Review

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Clinical Evidence for the Benefits of Neoadjuvant Chemotherapy and Immunotherapy in Colon Cancer: A Concise Review

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Neoadjuvant chemotherapy (NAC) has long been considered technically difficult in locally advanced colon cancer (LACC). However, the introduction of oxaliplatin-based regimens led to a growing interest in NAC for patients with LACC. Several cohort studies showed that NAC was safe and reduced the rate of incomplete resection in patients with LACC. This was followed by the pivotal phase III FOxTROT trials, which showed significant benefits of NAC in this population. However, in patients with deficient mismatch repair (dMMR), the response to a neoadjuvant fluoropyrimidine regimen may be poor, limiting the benefit of NAC in this subset of patients. Neoadjuvant immunotherapy is a potential alternative for NAC in LACC patients with dMMR. In this concise review, we present the published clinical evidence evaluating the efficacy and safety of NAC and/or neoadjuvant immunotherapy in patients with LACC. Overall, the evidence suggests that NAC can be associated with significant downstaging and tumor regression, which facilitate surgical resection. However, the impact of NAC on long-term survival is still under investigation. Despite the promising results of NAC in LACC, several concerns still exist that necessitate further evidence. On the other hand, LACC patients with dMMR can benefit from neoadjuvant immunotherapy; however, further trials are still needed to confirm its effectiveness, as well as biomarkers that can predict response.

Keywords: colon cancer; neoadjuvant; chemotherapy; immunotherapy; PD-1/PD-L blockade

Introduction

Patients with resectable locally advanced colon cancer (LACC) are at high risk of systemic recurrence. Thus, adjuvant chemotherapy, mainly fluoropyrimidine and oxaliplatin, has become the standard of care for LACC to reduce the risk of recurrence and improve overall survival (OS) [1–3]. A growing body of evidence recently suggested superior survival benefits of neoadjuvant chemotherapy (NAC) in solid malignancies [1,2]. With the introduction of oxaliplatin-based regimens, the interest in NAC benefits for LACC has grown, and several cohort studies demonstrated the safety and feasibility of NAC in LACC [4,5]. In the phase III FOxTROT trials, neoadjuvant FOLFOX [folinic acid (leucovorin), fluorouracil (5-FU), oxaliplatin] reduced the rate of incomplete resection and the risk of recurrence in patients with LACC [6,7].

Deficient mismatch repair (dMMR) presents in nearly 18% of patients with stage II-III colon cancer. Although LACC patients with dMMR exhibited better survival outcomes than patients with intact MMR [8], dMMR is associated with poor response to fluoropyrimidine therapy, limiting the benefit of NAC in this subset of patients [9]. Neoadjuvant immunotherapy is a potential alternative for NAC in LACC patients with dMMR. Phase II trials and cohort studies have shown promising results of neoadjuvant immunotherapy in patients with dMMR [10,11].

This concise review presents the published clinical evidence evaluating the efficacy and safety of NAC and/or neoadjuvant immunotherapy in patients with LACC.

The Rationale for Neoadjuvant Therapy—Chemotherapy or Immunotherapy

Previous animal models showed that tumor resection induces the release of growth-stimulating factors, leading to the proliferation and invasiveness of residual tumor cells. In return, tumor resection can potentially increase the risk of recurrence and micro-metastasis [12]. Post-resection residual tumor cell proliferation and vascularity were increased in human colorectal cancer (CRC) samples after resection [13]. Interestingly, pre-resection chemotherapy was found to inhibit residual tumor cell proliferation and induce an antitumor immune response [14,15]. NAC can induce tumor regression/downstaging, decrease the number of post-resection viable tumor cells, and, subsequently, re-

duce the risk of post-resection local and distant micrometastasis [16]. NAC reduced the pre-resection tumor burden in rectal and breast cancers, which is a significant predictor of recurrence [17–19]. NAC-induced downstaging may also increase the probability of complete resection and lead to less intraoperative tumor shedding [20].

