer has made important progress, highlighting the main role of a multimodality strategy approach, combining surgery, radiation therapy and chemotherapy. Nowadays, surgery remains the primary treatment and neo-adjuvant chemoradiotherapy, based on fluoropyrimidine (5-FU) continuous infusion, is considered the standard in locally advanced rectal carcinoma. The aim is to reduce the incidence of local recurrence and to perform a conservative surgery. To improve these purposes different drugs combination have been tested in the neo-adjuvant setting. At American Society of Clinical Oncology 2014 an important abstract was presented focusing on the role of adding oxaliplatin to concomitant treatment, in patients with locally advanced rectal carcinoma. Rodel *et al* reported on the CAO/ARO/AIO-04 randomized phase III trial that compared standard treatment with 5-FU and radiation therapy, to oxaliplatin plus 5-FU in

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In locally advanced rectal cancer, significant progress has been made over the past few decades for improving loco-regional control: total mesorectal excision standardization, radiotherapy dose fractionation, correct timing of treatment modalities, integration of diverse chemotherapy agent into the chemoradiotherapy regimes^[1]. The German Rectal Cancer Study Group addressed the last of those controversies, and in a multicentre randomised phase III study, the CAO/ARO/AIO-04 trial, compared oxaliplatin (OXP) and fluoropyrimidine (5-FU) in combination with radiation *vs* 5-FU with radiation as neoadjuvant long-course treatment^[2].

The essential function of OXP with 5-FU has been demonstrated in colon carcinoma; survival rates, both overall and disease-free, were significantly improved in

patients who received OXP and 5-FU as adjuvant treatment^[3]. Considering these results, several groups, despite the absence of a randomised comparison in neoadjuvant setting for rectal cancer, designed phase III studies to test the standard 5-FU-based neoadjuvant treatment *vs* analogous but new schedule where the monotherapy was replaced by a combination of 5-FU and OXP^[2,4-6]. This drugs-radiation combination have failed in increase primary tumor response in STAR-01 study^[4], ACCORD 12/0405-Prodige-2 study^[5] and NSABP-R04 study^[6], whereas the results of the CAO/ARO/AIO-04 study are intriguing^[2]. The second arm in the CAO/ARO/AIO-04 study represented a “experimental” schedule, which used a continuous venous infusion of 5-FU 200 mg/m² and a 2-h OXP infusion 50 mg/m². The 5-FU was delivered during days 1-14 and 22-35, whereas the OXP was delivered days 1, 8, 22 and 29. The primary end-point was disease-free survival (DFS) at 3 years, with acute toxicity, compliance and histopathological response as secondary endpoints. A total of 1265 patients were randomly enrolled, 637 were assigned to control arm and 628 to experimental arm. Acute treatment-related toxicity was similar in the two arms except for 7% grade 3-4 sensory neuropathy events in the OXP-5-FU arm - an obvious expected result of the pharmacokinetics of OXP adsorption. The compliance, defined as full prescribed dose of chemotherapy and full dose of radiotherapy was comparable. Pathological complete response (pCR) was gained in 17% of patients on OXP-5-FU *vs* 13% on 5-FU (*P* value = 0.038). With a median follow-up of 50 mo, the 3-years DFS rate was 75.9% in the OXP-5-FU arm *vs* 71.2% in the control (*P* = 0.03).

What deductions can we reach from this study? A key observation is that compliance to “experimental” schedule is high and successful disease control is achieved. The other published randomised trials - it is important to note that different OXP and fluoropyrimidine schedules were used in STAR-01 study^[4], ACCORD 12/0405-Prodige-2 study^[5] and NSABP-R04 study^[6] - used a continuous infusion of chemotherapy during radiation therapy. Therefore, the one week gap from the conventional administration of 5-FU and OXP is a valid option, with a more tolerable profile. Achieve pCR is a good end-point in rectal cancer, and could be used as prognostic factor - pCR is correlated to excellent long-term prognosis - to recommend a “wait and see” approach, without adjuvant chemotherapy^[7].

So where do we go from here? There is a considerable agreement in the administration of neoadjuvant chemotherapy plus radiotherapy for the treatment of locally advanced rectal cancer. In many of the trials undertaken and those that are ongoing, 5-FU-based chemoradiotherapy represents the cornerstone, due to fluoropyrimidine well-established potentiating effect with radiation. OXP should be added to influence the tumour cell sensitivity, resulting in a higher rate of down-staging, delineating different subgroups of patients and changing the risk of recurrences.

Although the addition of oxaliplatin to standard neoadjuvant regimen appears tolerable, it is true that the real benefit of OXP-5-FU remains unclear. The CAO/ARO/AIO-04 study has confirmed a DFS improvement; do we therefore conclude that OXP-5-FU combination provides indication of survival benefit in locally advanced rectal cancer? There are not randomized studies that have shown a statistical benefit from adding OXP to standard neoadjuvant chemoradiotherapy. Certainly, the results of the CAO/ARO/AIO-04 study represent a step in the right direction: it demonstrates the feasibility of neoadjuvant-intensified chemoradiotherapy in a multidisciplinary treatment approach setting for rectal cancer.

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