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Does the addition of oxaliplatin to preoperative chemoradiation benefit cT4 or fixed cT3 rectal cancer treatment? A subgroup analysis from a prospective study

K. Wiśniowska [a], A. Nasierowska-Guttmejer [b], W. Polkowski [c], W. Michalski [d], L. Wyrwicz [d,e], L. Pietrzak [a], A. Rutkowski [e], M. Malinowska [f], J. Kryński [e], E. Kosakowska [e], J. Zwoliński [e], M. Winiarek [e], J. Olędzki [g,h], J. Kuśnierz [i], L. Zając [e], M. Bednarczyk [e], M. Szczepkowski [j], W. Tarnowski [k], K. Paśnik [l], J. Radziszewski [m], M. Partycki [a], K. Bęczkowska [a], R. Styliński [n], R. Wierzbicki [o], P. Bury [p], M. Jankiewicz [c,q], K. Paprota [q], M. Lewicka [c], B. Ciseł [c], M. Skórzewska [c], J. Mielko [c], A. Danek [r], G. Nawrocki [s], R. Sopyło [s], L. Kępka [t], K. Bujko [a,*], for the Polish Colorectal Study Group

[a] *I Department of Radiotherapy, M. Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[b] *Department of Pathology, Clinical Hospital of Ministry of Internal Affairs and Administration, Warsaw, Poland*
[c] *Department of Surgical Oncology, Medical University of Lublin, Poland*
[d] *Bioinformatics and Biostatistics Unit, M. Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[e] *Department of Gastroenterological Oncology, M. Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[f] *Department of Pathology, M. Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[g] *Department of Colorectal Surgery, Medical University, Warsaw, Poland*
[h] *Medical Faculty, University of Rzeszów, Poland*
[i] *Department of Gynaecology, M. Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[j] *Department of Rehabilitation, Józef Piłsudski University of Physical Education and Clinical Department of General and Colorectal Surgery, Bielański Hospital, Warsaw, Poland*
[k] *Department of General, Oncologic and Digestive Tract Surgery, Medical Centre of Postgraduate Education, Orłowski Hospital Warsaw, Poland*
[l] *Department of General, Oncological, Metabolic and Thoracic Surgery, Military Institute of Medicine, Warsaw, Poland*
[m] *Department of General and Vascular Surgery, Multidisciplinary Hospital, Warsaw-Międzylesie, Poland*
[n] *1st Department of General Surgery, Transplantology and Nutritional Therapy, Medical University of Lublin, Poland*
[o] *Department of Surgery, MSW Hospital, Lublin, Poland*
[p] *Department of General and Gastrointestinal Surgery and Surgical Oncology of the Alimentary Tract, Medical University, Lublin, Poland*
[q] *Department of Radiotherapy, St. John's Cancer Centre, Lublin, Poland*
[r] *II Department of Radiotherapy, M. Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[s] *Department of Surgery, M. Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[t] *Department Radiotherapy, Independent Public Health Care Facility of the Ministry of the Interior and Warmian-Masurian Oncology Centre, Olsztyn, Poland*

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* Corresponding author. Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Centre, W.K. Roentgena 5, 02-781 Warsaw, Poland. Fax: +48 226439287.
E-mail address: bujko@coi.waw.pl (K. Bujko).

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Abstract

Background: Whether there is any benefit derived from adding oxaliplatin to fluoropyrimidine-based preoperative chemoradiation is currently unknown in cases of advanced cT3 or cT4 tumours. Our aim was to evaluate this issue by analysing a randomized trial, which compared two schedules of preoperative treatment (chemoradiation vs. 5 × 5 Gy with 3 cycles of consolidation chemotherapy) for cT4 or fixed cT3 rectal cancer.

Patients and methods: Delivery of oxaliplatin was mandatory to the first part of the study. For the second part, its delivery in both treatment-assigned groups was left to the discretion of the local investigator. We analysed a subgroup of 272 patients (136 in the oxaliplatin group and 136 in the fluorouracil-only group) from institutions that had omitted oxaliplatin in the second part of the study.