Patients with resectable tumors are usually fit before surgery and have a high chance of receiving a full NAC regimen. The administration of NAC may lower the number of required cycles of adjuvant chemotherapy and increase the probability of complete administration of adjuvant systemic therapy. Additionally, NAC-induced downstaging may allow for laparoscopic resection, leading to a lower risk of postoperative complications and a shorter hospital stay [4,20]. Response to NAC could potentially result in the requirement for a reduced dose of subsequent systemic therapy, thereby enhancing patient compliance [21]. NAC allows for proper assessment of pathological response and a better understanding of tumor biology, optimizing the selection of subsequent adjuvant systemic therapy [20].

Despite the potential advantages of NAC in LACC patients, the effect of NAC does not appear to be uniform across all LACC populations. Nearly 18% of the patients with LACC present with dMMR, which predicts poor response to fluoropyrimidine therapy [22]. The efficacy of neoadjuvant oxaliplatin-based chemotherapy in dMMR patients remains questionable [9]. In the FOxTROT trial, the pathological response was noted in only 7% of the patients with dMMR [7]. In these patients, neoadjuvant immunotherapy was proposed to improve the survival benefits. LACC patients with dMMR showed a higher CD8 cytotoxic T cells population with upregulated programmed death-1 (PD-1) checkpoints and tumor mutation burden (TMB) than other subsets of LACC patients. In the metastatic setting, PD-1/PD-L1 (programmed death-ligand 1) inhibitors showed promising results in patients with dMMR [23]. In return, NAC immunotherapy has gained momentum recently for LACC patients harboring dMMR.

Clinical Evidence for Neoadjuvant Chemotherapy

The quest for assessing the clinical benefits of NAC in LACC (Table 1, Ref. [4,5,10,11,16,24–31]) started in 2013 when Arredondo *et al*. [32] reported that four cycles of neoadjuvant capecitabine plus oxaliplatin (CAPOX) led to radiological responses and a median tumor volume reduction (TVR) of 62.5% in 22 patients with LACC. The NAC regimen was safe in all patients, and no surgical delays were reported. The same group published their updated experience in 2017 after adding the data of additional 43 patients (some patients received FOLFOX), which showed a similar rate of TVR (62.5%) and a pathological complete response (pCR) of 5% [16]. A more recent chart review of the Danish Colorectal Cancer Group Database showed that NAC was associated with significantly higher rates of R0 (86% vs. 81%) and pathological N0 (51% vs. 46%) [5]. In Zeng *et al*. [24] retrospective study, NAC led to a significant reduction in tumor size, downstaging of the tumor, and a significant or complete response in 14.4% of the patients.

The encouraging results of the retrospective studies led to the conduction of single-arm and randomized controlled trials (RCTs) investigating the role of NAC in LACC. In a phase II trial of 42 LACC patients who completed at least two cycles of CAPOX before surgery followed by adjuvant chemotherapy, a partial response (PR) was observed in 68% and a pCR in one patient. At least moderate tumor regression grade (TRG) was observed in 62% of the patients, and all patients underwent R0 resection. The NAC was generally well-tolerable, with four patients only reporting grade 3 toxicities and no reported mortalities [25]. A similar finding was demonstrated in a phase II trial by Jakobsen *et al*. [33]. However, in Jakobsen *et al*. [33], the CAPOX regimen was supplemented by panitumumab; the conversion rate was higher in patients with *RAS* (Rat sarcoma), *BRAF* (B-Rapidly Accelerated Fibrosarcoma), and *PIK3CA* (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha) mutations than wild-type group (51% vs 42%).

The addition of irinotecan to the standard FOLFOX (triplet FOLFOXIRI (5-FU + folinic acid + oxaliplatin + irinotecan) regimen) was investigated in a phase II trial, which included 23 patients with stage IIIb colon cancer; the patients received four cycles of neoadjuvant FOLFOXIRI, followed by adjuvant FOLFOXIRI or CAPOX for six cycles. The rate of TVR was 91%, with one patient experiencing pCR. Two patients showed progression during the NAC, and one had delayed surgery due to bone marrow suppression. The safety profile NAC was well-manageable, despite the high rate of grade 3/4 toxicities (57%) [26].

