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Commentary Article

Colon Cancer Neoadjuvant Chemotherapy

Mark Marino*

Editorial Office, International Journal of Collaborative Research on Internal Medicine and Public Health, USA.

Corresponding Author*

Mark Marino
Editorial Office,
International Journal of Collaborative Research on Internal Medicine and Public Health
USA
E-mail: Marino.marc@medicalres.com

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Abstract

Although neoadjuvant chemotherapy is routinely utilised in the treatment of a variety of solid tumours, it is still understudied in the treatment of locally advanced colon cancer. Early treatment of micro-metastatic disease, the capacity to reduce local disease burden, potentially leading to more effective resections, and enhanced treatment tolerance are all advantages of this technique extrapolated from other disease locations. Large, randomised clinical trials are investigating approaches for accurate staging and safe administration of systemic treatment, but the available data are either not mature enough or have not demonstrated a convincing argument for adoption into standard practice, necessitating further investigation. Although surgical resection is commonly used to treat early-stage colon cancer, not all patients achieve long-term remission. Adjuvant chemotherapy with fluoropyrimidine, with or without oxaliplatin, is often used to improve cure rates, but its efficacy in the neoadjuvant situation is unknown. Preoperative chemotherapy has been shown to be safe and effective in various gastrointestinal cancers, but there is a scarcity of evidence from big, prospective randomised trials, despite the fact that several are now underway. The theoretical risks and benefits, logistical challenges, and available safety and efficacy evidence relevant to the use of chemotherapy in locally advanced colon cancer will be discussed in this study.

Keywords: Colon cancer • Neoadjuvant • Chemotherapy • Immunotherapy

Introduction

In 2018, colon cancer was responsible for almost 1.1 million new cancer diagnoses and over 550,000 deaths worldwide. Furthermore, colon cancer is the world's third-biggest cause of cancer-related death. Over 70% of patients will have localised or regional disease, which means that mesocolic excision is the greatest option for cure. Following surgery, a surveillance plan is usually established to detect early recurrence, which includes a scheduled history and physical labs, which may include tumour markers, imaging, and endoscopic examinations. Adjuvant chemotherapy can be explored for stage II cancer, according to the National Comprehensive Cancer Network (NCCN) recommendations, with greater evidence to support its use as staging increases due to depth of invasion and lymph node involvement, as in stage III disease. To lower the likelihood of disease recurrence, a fluoropyrimidine with or without oxaliplatin (depending on stage and presence of high-risk characteristics) is usually given. Even with adjuvant chemotherapy, the chance of colorectal cancer recurrence after five years can be as high as 25%. There has recently been a surge in interest in the use of neoadjuvant chemotherapy (NAC) in the treatment of colon cancer. Although there have been few prospective randomised clinical trials to far, retrospective investigations and small institutional trials have suggested that there may be some benefit. Other gastrointestinal cancers, such as oesophagal, gastric, and rectal tumours, have already been treated with NAC [1-3]. There are several theories on the potential benefits of locally advanced colon cancer (LACC). First, NAC may help to eliminate micro-metastatic illness earlier and reduce the size/stage of the main tumour. Increased R0 (margin negative) resection rates could result as a result of this. Surgical stress causes locoregional metastases in animal models; however, tumour cell shedding could be reduced during surgery by using cytotoxic debulking with NAC. Furthermore, several observational studies have indicated that preoperative chemotherapy is better tolerated, resulting in fewer delays. However, there are several dangers associated with neoadjuvant chemotherapy. Peripheral neuropathy caused by oxaliplatin is a common side effect of colorectal cancer adjuvant chemotherapy, to the point where significant clinical trials have looked into the usefulness of decreasing treatment times. If patients have inaccurate radiographic staging, moving treatment into the pre-surgical space could result in overtreatment of low-risk patients. Although NAC allows for disease biology surveillance and chemo-responsiveness assessment, postponing surgery in nonresponsive tumours may result in tumour growth, predisposing patients to obstruction and/or perforation, necessitating emergency surgery with substantial morbidity and death. The evidence for and against the use of neoadjuvant chemotherapy in locally advanced colon cancer will be discussed in this paper, with a particular focus on recent randomised clinical studies and the implications of molecular subtypes. All clinical trial stages including neoadjuvant chemotherapy treatment in non-metastatic colon cancer were searched extensively in the literature. PubMed, clinicaltrials.gov, and a review of all major conference abstracts were all used in this search.

