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REVIEW ARTICLE

Evolution of Neoadjuvant Chemoirradiation in Rectal Cancer

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ABSTRACT

The treatment of rectal cancer is evolving and it nicely demonstrates the beauty of multimodality treatment. Unlike total mesorectal excision in surgery, which has probably marked the climax in the advancement of surgical treatment of rectal cancer, neoadjuvant chemoirradiation has an ever-expanding role. Based on the success of neoadjuvant 5-fluorouracil chemoirradiation, the use of capecitabine in the same setting has proven to be an equivalent, if not better, option. However, the improvement in local control has not been convincingly translated into survival benefit, and patients continue to die of distant metastasis. To tackle this problem, various approaches to intensifying systemic treatment have been tested in phase 3 clinical trials. Unfortunately, the addition of oxaliplatin or cetuximab has not shown early promise. Whether novel use of induction chemotherapy will provide additional benefit is also not known at this time. This article serves to review the available evidence and to speculate on the best strategy for treatment of rectal cancer.

Key Words: *Induction chemotherapy; Neoadjuvant therapy; Oxaliplatin; Rectal neoplasms*

中文摘要

新輔助放射化療治理直腸癌的演變

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直腸癌的治療正在不斷發展，這些治療體現了綜合治療的好處。全直腸繫膜切除手術標誌著手術治療直腸癌的極點。與全直腸繫膜切除手術不同，新輔助放射治療結合化療治理直腸癌有不斷擴展的空間。藉著新輔助5-fluorouracil化療結合放射治療的成功，利用capecitabine在同一環境下作化療的成效已證明有過之而無不及。可惜的是，改良了的局部控制並不代表能提高病人存活率，直腸癌患者仍然因遠處轉移癌而死亡。為解決這問題，在第三期臨床試驗中實施了針對全身治療的不同方案。可是，新增的oxaliplatin或cetuximab還是不能改善情況。使用誘導化療是否能提供額外的好處到目前為止仍是未知之數。本文回顧現有的實證，並推斷治療直腸癌的最佳策略。

INTRODUCTION

Nearly 1700 cases of rectal cancer are diagnosed every year in Hong Kong and the disease causes more than 500 deaths.[1] Most patients present with locally advanced disease and neoadjuvant chemoirradiation represents the standard of care, but a survival benefit has not been convincingly demonstrated.[2-5] Moreover, around 30% of radically treated patients will eventually develop distant metastasis and die from the disease. It is with this background that not only are new

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agents needed but also novel treatment strategies are warranted.

CAPECITABINE WITH CONCURRENT RADIOTHERAPY

Continuous intravenous infusion of 5-fluorouracil (5-FU) has been shown to be superior to bolus injection in terms of efficacy[6] and toxicity,[7] but this method of administration is inconvenient. Capecitabine offers a convenient route of administration as an orally bioavailable fluoropyrimidine derivative. Capecitabine is converted into fluorouracil through multiple enzymatic steps, the last of which is mediated by thymidine phosphorylase. The high concentration of thymidine phosphorylase is central to the preferential activation of capecitabine in tumour tissue. Studies have shown that a significantly higher concentration of fluorouracil is present in tumour tissue than in normal tissue with the use of capecitabine.[8-10] In both the adjuvant and metastatic setting, capecitabine has been shown to be at least equivalent to, if not better than, 5-FU for the treatment of colorectal cancer.[11,12] Compared with 5-FU, capecitabine also has a more pronounced additive effect with radiotherapy, and this may be explained by the fact that the activity of thymidine phosphorylase is upregulated by radiotherapy.[13]

The results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 Intergroup study[14] and the MARGIT study[15] provide strong evidence for the use of capecitabine in clinical practice. The NSABP R-04 study is a four-arm study that included the comparison of capecitabine and 5-FU as one of the study objectives. Capecitabine 825 mg/m^2 was given for five days every week in conjunction with radiotherapy. The interim results showed that both chemotherapy drugs achieved similar rates of pathologically complete response (18.8% vs. 22.2%; p = 0.12), sphincter-saving surgery (61.2% vs. 62.7%; p = 0.59), surgical downstaging (20.7% vs. 23.0%; p = 0.62), and grade 3/4 diarrhoea (12.2% vs. 10.8%; p = 0.86).[14] The result for addition of oxaliplatin will be discussed in another section of this review.