Results: Circumferential resection margin negative (CRM−) status rate was 68% in the oxaliplatin group and 70% in the fluorouracil-only group, $p = 0.72$. The pathological complete response rate (pCR) was correspondingly 14% vs. 7%, $p = 0.10$. Following multivariable analysis, when comparing the CRM− status in the oxaliplatin group to the fluorouracil-only group, the odds ratio was 0.79 (95 CI 0.35−1.74), $p = 0.54$; there being no interaction between concomitant chemoradiation and 5 × 5 Gy with consolidation chemotherapy; $p_{interaction} = 0.073$. For pCR, the corresponding results were 0.47 (95 CI 0.19−1.16), $p = 0.10$, $p_{interaction} = 0.84$.

Conclusion: No benefit was found of adding oxaliplatin in terms of CRM nor pCR rates for either concomitant or sequential settings in preoperative radiochemotherapy for very advanced rectal cancer.

Keywords: Rectal cancer; Preoperative chemoradiation; Oxaliplatin

Introduction

Seven randomized trials have evaluated the addition of oxaliplatin to fluoropyrimidine-based preoperative chemoradiation in rectal cancer.[1–10] Only the CAO/ARO/AIO-04 trial showed improvement in the pathological complete response (pCR) rate, disease-free survival and no increase in acute toxicity when using oxaliplatin.[6] Overall survival in this trial was similar in the two groups. The other six trials showed increased acute toxicity when using oxaliplatin and no benefit of adding oxaliplatin in terms of negative circumferential resection margin (CRM−) status, pCR, downstaging, local control, disease-free survival and overall survival. A meta-analysis of four of these trials showed significantly improved pCR in patients given oxaliplatin with an absolute difference of 2.5%; there being no differences in the rates of CRM+ and surgical complications.[11] However, in all these trials, the proportion of patients with cT4 and cT3 threatening mesorectal fascia (cT3mrf+) tumours was low. It is thus unknown whether oxaliplatin benefits patients with such advanced cancer where tumour shrinkage is needed before surgery. One may argue that in such tumours, adding oxaliplatin to fluoropyrimidine-based preoperative chemoradiation improves the radical resection rate, because in metastatic disease such a combination enhances tumour shrinkage as compared with fluoropyrimidine alone.[12] Results from one retrospective analysis support this hypothesis.[13]

Recently we published a phase III randomised trial comparing two schedules of preoperative treatment for cT4 or fixed cT3 rectal cancer; chemoradiation vs. 5 × 5 Gy with three cycles of consolidation chemotherapy.[14] No differences were observed in local efficacy between the two schedules. Nevertheless, an improved overall survival and lower acute toxicity favoured 5 × 5 Gy with consolidation chemotherapy. In the two treatment-assigned groups, 72% of the patients received oxaliplatin along with 5-fluorouracil and leucovorin while the remaining 28% of patients received only 5-fluorouracil and leucovorin. This has thereby created an opportunity to evaluate whether adding oxaliplatin to chemoradiation (either in a simultaneous or sequential setting) is beneficial for treating such advanced cancer. The aim of the current report is to present this evaluation.

Material and methods

The trial received ethical committee approval and is registered under ClinicalTrials.gov number NCT00833131. The study design, entry criteria, treatment details and results have been published previously.[14] In summary, eligibility criteria were as follows: primary or locally recurrent rectal cancer involving or abutting adjacent organs or structures (cT4) or a palpably fixed cT3 lesion, pathologically proven adenocarcinoma, ≤75 years of age, WHO performance status ≤2 in patients fit for major surgery and chemotherapy along with informed written consent signed by patients. Work-up included colonoscopy or rectoscopy, pelvic MRI or CT, CT of the abdomen, chest CT or radiography, blood count and biochemistry. Pelvic MRI was not mandatory, because of the long waiting time for this examination in Poland. The CRM− resection rate was the main endpoint. CRM− surgery was defined when a tumour was resected with at least a 1 mm free margin. The secondary endpoints were acute toxicity of preoperative treatment, incidence of postoperative complications, pCR rate and long-term oncological results. The

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