Staging *via* radiography

The capacity to appropriately stage patients using imaging is a critical component of the optimal administration of NAC in the preoperative setting in colon cancer. Adjuvant therapy has always been recommended based on pathologic staging, which is the gold standard. However, due to projected tumour regression, pathologic staging becomes less effective in determining the need for adjuvant treatment after cytotoxic chemotherapy. In early investigations using computed tomography (CT) to stage LACC, radiologists correctly identified T and N staging in 60% and 62 percent of cases, respectively. The sensitivity and specificity for distinguishing T3/T4 vs. T1/T2 through tumour infiltration beyond the muscularis propria were 95 percent and 50 percent, respectively, in a pilot study for the FOxTROT clinical trial (described below). A major retrospective investigation of the National Cancer Database (NCDB) looked at 105,569 individuals with clinical and pathologic staging and found that the correlation for the T stage was 80% and the correlation for the N stage was 83 percent. With higher T and N stages, agreement increased, implying that early-stage disease is more difficult to accurately assess. Other modalities, including as MRI and CT colonography, have been studied for usage, but they have not yet replaced CT as the gold standard in this field, owing to expense and invasiveness. Understanding the role of each radiographic staging modality and when to utilise it can help improve diagnostic accuracy and ensure that patients get the right treatment for their condition [4,5].

Retrospective research

Arredondo et al. in 2013 were one of the first to report the possible benefit of neoadjuvant therapy in LACC. Between 2009 and 2010, they looked at 22 patients with stage III colon cancer who were given preoperative CAPOX (capecitabine 1000 mg/m2 twice daily on days 1-7, oxaliplatin 85 mg/m^2 on day 1 every other week)4. They received four further cycles of adjuvant CAPOX after resection. All of the patients had a radiographic response, with a median tumour volume reduction of 69.5 percent. During preoperative treatment, no disease progressed. At 14.4 months after surgery, the actuarial overall survival (OS) and progression-free survival (PFS) were both 100%. Between 2009 and 2014, 43 more patients were assessed using the same technique (infusional 5-FU was used in some cases). With a median start time of 71 days from chemotherapy to surgery, the majority of 65 patients (93.8 percent) completed planned treatment and no procedures were delayed. The CT scan revealed a 62.5 percent reduction in tumour volume. In 4.6 percent of patients, pathologic complete response (pCR) was observed. Although only 60% of patients received adjuvant treatment, the

five-year actuarial OS rate was over 95%. These findings served as the foundation for ELECLA (NCT04188158), a larger, randomised phase II research of neoadjuvant CAPOX in LACC that is now underway. Many of the retrospective evidence on neoadjuvant chemotherapy comes from patients with T4b illness, which is defined as a tumour that invades or attaches to nearby tissues directly. Following the addition of NAC as a treatment option in T4b illness to NCCN recommendations in 2016, two large retrospective reviews of national databases were published. Dehal et al. presented a retrospective review of 921 individuals who had neoadjuvant chemotherapy between 2006 and 2014 in the NCDB in 2017. To compare this cohort to a standard of care group treated with upfront surgery and adjuvant chemotherapy, propensity score matching was performed. In comparison to the adjuvant group, patients treated with NAC were younger, had higher-grade histology, and advanced clinical T stage, but less advanced N stage. Three-year OS was 74 percent in the T4b neoadjuvant cohort after a median follow-up of 3.6 years, compared to 66 percent following adjuvant chemotherapy (hazard ratio (HR) 0.7, 95 percent CI 0.56–0.87; p = 0.0002). After propensity score matching, this comparison remained statistically significant. There was no difference in survival between the T3 and T4a cohorts [6-8].

In 2019, data from the Netherlands Cancer Registry was used in a similar investigation. 149 patients with clinical T4 LACC treated with neoadjuvant chemotherapy were evaluated using propensity score matching. In contrast to the NCDB research, only 77 percent of those treated with NAC obtained R0 resection, compared to 86 percent of those treated with adjuvant chemotherapy (p=0.037).