To date, two published RCTs reported the outcomes of NAC in LACC. The PRODIGE 22–ECKINOXE was a phase II open-label RCT that compared four cycles of neoadjuvant FOLFOX followed by resection and eight cycles of adjuvant FOLFOX versus resection and adjuvant FOLFOX only in LACC patients. Cetuximab was administered in the neoadjuvant group in RAS wild-type patients, but it was stopped later due to the high rate of postoperative morbidity. The rate of major and significant tumor regression was 44% in the NAC group compared to 8% in the control group ($p < 0.001$). However, the rate of major pathological regression was only 8% in the NAC group. Thus, even though the study confirmed the safety of NAC, it did not show a meaningful difference in pathological response between NAC and adjuvant settings [27].

The FOxTROT phase III trial compared three cycles of neoadjuvant FOLFOX followed by resection and nine cycles of FOLFOX to resection and adjuvant FOLFOX on

Table 1. Findings of pivotal trials and retrospective studies of the effectiveness and safety of neoadjuvant chemotherapy and immunotherapy in locally-advanced colorectal cancer.

Author, Year	Design	Mutations type and %	Neoadjuvant therapy	No.	Pathologic response	pCR	R0 resection rate	Down-staging rate	TRG	Reductions in tumor volume, Mean	OS rate	Grade 3–4 AE%
Chemotherapy												
Arredondo, 2017 [16]	Retro	NR	CAPOX or FOLFOX	65	3 (4.6)	3 (4.6)	65 (100)	22 (33.9)	Grade 0, 1, 2 (63.1) Grade 3 (23.1) Grade 3+, 4 (13.8)	62.5%	Five-year actuarial OS was 95.3 %	NR
de Gooyer, 2020 [4]	Retro	NR	-	192	8 (4.2)	8 (4.2)	150 (78.1)	88 (45.8)	NR	NR	5-year overall survival was 67%	NR
Laursen, 2022 [5]	Retro	NR	-	179	4 (2.4)	4 (2.4)	118 (86)	28 (15.6)	NR	NR	NR	Post-op
Zeng, 2022 [24]	Retro	NR	Neoadjuvant CT	42	2 (4.8)	2 (4.8)	40 (95.24)	4 (9.5)	NR	NR	5-year overall survival rate was 88.1%	4 (9.52)
Zhou, 2016 [26]	Phase II	NR	FOLFOXIRI or XELOX	23	1 (4.348)	1 (4.348)	20 (86.957)	21 (91.3)	Grade 1 = 1 (4.348) Grade 2 = 7 (30.435) Grade 3 = 9 (39.13) Grade 4 = 5 (21.739) Grade 5 = 1 (4.348)	52.9 (SD = 20.3)	2-year OS rate is 95.7%	13 (56.5)
Liu, 2016 [25]	Phase II	NR	CAPOX	47	32 (68)	1 (2)	47 (100)	8 (17)	Grade = 0–1 (2) Grade 1 = 2 (4) TRG 2 29 (62) TRG 3 15 (32)	NR	NR	4 (9)
PRODIGE 22 [27]	Phase II RCT	NR	FOLFOX	52	8%	NR	94%	16 (33)	TRG 1–2 = 44%	NR	3-year OS 90.4%	NR
FOxTROT [28]	Phase III RCT	NR	FOLFOX	698	NR	25 (4%)	648 (94%)	35 (10)	Complete response = 24 (4%), marked, moderate, or mild regression = 412 (62%)	NR	NR	NR
Immunotherapy												
Chalabi, 2020 (NICHE) [29]	Phase II	dMMR (57.14)	dMMR/pMMR: Preoperative ipilimumab; nivolumab pMMR: Preoperative ipilimumab; nivolumab; celecoxib	20 15	20 (100) 4 (27)	12 (60) 3 (20)	100	NR NR	NR	NR	NR	Treatment related A.Es = 5 (12) Surgery related A.Es = 8 (20)

Table 1. Continued.

