The "addition" and "subtraction" of adjuvant chemotherapy for locally advanced colorectal cancer: where to go next?

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Compared with surgery alone, post-operative adjuvant chemotherapy (ACT) for local colorectal cancer (CRC) can significantly improve survival.[1,2] The benefit of adjuvant fluorouracil (5-FU)-based chemotherapy in stage III CRC was established in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol C-01 trial[3] and consolidated in subsequent studies.[1,4] Thus, 5-FU has been widely used as a basic ACT for CRC since then. More encouragingly, the addition of oxaliplatin could further confer a survival advantage in patients receiving 5-FU-based ACT according to three large phase III randomized clinical trials (RCTs): the 2004 Multicenter International Study of Oxaliplatin/5-FU/leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, the NSABP C-07 trial, and the NO16968 trial.[5-9] The MOSAIC trial showed the superiority of the addition of oxaliplatin to 5-FU plus leucovorin (FL) over FL alone in terms of 3-year disease-free survival (DFS) and 5-year DFS.[5,6] Similar results were observed in the NSABP C-07 trial, in which the addition of oxaliplatin increased the 3-year DFS by 6.6%.[7] The NO16968 trial[9] reported a 7-year DFS of 63.0% for capecitabine plus oxaliplatin (CAPOX) *vs.* 56.0% for bolus 5-FU/folinic acid (hazard ratio [HR] = 0.80, 95% confidence interval [CI] 0.69–0.93; *P* = 0.0045). Therefore, the oxaliplatin-based 6-month regimen has become the gold standard of post-operative ACT for patients with stage III CRC who are in good condition and can tolerate more aggressive cytotoxic chemotherapeutics.[10] Hence, oncologists were inspired to extend the addition of oxaliplatin to neoadjuvant chemotherapy and even neoadjuvant chemoradiotherapy over the past decade. However, where is the "limit" of the extended use? Notably, the survival benefit with oxaliplatin-combined ACT for 6 months comes with severe toxicities, including myelosuppression, gastrointestinal toxicity, and neurotoxicity. In particular, cumulative dose-dependent neurotoxicity can even be irreversible and adversely affect overall quality of life. Furthermore, excessive ACT can have an impact on the immune status of patients as a result of therapeutic toxicities.[11,12] In other words, excessive ACT does not necessarily have benefits, but can instead be counterproductive.

Rational "addition" and "subtraction" in ACT may reduce post-operative recurrence and prolong survival time without undermining the quality of life. Hence, future treatment research should focus on determining the tailored chemotherapy for specific subgroups to improve efficacy and reduce side effects.

In 2004, the MOSAIC study[5,6] demonstrated that a 6-month ACT regimen of oxaliplatin combined with 5-FU was superior to the FL regimen, establishing a standard protocol based on 6 months of oxaliplatin. This trial randomized 2246 patients with stage II or III CRC who had undergone curative resection to receive FL alone or with oxaliplatin for 6 months. After long-term follow-up, it was demonstrated that adding oxaliplatin could significantly improve both DFS and overall survival (OS).[5,6] Subsequently, the NSABP C-07[7,8] study, in which 2047 participants were randomized to receive an ACT regimen of FL regime or FL with oxaliplatin, further affirmed the role of oxaliplatin in ACT. The results showed that the addition of oxaliplatin significantly improved the 3-year DFS (71.8% *vs.* 76.1%; HR = 0.80; 95% CI 0.69–0.93; *P* = 0.003) and even remained superior in terms of DFS after a median of 8 years of follow-up. Similarly, the superiority of DFS was also observed with the addition of oxaliplatin to capecitabine in the NO16968 trial.[9] A meta-analysis[13] of evolving 12,233 patients also confirmed that the addition of oxaliplatin to 5-FU-based ACT had a significantly positive impact on outcomes in patients with stage III CRC. To further investigate the community effectiveness of the addition of oxaliplatin in CRC, Sanoff

