Editorial

Preoperative chemotherapy for locally advanced resectable colon cancer - a new treatment paradigm in colon cancer?

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Adjuvant therapy in locally advanced resectable colon cancer

Since 2004, the treatment of locally advanced, resectable colon cancer including high risk stage II or stage III disease is surgery followed by postoperative adjuvant chemotherapy with an oxaliplatin containing regimen. Combination therapy with oxaliplatin and a fluoropyrimidine, including capecitabine, has shown clear superiority to fluoropyrimidine therapy alone (FU/LV) in mitigating risk of recurrence and improving long-term survival (1-6). The results of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial (1,2) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 (4,5), showed that regimens with oxaliplatin (FOLFOX4 or FLOX) compared to FU/LV significantly improved disease-free survival (DFS) as well as overall survival (OS) especially in stage III patients, resulting in a 5-6% absolute improvement in 5-year DFS (73% *vs*. 67% in MOSAIC; 69% *vs*. 64% in NSABP-07), and a 3-4% increment in long-term OS in stage III cancer (73% *vs*. 69% 6-yr OS in MOSAIC; 77% *vs*. 74% 5-yr OS in NSABP C-07).

Current evidence on neoadjuvant therapy in several GI malignancies

Given proven efficacy in the adjuvant setting, the trend has been to test the benefits of *pre*operative or *peri*operative therapy for other GI malignancies including esophageal, gastric and rectal cancers (7-11). A neoadjuvant treatment strategy is attractive with theoretical benefits that could result in eradication of micrometastases and reduction of tumor cell shedding during surgery. Furthermore, patients will likely better tolerate full intensity chemotherapy when administered prior to surgery rather than post-operatively. Neoadjuvant treatment also allows the assessment of initial tumor response and toxicity profile of the same regimen that might be considered for additional systemic therapy given in the adjuvant setting. Use of *pre*operative therapy has resulted in significant downstaging with improved resectability and a better progression-free (PFS) and overall survival (OS) in several GI cancers. The magnitude of such improvement in the case of *esophageal cancer*, as shown by the MRC Working Party study (7), was 6% (60% *vs*. 54%) increase in complete resection rate and 20% improvement of relative risk in 5 year OS with preoperative chemotherapy (two 4-day cycles of cisplatin/continuous infusion 5-FU) compared to surgery alone (HR: 0.79, 95% CI: 0.67-0.93). A greater benefit was reported in the recent CROSS trial (8), where preoperative chemoradiation therapy (weekly carboplatin/paclitaxel for 5 weeks and concurrent radiotherapy) increased the complete resection rate by 23% compared to surgery alone (92% *vs*. 69%). Overall survival was significantly better in the preoperative chemoradiation group (HR: 0.66, 95% CI: 0.50-0.87), leading to a difference in median OS of 25 months (49.4 *vs*. 24 months). An example of perioperative chemotherapy (three 3-week cycles of ECF before and after surgery) as reported by the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial (9) for *gastric*

cancer resulted in a 25% improvement in OS compared to surgery alone (HR: 0.75, 95% CI: 0.60-0.93). The MRC CR07 and NCIC-CTG C016 study (10) established the beneficial role of preoperative radiotherapy compared to initial surgery with selective postoperative chemoradiation in *rectal cancer*. The study noted a 61% reduction in the relative risk of local recurrence for patients receiving preoperative radiotherapy (HR: 0.39, 95% CI: 0.27-0.58), and an absolute difference of 6.2% (95% CI: 5.3-7.1%) at 3 years. There was a 24% improvement in DFS associated with preoperative radiotherapy (HR 0.76, 95% CI: 0.62-0.94); an absolute difference of 6.0% (95% CI: 5.3-6.8%) at 3 years (77.5% *vs*. 71.5%). Notably, overall survival did not differ between the two groups (HR: 0.91, 95% CI: 0.73-1.13). Neoadjuvant chemotherapy regimens combined with radiation as multimodality treatment in locally advanced rectal cancer have been reported. All include a fluorouracil based regimen with or without oxaliplatin. The NSABP R-04 trial (11) compared 4 neoadjuvant regimens (infusional 5-FU or capecitabine, each with or without oxaliplatin) with concurrent preoperative radiation. The result showed similar efficacy overall for complete pathologic response (pCR) (~20%), sphincter-saving surgery (~60%) and surgical downstaging (~20%). Incremental benefit of adding oxaliplatin in this setting was minimal with added toxicity, results which are similar to other reports.

Evidence on preoperative chemotherapy in colon cancer with potentially resectable liver metastasis

The standard use of perioperative chemotherapy for patients with resectable liver metastasis remains controversial (12-15). It should be noted that only a minority of patients with liver metastases are technically resectable at diagnosis. Patients with initially unresectable liver tumors are first treated with chemotherapy and some of them can be converted to resectability with 5-year survival comparable to those who were initially resectable (16). A representative study supporting the perioperative chemotherapy for resectable liver only metastases is the EORTC intergroup phase III study 40983 (17-19), which compared perioperative FOLFOX4 chemotherapy (6 cycles pre- and post-surgery) to surgery alone in selected patients. Among 364 (1:1) randomized patients, the result showed borderline improvement in PFS (HR: 0.79, 95% CI: 0.62-1.02), although no difference in OS (HR: 0.87, 95% CI: 0.66-1.14) over surgery alone in a recent updated report (17).