Author, Year	Design	Mutations type and %	Neoadjuvant therapy	No.	Pathologic response	pCR	R0 resection rate	Down-staging rate	TRG	Reductions in tumor volume, Mean	OS rate	Grade 3–4 AE%
Avallon, 2020 (NICOLE) [30]	Phase II	dMMR (13.636)	Preoperative nivolumab	3	0	0	NR	NR	NR	NR	NR	1 (4.5)
Pei, 2023 [11]	Retro	dMMR (100)	Preoperative PD-1 monoclonal antibody	10	10 (100)	9 (90)	NR	7 (70)	Grade 0 = 9 (90) Grade 1 = 1 (10)	NR	Disease Free Survival (days), mean (SD) = 314.6 (225.369)	0
Zhang, 2022 [31]	Retro	dMMR-MSI-H (100)	Preoperative pembrolizumab, sintilimab, or tiselizumab	24	22 (91.7)	17 (70.8)	24 (100)		Grade 1 = 3 (12.5) Grade 2 = 2 (8.3) Grade 3 = 0	NR	NR	0
Hu, 2022 [10]	Phase II	NR	Preoperative toripalimab + celecoxib	17	NR	15 (88)	34 (100)	NR	NR	NR	NR	1 (5.88)
			Preoperative toripalimab	17	NR	11 (65)		NR	NR	NR	NR	1 (5.88)

Retro, retrospective; NR, not reported; CAPOX, capecitabine plus oxaliplatin; FOLFOX, folinic acid (leucovorin), fluorouracil (5-FU), oxaliplatin; No., number; pCR, pathologic complete response; R0, No residual cancer; TRG, tumor regression grade; OS, overall survival; AE, adverse events; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair; CT, chemotherapy; SD, standard deviation; RCT, randomized controlled trial; PD-1, programmed death-1; MSI-H, microsatellite instability-high; FOLFOXIRI, 5-FU + folinic acid + oxaliplatin + irinotecan; XELOX, oxaliplatin and capecitabine.

Table 2. Ongoing trials of neoadjuvant chemotherapy and immunotherapy in locally-advanced colorectal cancer.

Reg No.	NAC/Neoadjuvant immunotherapy	Population	Phase	Accrual goal	Location	Primary endpoint
NCT03125980	CAPOX ×4	LACC	III	1370	China	3-year DFS
NCT03426904	FOLFOX ×4	LACC	III	560	Korea	RFS
NCT01918527	CAPOX ×3	LACC	III	250	Europe	2-year DFS
NCT02972541 (NACSOC)	FOLFOX ×3 or CAPOX ×2	LACC	II	248	China	DFS
NCT04188158 (ELECLA)	CAPOX ×3	LACC	II	238	Spain	2-year DFS
NCT01675999 (ECKINOXE)	FOLFOX ×4 ± cetuximab	LACC	II	186	France	Tumor response by TRG
NCT03484195	FOLFOXIRI ×4	LACC	II	30	China	Tumor downstaging
NCT03026140 (NICHE)	Ipilimumab + nivolumab ± celecoxib	Stages I–III CC	II	60	Netherlands	Safety
NCT04231526	Pembrolizumab	LACC	II	46	USA	Feasibility
NCT03985891	toripalimab + FOLFOX ×6	LACC	I/II	40	China	pCR rate

NAC, neoadjuvant chemotherapy; CAPOX, capecitabine plus oxaliplatin; LACC, locally advanced colon cancer; DFS, disease-free survival; FOLFOX, 5-fluorouracil+folinic acid + oxaliplatin; RFS, relapse-free survival; TRG, tumor regression grade; CC, colon cancer; pCR, pathologic complete response; FOLFOXIRI, 5-FU + folinic acid + oxaliplatin + irinotecan.

-ly. Patients with *KRAS*-wild LACC received panitumumab as well. The trial design also allowed the investigators to replace 5-FU with capecitabine in elderly or intermediate-risk patients. The mature analysis showed the rate of downstaging and R0 resection was significantly higher in the NAC arm than in the control group. The R0 rate was 94% in the NAC versus 89% in the control group. A numerically lower 2-year failure rate was noted in the NAC than in adjuvant chemotherapy (16.9% vs. 21.5%) [28].

