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Rectum

Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase III trial.

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BACKGROUND

Treatment of locally advanced rectal cancer with chemoradiotherapy, surgery, and adjuvant chemotherapy controls local disease, but distant metastases remain common. We aimed to assess whether administering neoadjuvant chemotherapy before preoperative chemoradiotherapy could reduce the risk of distant recurrences.

METHODS

We did a phase III, open-label, multicentre, randomised trial at 35 hospitals in France. Eligible patients were adults aged 18-75 years and had newly diagnosed, biopsy-proven, rectal adenocarcinoma staged cT3 or cT4 M0, with a WHO performance status of 0-1. Patients were randomly assigned (1:1) to either the neoadjuvant chemotherapy group or standard-of-care group, using an independent web-based system by minimisation method stratified by centre, extramural extension of the tumour into perirectal fat according to MRI, tumour location, and stage. Investigators and participants were not masked to treatment allocation. The neoadjuvant chemotherapy group received neoadjuvant chemotherapy with FOLFIRINOX (oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, leucovorin 400 mg/m2, and fluorouracil 2400 mg/m2 intravenously every 14 days for six cycles), chemoradiotherapy (50 Gy during five weeks and 800 mg/m2 concurrent oral capecitabine twice daily for five days per week), total mesorectal excision, and adjuvant chemotherapy (3 months of modified FOLFOX6 [intravenous oxaliplatin 85 mg/m2 and leucovorin 400 mg/m2, followed by intravenous 400 mg/m2 fluorouracil bolus and then continuous infusion at a dose of 2400 mg/m2 over 46 h every 14 days for six cycles] or capecitabine [1250 mg/m2 orally twice daily on days 1.0-14 every 21 days]). The standard-of-care group received chemoradiotherapy, total mesorectal excision, and adjuvant chemotherapy (for 6 months). The primary endpoint was disease-free survival assessed in the intention-to-treat population at three years. Safety analyses were done on treated patients. This trial was registered with EudraCT (2011-004406-25) and ClinicalTrials.gov (NCT01804790) and is now complete.

FINDINGS

Between 5 June 2012, and 26 June 2017, 461 patients were randomly assigned to either the neoadjuvant chemotherapy group (n=231) or the standard-of-care group (n=230). At a median follow-up of 46·5 months (IQR 35·4-61·6), three-year disease-free survival rates were 76% (95% CI 69-81) in the neoadjuvant chemotherapy group and 69% (62-74) in the standard-of-care group (stratified hazard ratio 0·69, 95% CI 0·49-0·97; p=0·034). During neoadjuvant chemotherapy, the most common grade 3.0-4.0 adverse events were neutropenia (38 [17%] of 225 patients) and diarrhoea (25 [11%] of 226). During chemoradiotherapy, the most common grade 3.0-4.0 adverse event was lymphopenia (59 [28%] of 212 in the neoadjuvant chemotherapy group vs 67 [30%] of 226 patients in the standard-of-care group). During adjuvant chemotherapy, the most common grade 3.0-4 adverse events were lymphopenia (18 [11%] of 161 in the neoadjuvant chemotherapy group vs 42 [27%] of 155 in the standard-of-care group),

neutropenia (nine [6%] of 161 vs 28 [18%] of 155), and peripheral sensory neuropathy (19 [12%] of 162 vs 32 [21%] of 155). Serious adverse events occurred in 63 (27%) of 231 participants in the neoadjuvant chemotherapy group and 50 (22%) of 230 patients in the standard-of-care group (p=0·167), during the whole treatment period. During adjuvant therapy, serious adverse events occurred in 18 (11%) of 163 participants in the neoadjuvant chemotherapy group and 36 (23%) of 158 patients in the standard-of-care group (p=0·0049). Treatment-related deaths occurred in one (<1%) of 226 patients in the neoadjuvant chemotherapy group (sudden death) and two (1%) of 227 patients in the standard-of-care group (one sudden death and one myocardial infarction).

INTERPRETATION

Intensification of chemotherapy using FOLFIRINOX before preoperative chemoradiotherapy significantly improved outcomes compared with preoperative chemoradiotherapy in patients with cT3 or cT4 M0 rectal cancer. The significantly improved disease-free survival in the neoadjuvant chemotherapy group and the decreased neurotoxicity indicates that the perioperative approach is more efficient and better tolerated than adjuvant chemotherapy. Therefore, the PRODIGE 23 results might change clinical practice.