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Mini Review Open Access

Neoadjuvant Treatment for Locally Advanced Colon Cancer

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Abstract

With the development of surgical techniques and implementation of adjuvant chemotherapy, the outcomes for patients with locally advanced colon cancer are improved. The necessity of neoadjuvant treatment has led to increasing interest. This Mini review summarizes the progress in neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy.

Keywords: Neoadjuvant chemoradiotherapy; Neoadjuvant chemotherapy; Locally advanced colon cancer

Introduction

Neoadjuvant treatment has displayed beneficial effect in several cancers and now forms part of the standard treatment in e.g. breast, rectal, esophageal, and gastric cancer, but it has not been systematically explored in colon cancer [1-4]. High-risk locally advanced colon cancer patients (stage T4 or T3 with ≥ 5 mm tumour invasion beyond the muscularis propria) have a 53% 3-year recurrence-free survival as compared to 87% in the good (T1/T2) or intermediate (T3 and<5 mm tumour invasion beyond the muscularis propria) prognostic groups [5]. This raises one issue that whether the neoadjuvant treatment should be applied in high-risk locally advanced colon cancer. This review will cover neoadjuvant chemoradiotherapy and chemotherapy.

Neoadjuvant chemoradiotherapy (NCRT)

Resection of locally advanced colon cancer e.g. T4 tumor remains challenging as compared with lower T stages. A paucity of data about the effect of NCRT on T4 colon cancer has been published. A prospective study from China investigated the feasibility and efficacy of NCRT followed by surgery for patients with unresectable locally advanced sigmoid colon cancer [6]. Twenty-one patients were recruited and received external beam radiotherapy to 50 Gy and capecitabine-based chemotherapy every 3 weeks, followed by surgery at an interval of 6-8 weeks. All patients conducted NCRT and surgery. The R0 resection (resection with microscopically negative margins) was observed in 20 patients (95.2%). Pathologic complete response was observed in 8 patients (38.1%). The cumulative probability of 3-year overall survival (95.2%) was achieved for all 21 patients with well-preserved bladder function. For patients with unresectable locally advanced sigmoid colon cancer, NCRT followed by surgery can be performed safely and may improve the 3-year survival rate.

Krishnamurty et al. conducted a study to determine the effect of NCRT on outcomes for resected clinical T4, non-metastatic colon cancer [7]. One hundred and thirty-one patients were included and 23 (17.4%) received NCRT. NCRT group showed non-statistically significant improvement in R0 resection rate (NCRT 95.7% vs non-NCRT 88.0%; p=0.27) and local recurrence (NCRT 4.3% vs non-NRT 15.7%; p=0.15) when compared to non-NCRT group. There was a significant difference in T-stage downstaging between these two groups (NCRT 30.4% vs non-NCRT 6.5%; p=0.007). In a multivariable analysis, improved overall survival for NCRT group was not significant.

Whether the down-stage impact of NCRT on patients with clinical T4 colon cancer can be translated to the survival benefit remains still unclear, and further phase III randomized trials are needed (Table 1).

Neoadjuvant chemotherapy (NCT)

The current stand of care for locally advanced colon cancer (high risk stage II and stage III) is curative surgery followed by adjuvant chemotherapy. However, 30% to 40% of these patients suffer from local recurrences or distant metastases. Based on the potential effects of NCT on clearing micrometastases and lowering the recurrence in rectal cancer, a small amount of trials has been conducted to investigate the role of NCT in locally advanced colon cancer.

A phase II trial from Denmark showed that high-risk colon cancer patients (n=77) with histopathological verification of adenocarcinoma, T3 tumor on CT scan with extramural depth of tumor invasion more than 5 mm or T4 tumor received 3 cycles of CAPOX (KRAS, BRAF or PIK3CA mutation or unknown mutational status) or CAPOX + panitumumab (KRAS, BRAF or PIK3CA wild-type) [5]. After the operation, patients were categorized into two groups including omitting adjuvant chemotherapy group (converted patients) and adjuvant chemotherapy group (unconverted patients) based on the criteria for pathological high-risk stage II and III. The primary endpoint was the percentage of converted patients. Secondary endpoints involved recurrence rate, 3-year disease-free survival (DFS), and toxicity. The cumulative recurrence rate was 6% in converted versus 32% in unconverted patients (p=0.005) translating into a 3-year DFS benefit with 94% versus 63% (p=0.005). Adding panitumumab to CAPOX resulted in a worse outcome as that demonstrated by data from the New EPOC study [8]. This study raised the concept of "less treatment, better results".