Currently, pathological and clinical responses are the main endpoints of the trials investigating NAC due to the short median follow-up. In the updated analysis of the PRODIGE 22 trial, the three-year OS, disease-free survival (DFS), and recurrence-free survival (RFS) were 90.4%, 76.8%, and 73%, respectively; these figures were not significantly different from the adjuvant group [34]. While the phase II trial by Jakobsen *et al*. [33] showed a three-year DFS of 94% and 63% in the patients with mutations and the wild-type group, respectively. The triplet FOLFOXIRI regimen showed a 2-year OS of 95.7%, with a 2-year recurrence rate of 26.1% [26]. In Zeng *et al*. [24] retrospective study, the 5-year OS and DFS were 88.1% and 75.1%. Notably, the 5-year rate of distant recurrence was significantly lower in the NAC group than in the adjuvant group (9.6% vs. 29.9%). In Arredondo *et al*. [16] retrospective review, the five-year OS was 95%.

To sum up, two recent meta-analyses investigated the safety and benefits of NAC in LACC. The pooled analyses showed that NAC was safe and showed a trend towards oncological benefits for downstaging and R0 resection rate. Patients on NAC had significantly higher rate of R0 resection higher R0 resection rates in both meta-analyses (odds ratio [OR] 2.35, 95% CI: 1.04–5.32 and relative risk [RR] = 0.47) were observed in the NAC group. However, the NAC was not associated with better OS (Hazard ratio [HR]: 0.90, 95% CI: 0.66–1.23) than adjuvant chemotherapy [35,36].

Clinical Evidence for Neoadjuvant Immunotherapy

Adjuvant chemotherapy remains the standard of care for LACC patients. However, as mentioned before, the efficacy of adjuvant fluoropyrimidine-based therapy may be limited in patients with dMMR. Several clinical trials investigated the efficacy of adjuvant immune checkpoint inhibitors in patients with localized dMMR colon cancer [37]. Emerging evidence also investigated the feasibility and effectiveness of neoadjuvant immunotherapy (Table 1).

The phase II NICHE study investigated the benefits of neoadjuvant ipilimumab plus nivolumab, with or without celecoxib, in patients with early-stage colon cancer. The results showed that the rates of major pathological response and pCR were 95% and 60% in dMMR patients, respectively, compared to 20% and 0% in proficient MMR (pMMR) patients. The trial also showed that treatment was well-tolerated, with no reported cases of surgical delay [29]. The phase II NICOLE trial evaluated neoadjuvant nivolumab in 22 patients with early colon cancer (three patients had dMMR). The treatment was safe in all cases, with no surgical delays or complications. The rate of major pathological responses was 15.6% in pMMR cases, compared to no response in the three dMMR cases [30]. Another phase II study on dMMR CRC patients reported a pCR of 90.9% following neoadjuvant PD-1 blockade. More recently, an open-label phase II trial compared neoadjuvant toripalimab with celecoxib versus toripalimab monotherapy in CRC patients with dMMR/MSI (microsatellite instability)-high. The neoadjuvant toripalimab was well-tolerable, and the R0 resection was achieved in all patients. Besides, the rates of pCR were 88% and 65% in the combination and monotherapy groups, respectively [10].

Zhang *et al*. [31] assessed the real-world safety and effectiveness of a neoadjuvant single-agent PD-1 inhibitor in 24 patients with locally advanced CRC and dMMR/MSI-high. Of them, 22 patients achieved a pathological response, and 17 achieved pCR. Additionally, the rate of R0 resection was 100%. The neoadjuvant strategy was well-tolerable, with no incidence of grade 3/4 toxicities.

More recently, there has been a growing interest in the use of neoadjuvant immunotherapy combined with NAC. In Kothari *et al*. [38], four patients received chemotherapy before neoadjuvant immunotherapy and achieved pCR. In Liu *et al*. [39], immunotherapy combined with NAC led to pCR and major pathological response rates of 35.3% and 58.8% (40/68), respectively. Still, further trials are needed to assess the feasibility and effectiveness of combined neoadjuvant immunotherapy and chemotherapy in LACC.