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et al[14] compared OS among 4060 patients with CRC treated with oxaliplatin and non-oxaliplatin-containing ACT. Encouragingly, these analyses suggested that the addition of oxaliplatin to 5-FU conferred a survival advantage that was even maintained in older and minority groups and in those with higher comorbidity, who are usually not included among RCT participants. Therefore, the NCCN currently recommends oxaliplatin combined with FL for adjuvant treatment of stage II or III CRC after radical surgery, except for those with stage IIA disease (no risk factors). On this basis, the addition of oxaliplatin to neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy has become a popular research direction. However, the results of most attempts have been shown to be negative. The FOWARC trial[15] randomized participants to receive 5-FU with radiation (RT) (FU-RT arm), perioperative 5-FU and oxaliplatin (mFOLFOX6) with RT (FOLFOX-RT arm), or 4 to 6 cycles of mFOLFOX6 alone (FOLFOX arm), and its primary endpoint results indicated that neither the FOLFOX-RT group nor the FOLFOX group showed any improvement in 3-year DFS compared with the FU-RT group (FU-RT group *vs.* FOLFOX-RT group *vs.* FOLFOX group: 75.7 ± 3.8% *vs.* 77.1 ± 3.6% *vs.* 74.9 ± 3.6%, $P = 0.970$). Similarly, the PETACC-6 trial,[16] which focused on investigating the role of oxaliplatin in combination with pre-operative capecitabine-based chemoradiation and post-operative capecitabine, also confirmed that the addition of oxaliplatin did not yield survival benefits in terms of DFS or OS. Consistently, the results of the ACCORD12 trial,[17] STAR-01 trial,[18] and the NSABP R-04 trial[19] all indicated that the addition of oxaliplatin to neoadjuvant chemotherapy regimens did not significantly improve the tumor response rate, DFS or OS. The results of the ACCORD12 trial,[17] which included rectal cancer patients with intermediate-risk factors, showed that a CAPOX50 (RT 50 Gy + capecitabine and oxaliplatin) regimen did not improve local control, DFS, or OS compared with a CAP45 (RT 45 Gy + capecitabine) regimen after a median follow-up of 60.2 months. The results of the STAR-01 trial[18] suggested that adding oxaliplatin to 5-FU-based pre-operative chemoradiotherapy significantly increased toxicity without improving the primary tumor response. Moreover, the NSABP R-04 trial[19] demonstrated that the addition of oxaliplatin did not reverse the 3-year local-regional recurrence rate, the 5-year DFS, or the 5-year OS in any patient risk group, but did add considerable toxicity. Therefore, the role of oxaliplatin in the chemotherapy regimens for CRC has evolved from "addition is better" to "less is more" during different periods in the chemotherapy process. However, how has the duration of chemotherapy evolved during this process?