The French phase II randomized trial PRODIGE 22-ECKINOXE was displayed in 2017 ESMO annual meeting, which aimed to compare neoadjuvant FOLFOX4 versus FOLFOX4 with cetuximab (dropping of cetuximab arm based upon lack of tumor regression grade (TRG)

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Country, Year	Published Journal	No. of patients	Study Arm	Notes	References
China, 2016	Chin J Cancer	21	NCRT	3-y OS: 95.2%; R0 rate: 95.20%; pCR: 38.1%	[6]
USA, 2018	J Gastrointest Surg	131	NCRT	5-y OS: 76.4%; R0 rate: 95.70%	[7]
			Non-NCRT	5-y OS: 51.5%; R0 rate: 88.00%	
Denmark, 2015	Acta Oncol	77	Converted patients	3-y DFS: 94%	[5]
			Unconverted patients	3-y DFS: 63%	
France, 2015	2017 ESMO Congress	120	FOLFOX4	TRG 1-2: 44.2%	[9]
			FOLFOX4+Cetuximab	TRG 1-2: 6.3%	
			Immediate surgery	TRG 1-2: 7.7%	
UK, 2012	Lancet Oncol	150	Preoperative chemo	APN+: 1%; RM+: 4%	[10]
			Postoperative chemo	APN+: 20%; RM+: 20%	

Note: OS: Overall Survival; pCR: Pathologic Complete Response; DFS: Disease Free Survival; TRG: Tumor Regression Grade; APN+: Apical Node Positive; RM+: Resection Margin Involvement

Table 1: Clinical trials of neoadjuvant treatment for colon cancer.

from 13 patients) versus upfront surgery in locally advanced colon cancer [9]. The primary endpoint was tumor response (Ryan TRG system). Although this study failed to meet the primary endpoint that neoadjuvant FOLFOX4 was not associated with major histological response (TRG1), it resulted in significant tumor regression as compared to immediate surgery (TRG 1-2: 44.2% vs. 7.7% $p<0.001$).

Discussion

Early in 2012, the priliminary data of 150 colon patients recruited in the pilot FOxTROT trial was published in Lancet [10]. Oncology, which aimed to investigate the feasibility, safety, and efficacy of preoperative chemotherapy for high-risk (T3 with ≥ 5 mm invasion beyond the muscularis propria or T4) colon cancer patients. In the pilot study, patients were randomly assigned (2:1) to preoperative (three cycles of OxMdG [oxaliplatin 85 mg/m^2, l-folinic acid 175 mg, fluorouracil 400 mg/m^2 bolus, then 2400 mg/m^2 by 46 h infusion] every 2 weeks followed by surgery and a further nine cycles of OxMdG) or standard postoperative chemotherapy (12 cycles of OxMdG). Compared with the postoperative group, significant downstaging of T or N was observed in preoperative therapy group ($p=0.04$) including two pathological complete responses, apical node positivness (1% [one of 98] vs 20% [ten of 50], $p<0.0001$), resection margin involvement (4% [four of 99] vs 20% [ten of 50], $p=0.002$), and blinded centrally scored tumour regression grading: 31% (29 of 94) vs 2% (one of 46) moderate or greater regression ($p=0·0001$). The study has proceeded to the phase III trial, to explore whether the encouraging pathological responses seen with preoperative therapy translates into improved long-term survival benefit. The 2018 ESMO annual meeting reported the interim data for phase III FOxTROT trial, for instance, excellent safety profile, significant downstaging of primary disease and lymph nodes, a good response to chemotherapy in about 30% cases. Three-year DFS and five-year OS are now awaited.

Another study from Memorial Sloan Kettering Cancer Center (MSKCC) showed that CT colonography (CTC) in preoperative staging of colon cancer might be a feasible imaging modality for evaluation of FOxTROT inclusion criteria for neoadjuvant therapy [11]. Totally, NCT performed in patients with high-risk stage II and stage III colon cancer highly selected by CTC-based assay could remarkably downstage tumor. However, the survival data were immature.

Conclusion

Taken together, accumulated evidences have suggested that neoadjuvant treatment for locally advanced colon cancer results in significant downstaging of tumor with immature DFS and OS data. When searched Medline and Embase for the MeSH and free terms: “neoadjuvant” and “locally advanced colon cancer”, 25 studies including some Chinese ongoing trials were found. If preoperative therapy results in fewer recurrences, as well as tumor downstaging and better survival, the established pathway of surgery then chemotherapy in the management of colon cancer could potentially change.

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