In summary, exploring neoadjuvant immunotherapy in LACC patients with dMMR has shown promise in early-phase clinical trials and real-world studies. Overall, the evidence increasingly supports neoadjuvant immunotherapy as a safe, tolerable, and potentially effective treatment strategy for LACC patients with dMMR.

Challenges and Limitations

As described above, cohort studies and clinical trials suggest the oncological benefits of NAC in LACC; however, several considerations and concerns are associated with applying NAC in clinical practice. Inaccurate assessment of radiological response has been described in clinical practice, which can lead to overtreatment due to underestimated response. In PRODIGE 22, 33% of the patients in the adjuvant arm were found to have a lower stage after resection, reflecting that these patients could have been overtreated with NAC [27]. Although positron emission tomography (PET) can improve radiological assessment, limited data are available regarding its accuracy in LACC [40]. The lack of a highly accurate preoperative staging system may preclude the wide adoption of NAC in clinical practice.

Data regarding the feasibility of NAC in elderly patients are unavailable, and this should be studied further. Previous population-based studies showed that the elderly were less likely to receive and tolerate adjuvant oxaliplatin-based chemotherapy, which is the currently utilized NAC regimen [41,42]. The concern with neoadjuvant oxaliplatin-based chemotherapy also extends to patients with comorbidities; comorbidities (such as diabetes and alcohol use) were found to increase the risk of oxaliplatin-associated neuropathy in some cohorts, though these findings are inconclusive [43]. The feasibility of NAC in LACC patients with comorbidities is still unknown, particularly given that only patients with relatively normal renal and hepatic functions were included in the FOxTROT trial.

Alongside the risk of overtreatment and lack of data in special populations, the risk of preoperative progression is another concern in adopting NAC. However, the low rate of incomplete surgical resection in the published studies (Table 1) assures a low chance of significant preoperative progression. Lastly, the readiness of the healthcare system to adopt NAC in clinical practice is questionable due to the need to adopt an enhanced referral system for clinical oncologists before surgery [44].

Conclusion and Future Directions

NAC appears to be feasible and safe in LACC patients. It can be associated with significant downstaging and tumor regression, which facilitate surgical resection and potentially improve DFS. However, the impact of NAC on long-term survival is still under investigation. Despite the promising results of NAC in LACC, several concerns still exist that necessitate further evidence.

On the other hand, LACC patients with dMMR can benefit from neoadjuvant immunotherapy. Several ongoing trials are investigating the feasibility and effectiveness of neoadjuvant immunotherapy in LACC patients with dMMR. Initial results suggested that neoadjuvant immunotherapy was associated with high rates of pCR, with no surgical delays or high incidence of major complications, in dMMR patients. Further trials are still needed to confirm its effectiveness, as well as biomarkers that can predict response.

Several trials are ongoing to investigate the effectiveness and safety of different NAC and neoadjuvant immunotherapy regimens in LACC (Table 2). Ongoing trials are evaluating neoadjuvant FOLFOX, capecitabine plus oxaliplatin, ipilimumab plus nivolumab, and pembrolizumab in LACC. The triplet FOLFOXIRI regimen is currently under investigation in a phase II trial that utilizes PET scans and circulating tumor DNA to assess treatment response (NCT03484195). The ECKINOXE is also assessing the effectiveness of NAC plus cetuximab in LACC patients. Interestingly, a phase I/II trial is currently evaluating the response to neoadjuvant toripalimab plus FOLFOX (NCT03985891). In early-phase trials, immunomodulation using anticancer vaccines and chimeric antigen–receptor T cells is also being investigated as neoadjuvant therapy (NCT0382796). Neoadjuvant chemoradiotherapy is another area of interest, which has shown promising results in a small cohort study [45], an ongoing phase III trial (NCT03970694).

Author Contributions

KG performed the research, drafting, and editing of the manuscript. AE and EP conducted the research and performed the drafting and editing of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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