Rectum

Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Patients With Locally Advanced Rectal Cancer: Long-term Results of the CAO/ARO/AIO-12 Randomised Clinical Trial.

Fokas E, Schlenska-Lange A, Polat B, Klautke G, Grabenbauer GG, Fietkau R, Kuhnt T, Staib L, Brunner T, Grosu AL, Kirste S, Jacobasch L, Allgäuer M, Flentje M, Germer CT, Grützmann R, Hildebrandt G, Schwarzbach M, Bechstein WO, Sülberg H, Friede T, Gaedcke J, Ghadimi M, Hofheinz RD, Rödel C; German Rectal Cancer Study Group.

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IMPORTANCE

Total neoadjuvant therapy has been increasingly adopted for multimodal rectal cancer treatment. The optimal sequence of chemoradiotherapy (CRT) and chemotherapy needs to be established.

OBJECTIVE

To report the long-term results of the secondary end points prespecified in the Randomised Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy (CAO/ARO/AIO-12 trial) for Locally Advanced Rectal Cancer.

DESIGN, SETTING, AND PARTICIPANTS

This secondary analysis of a randomised clinical trial included 311 patients who were recruited from the accrued CAO/ARO/AIO-12 trial population from 15 June 2015, to 31 January 2018, from 18 centers in Germany. Patients with cT3-4 and/or node-positive rectal adenocarcinoma were included in the analysis. Data were analysed from 15 June, 2015, to 31 January 2018. The follow-up analysis was conducted between 31 January 2018, and 30 November, 2020.

INTERVENTIONS

Patients were randomly assigned to group A for three cycles of fluorouracil, leucovorin, and oxaliplatin before fluorouracil/oxaliplatin CRT (50.4 Gy), or to group B for CRT before chemotherapy. Total mesorectal excision was scheduled on day 123 after the start of total neoadjuvant therapy in both groups.

MAIN OUTCOMES AND MEASURES

The end points assessed in this secondary analysis included long-term oncologic outcomes, chronic toxicity, patient-reported outcome measures for global health status (GHS) and quality of life (QoL), and the Wexner stool incontinence score.

RESULTS

Of the 311 patients enrolled, 306 were evaluable, including 156 in group A (mean [SD] age, 60 [11] years; 106 men [68%]) and 150 in group B (mean [SD] age, 62 [10] years; 100 men [67%]). After a median follow-up of 43 months (range, 35-60 months), the 3.0-year disease-free survival was 73% in both groups (hazard ratio, 0.95; 95% CI, 0.63-1.45, P = .82); the 3.0-year cumulative incidence of locoregional recurrence (6% vs 5%, P = .67) and distant metastases (18% vs 16%, P = .52) were not significantly different. Chronic toxicity grade 3.0 to 4.0 occurred in 10 of 85 patients (11.8%) in group A and 8.0 of 66 patients (9.9%) in group B at 3.0 years. The GHS/QoL score decreased after total mesorectal excision but returned to pretreatment levels 1.0 year after randomisation with no difference between the groups. Stool incontinence deteriorated 1.0 year after randomisation in both groups and only improved slightly at 3.0 years, but never reached baseline levels.

CONCLUSIONS AND RELEVANCE

This secondary analysis of a randomised clinical trial showed that CRT followed by chemotherapy resulted in higher pathological complete response without compromising disease-free survival, toxicity, QoL, or stool incontinence and is thus proposed as the preferred total neoadjuvant therapy sequence if organ preservation is a priority.