Single-arm prospective studies

The feasibility of the NAC method in LACC has been tested in a number of prospective, single-arm investigations. If they had a KRAS, BRAF, or PIK3CA mutation, or if their mutational status was unknown, Jakobsen et al. enrolled 77 patients with high-risk T3/T4 colon cancer and assigned them to receive three cycles of CAPOX (capecitabine 2000 mg/m2 daily on days 1–14 and oxaliplatin 130 mg/m2 on day 1 every 3 weeks) if they had a KRAS, BRAF CAPOX with panitumumab was given to wildtype patients. Patients who would have received adjuvant chemotherapy based on pathologic response continued to receive CAPOX 5 rounds without panitumumab. They were observed if they were converted to a lower stage and did not fit the criteria for adjuvant treatment. The rate of conversion from a higher clinical-stage to a lower pathologic stage that no longer required adjuvant treatment was the primary goal. The wildtype group had a conversion rate of 42%, compared to 51% in individuals with a mutation, with three patients obtaining a complete response. The converted group had a 3-year DFS of 94 percent against 63 percent in the non-converted group (p = 0.0005). Liu et al. used a similar approach in a single-arm phase II trial assessing neoadjuvant CAPOX for patients with LACC shortly after. A total of 47 patients were enrolled, with 42 of them receiving two to four cycles of NAC (depending on response) prior to resection, followed by eight cycles of adjuvant chemotherapy. The overall clinical response rate was 70.7 percent, with one partial. response rate (PR) of 68.3 percent. Notably, three patients with perforation or obstruction required emergency surgery, but perioperative morbidity and death were modest. After the efficacy of triplet therapy with a fluoropyrimidine, irinotecan, and oxaliplatin in metastatic colorectal cancer was proven, a feasibility study in localised disease in the neoadjuvant setting was done. Twenty-three patients with stage IIIB colon cancer were given four cycles of FOLFOXIRI, then resection and either FOLFOXIRI or CAPOX for another six cycles. Tumor volume decrease was observed in 91.3 percent of patients (including one pCR), with 56.6 percent incurring grade 3–4 toxicities, albeit no significant surgical complications. One patient's surgery was delayed due to continued bone marrow suppression, while two patients progressed during neoadjuvant treatment. Because of toxicity, only 52.2 percent of patients completed all four cycles of neoadjuvant chemotherapy. The 2-year OS rate was 95.7 percent at a median follow-up duration of 28 months, with a 26.1 percent recurrence rate.

Therapy tailored to the individual

Immune checkpoint inhibition (ICPI) has been demonstrated to be effective in the treatment of metastatic colorectal cancer, and it was recently approved as a first-line treatment for patients with microsatellite instability "high" (MSI-H). Following results in other cancers, interest in using ICPI in the neoadjuvant setting for colon cancer has developed. Investigators recommended using ICPI in both dMMR and pMMR LAC in the exploratory NICHE project. They hypothesised that early stage pMMR colon cancer could be more effective than late stage because of the increased degree of T-cell infiltration in the former. Celecoxib was also added to the pMMR group, based on preclinical indications that it may work synergistically with ICPI and boost tumour-promoting inflammation. Patients were given a dual ICPI of ipilimumab (day 1) and nivolumab (days 1 and 15), followed by surgery six weeks after study consent. In this phase II trial, the key goals were safety and feasibility. The analysis included 20 dMMR patients and 20 pMMR patients out of a total of 21 dMMR and 20 pMMR patients. There were no delays in surgery, and adverse events were consistent with the medicines' reported side effect profiles. A pathologic response was observed in 100% of the dMMR cohort (60 percent had a pCR). A pathologic response was observed in 27% of the pMMR tumours (13 percent pCR). After resection, four patients (1 dMMR, 3 pMMR) received adjuvant chemotherapy. All dMMR patients were alive and well after a median follow-up of nine months. One pMMR patient had metastatic illness, which was treated with palliative chemotherapy, and another died unexpectedly. Patients are still being enrolled in this trial [8].

Conclusion

As more evidence becomes available, neoadjuvant chemotherapy will most certainly find a place in the treatment of locally advanced colon cancer. It will be required to use molecular characterization and radiographic response to figure out which populations are likely to benefit. It will also be critical to avoid operational delays in patients who have a low likelihood of responding to cytotoxic treatment. Outside of standard chemotherapy, combining innovative techniques with immunotherapy or other targeted drugs could provide considerable survival benefits, including a tailored approach. The generalizability of any of these techniques must be considered, particularly with a growing young adult cohort that may be suitable for treatment intensification and an elderly patient population that is older than the median age indicated in the aforementioned trials. With increased developments in diagnostic imaging, molecular characterisation, and clinical trial enrolment, neoadjuvant treatment of colon cancer has the potential to grow into a new standard of care.

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