Since the 1980s, there has been an ongoing evolution of the overall duration of adjuvant therapy. The first effective adjuvant regimen, MOF (5-FU, semustine, and vincristine), was administered for 18 months in the NSABP C-01 study in the late 1980s.[3] In subsequent studies, 12-month was selected as the treatment duration.[1,20,21] Since 2004, 6 months of oxaliplatin plus 5-FU chemotherapy have become the standard ACT regimen for patients with stage III CRC. After modifications to this regimen, 6 months of FOLFOX or CAPOX chemotherapy have gradually become the standard treatment.[5,6] Subsequent studies have confirmed that the efficacy of 6 months of ACT was not worse than that of 12 months, and the toxic side effects of chemotherapy were significantly reduced.[9,22] However, oxaliplatin has cumulative neurotoxicity, affecting both the everyday life and physical health of patients.[22] To reduce the toxic side effects without affecting the efficacy, clinicians again attempted to reduce the duration of chemotherapy in selected patients. A meta-analysis[23] in 2010 with a total of 10,326 patients compared two durations of adjuvant treatment, 6 months *vs.* 9 to 12 months, and the results suggested that the duration of ACT need not last more than 6 months. Although this meta-analysis did not favor either a 3-month or a 6-month duration, it matters significantly for helping the design of subsequent trials comparing different durations of continuous treatment. Excitingly, the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration went one step further. It collected the data from a total of 12,834 patients in six large randomized controlled trials (four from Europe, one from Japan, and one from the United States) that explored whether the treatment effects of FOLFOX and CAPOX at 6 months were comparable to those in selected patients if the regimens were reduced by half (3 months).[24] Among the primary endpoint results, the DFS time of the 3-month group was inferior to that of the 6-month group (74.6% *vs.* 75.5%, DFS HR = 1.07, 95% CI 1.00–1.15). However, a subgroup analysis showed that the DFS time of patients with T3N1 CRC in the 3-month group was not inferior to that of patients in the 6-month group (DFS HR = 1.01, 95% CI 0.90–1.12) or to that of patients treated with CAPOX (DFS HR = 0.95, 95% CI 0.85–1.06), while the reduced duration of ACT was, as expected, associated with a significant decrease in long-term side effects and a substantial reduction in health-related costs.[24] Moreover, a recent systematic review and meta-analysis further showed that shorter durations of ACT with combination regimens were not associated with worse survival in patients with stage III CRC.[25] Therefore, individualizing the ACT duration (3 months) based on the specific treatment regimen (CAPOX) and the patient's specific disease characteristics (low-risk disease, T1-3N1) is possible. Accordingly, the American Society of Clinical Oncology (ASCO) convened an expert panel to determine the duration of oxaliplatin-containing adjuvant therapy and ultimately proposed a shared decision-making approach that taken into account patient characteristics, values, and preferences, as well as discussion of the potential for benefit and risks of harm associated with ACT duration.[26]

The implications of these studies indicate that the "subtraction" of oxaliplatin at some part of the chemotherapy process may be warranted for selected patients with CRC on the basis of current standards to achieve more tailored treatment strategies for specific subgroups. Based on our review of the evidence to date, we propose that future studies should explore the ACT duration as an ordinal variable with three or more groups on the basis of 6 months to allow for the exploration of a threshold effect in real-world settings. Is the current ACT regime truly

necessary with both oxaliplatin and fluoropyrimidine for a duration of 6 months, or is it possible to use only 3 months of oxaliplatin followed by 3 months of 5-FU monotherapy?

In addition, since the addition of oxaliplatin to neo-adjuvant chemotherapy or neoadjuvant chemoradiotherapy regimens failed to improve prognosis, might this "subtraction" be extended to selected patients who originally underwent hyperthermic intra-peritoneal chemotherapy (HIPEC), which is a relatively frequently used local chemotherapy for CRC after extensive resection? The PRODIGE 7 trial, the first prospective RCT assessing HIPEC for colorectal peritoneal carcinomatosis, has shown that the addition of oxaliplatin-HIPEC to cytoreductive surgery does not improve OS or relapse-free survival, while the 60-day complication rate was significantly higher.[27] This finding suggests that local chemotherapy might be reduced in selected patients based on the peritoneal carcinomatosis index (PCI). Enlightened by the above research, "subtraction" might be cautiously explored further to identify subgroups of patients who will benefit from the specific "subtraction" of HIPEC therapies. Better selection of subgroups, including specific genotypes, primary tumor sites, specific ranges of PCI, and other biologic characteristics, could influence the therapeutic effects of HIPEC.

Recently, Taieb et al[28] proposed their perspectives on refining adjuvant therapy for non-metastatic CRC. In their opinion, to improve patient management in the near future, the subsequent research should focus on molecular profiling to identify specific subgroups that might receive optimal benefit from specific agents and durations, to tailor adjuvant treatment, and to reduce toxicity and health-related costs. Thus, it is critical to clinically identify the biologic characteristics of CRC in different populations and to develop corresponding individualized treatment strategies. Regarding the research directions of chemotherapy for CRC, studies at the molecular biology level will be crucial for simultaneously predicting clinical efficacy and guiding clinical treatment. The selection of different genotypes, primary tumor sites, and other factors could help make treatment regimens more tailored and rational.

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Conflicts of interest

None.

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