Preoperative chemotherapy in locally advanced, resectable colon cancer

In a recent issue of Lancet Oncology (20), the investigators from the FOxTROT Collaborative Group (Fluoropyrimidine Oxaliplatin and Targeted Receptor Pre-Operative Therapy) reported results from the feasibility phase of a randomized study which was the first to examine the value of preoperative therapy in patients with locally advanced operable colon cancer. One hundred fifty high risk stage II and stage III patients, with T3 (≥5 mm invasion beyond the muscularis propria) or T4 cancer were randomized in a 2:1 ratio to 6 weeks [3 cycles of OxMdG, equivalent to FOLFOX6 (21)] preoperative plus 18 weeks (9 cycles) postoperative adjuvant chemotherapy *versus* postoperative chemotherapy only for 24 weeks (12 cycles). Notably, there was a second randomization in each arm to receive anti-EGFR therapy using panitumumab in KRAS wild-type patients (72% of those with known KRAS status) (22,23), of whom 31% were assigned to panitumumab. Although lacking disease progression or survival outcomes, results from this feasibility study showed significant tumor downstaging compared with the postoperative group (P=0.04). There was also less apical node involvement (1% *vs*. 20%, P<0.0001) and fewer positive margins (4% *vs*. 20%, P=0.002). Blinded centrally scored tumor regression grading showed moderate or greater regression of 31% *vs*. 2% (P=0.0001), favoring the preoperative group. The study concluded that preoperative chemotherapy in locally advanced operable primary colon cancer was feasible with acceptable toxicity and perioperative morbidity. The decision was to proceed to a phase 3 study to examine clinical outcomes in correlation with the favorable pathological responses as a result of preoperative therapy including survival.

The FOxTROT trial represents an effort in response to the rising enthusiasm to change the treatment paradigm for patients with resectable and potentially curable colon cancer. The neoadjuvant approach has the potential to improve patient tolerance and acceptance of chemotherapy and would determine if a patient's tumor is "chemo-sensitive". For those who did not respond to neoadjuvant therapy, new therapeutic strategies would be essential, including the development of biologically-driven clinical trials. The ability to access tissue pre- and post-neoadjuvant therapy offers an opportunity to explore biologic targets and

to develop potential agents that would affect these targets and is a strategy under development for neoadjuvant therapy for rectal cancer. For those patients with deficient DNA mismatch repair tumors (dMMR, MSI-H), particularly for stage II colon cancers, survival is excellent and adjuvant chemotherapy has been shown to offer no additional benefit and may in fact be harmful (24). Therefore it may be important to first evaluate patients to determine MSI status prior to neoadjuvant chemotherapy.

In addition, clinical staging prior to neoadjuvant therapy does have limitations compared to pathologic stage; thus, patients who received neoadjuvant therapy may be "over-treated" with neoadjuvant therapy particularly for stage II disease. Thus, there is a concern that inaccurate radiological staging might result in inappropriate chemotherapy for low-risk patients in the preoperative setting. Accuracy of radiological staging was assessed by the authors compared to pathological staging after surgery. CT imaging accurately identified invasion of the muscularis propria in 98% of patients, although was less accurate in discriminating between T3 and T4 stage in half of the evaluated cases. CT was sensitive in detecting nodal spread, yet with a low specificity as a result of overestimation of involved nodes.

The optimal duration of neoadjuvant therapy is also a question and whether 2-3 months of neoadjuvant therapy plus 3 months of postoperative adjuvant therapy is necessary. Advanced disease trials demonstrated that the greatest reduction in tumor size occurs during the first 2-3 months of combination therapy for metastatic colorectal cancer, after which time there is less tumor size decrease and more of a stabilization pattern (25,26). There is a world-wide effort to study 3 months (FOLFOX 6 cycles) *vs*. standard 6 months (FOLFOX 12 cycles) of adjuvant therapy for stage III colon cancer which should help determine the optimal duration of treatment.

Among the current trial subjects who had high T stage colon cancer, the potential risk of tumor growth during the preoperative treatment phase that could lead to bowel obstruction or perforation hence emergency surgery was not demonstrated. One out of the 99 patients assigned to preoperative chemotherapy proceeded directly to surgery due to localized perforation before the start of treatment and there were no cases requiring emergency surgery because of incipient obstruction during the 6-week preoperative treatment. The mean time from randomization to start of chemotherapy was 13 (SD 6) days, and the mean time to surgery from start of chemotherapy of 61 (SD15) days. This included at least a 3 week designated delay to surgery after completion of preoperative chemotherapy. Despite the differences in time course, the safety, tolerance and surgical related complications rates were comparable between the 2 treatment arms. There was also a notable higher chemotherapy completion rate in the pre- plus post-operative therapy group compared to the postoperative chemotherapy group (68% *vs*. 57%).

The use of the anti-EGFR antibody (panitumumab) for KRAS wild-type patients in the neoadjuvant setting was included in the FOxTROT trial because of the increase in response rate when panitumumab or cetuximab has been added to chemotherapy in metastatic colorectal cancer clinical trials (27,28); however, the investigators did not report whether there was any difference in response or resectability rates between the two pre-operative groups (chemotherapy with or without panitumumab). The continuation of panitumumab in the adjuvant setting is of potential concern in FOxTROT since the North American GI intergroup study of adjuvant cetuximab in addition to chemotherapy showed no difference in survival and in fact was detrimental (29).

In summary, the FOxTROT trial was the first randomized study in assessing preoperative chemotherapy in locally advanced operable colon cancer, and has shown promising results from the feasibility phase of the study. The phase III study will determine if neoadjuvant chemotherapy is a viable option for patients and whether the "standard of care" will change. The addition of panitumumab in the trial design is a concern given the previous negative results from a large stage III colon cancer trial comparing adjuvant chemotherapy with or without cetuximab.

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