The MARGIT study[15] started in 2002 and was initially designed to compare capecitabine with 5-FU with adjuvant chemoirradiation for stage II-III rectal adenocarcinoma. However, the protocol was amended after the results of the German Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the German Cancer Society (CAO/ARO/AIO)-94 study[2] were published, such that a neoadjuvant cohort was allowed. The primary endpoint was overall survival (OS), and non-inferiority of capecitabine in terms of the five-year OS was tested with a 12.5% margin. In the neoadjuvant cohort, patients received capecitabine 825 mg/m^2 twice daily, including weekends, throughout the course of radiotherapy (50.4 Gy/28 fractions for 5 days per week), and an additional five cycles of capecitabine 1250 mg/m^2 twice daily from days 1 to 14 every 21 days were given after surgery. The regimen used in the CAO/ARO/AIO-94 study comprised the treatment for the control arm. After a median follow-up of 52 months, the five-year OS of the capecitabine group was non-inferior to that of the 5-FU group and an exploratory post-hoc test for superiority favoured capecitabine (p = 0.05). Better survival was shown in both the adjuvant (81% [95% confidence interval (CI), 71-78] vs. 71% [95% CI, 60-79]) and the neoadjuvant (66% [95% CI, 46-81] vs. 61% [95% CI, 46-73]) cohorts, while the difference in cohort effect was not statistically significant. Despite a similar rate of local recurrence (6% vs. 7%; p = 0.67), the use of capecitabine resulted in a significant reduction in the rate of distant metastasis (19% vs. 28%; p = 0.04) compared with patients in the 5-FU group, and more patients in the capecitabine group achieved pathologically complete response (ypCR) [14% vs. 5%; p = 0.09] and ypT-downstaging (55% vs. 39%; p = 0.06). Concerning toxicity, more hand-foot syndrome, proctitis, and fatigue were seen with capecitabine while more leukopenia were seen with 5-FU.[15]

In the neoadjuvant chemoirradiation of rectal cancer, capecitabine is an active agent with favourable toxicity profile and convenient route of administration. Whether it should be given five days per week or throughout the whole period of radiotherapy is quite empirical as both schedules are supported by data from phase I studies.[16,17] Nevertheless, its potential to reduce distant metastasis and improve survival made it a promising substitute for 5-FU in both daily practice and future clinical trials.

ADDITION OF OXALIPLATIN

The addition of oxaliplatin to existing chemoirradiation regimens carried high expectation for several reasons. Firstly it has shown activity in both adjuvant and metastatic setting for colorectal cancer.[18-20] Secondly, preclinical studies have demonstrated its radiosensitising activity as well as its synergism with 5-FU against colon cancer cells.[21,22] Subsequently, four major phase III randomised multicentre clinical trials

studied the clinical benefit of adding oxaliplatin to fluoropyrimidine-based chemoirradiation. The Table summarises phase III clinical trials using oxaliplatin concurrent with radiotherapy.

In the Action Clinique COordonnées en Cancérologie Digestive (ACCORD) 12/0405 Partenariat de Recherche en Oncologie Digestive (PRODIGE) 2 study, 598 patients with T3 or resectable T4 rectal cancer were enrolled.[23] The primary endpoint was rate of ypCR. The treatment in the control arm, also known as 'CAP 45', comprised capecitabine 800 mg/m^2 twice daily for five days every week with concurrent radiotherapy of 45 Gy in 25 daily fractions. In the experimental arm, also known as 'CAPOX 50', the same schedule of capecitabine was given with five-weekly doses of oxaliplatin 50 mg/m^2, which were administered concurrently with radiotherapy 50 Gy in 25 daily fractions. The study not only failed to meet its primary endpoint of increased rate of ypCR, but also resulted in a significantly increased rate of grade 3/4 toxicity. The rate of grade 3/4 diarrhoea was 12.6% with CAPOX 50 and 3.2% with CAP 45.[23]

Although the primary endpoint of increased rate of ypCR was not achieved, further analysis showed that the tumour response was more favourable in the experimental arm. With the addition of oxaliplatin, more patients achieved ypCR or pathologically few residual cells (39.4% vs. 28.9%; p = 0.008). However, the interpretation of the result is not straightforward since the benefit of intensification of both radiotherapy and chemotherapy were tested in the same setting. It should be noted that the 50 Gy/25 fractions/5 weeks regimen represented a dose increase of 15%, using the linear quadratic formula and an α/β ratio of 4 for the tumour over the 45 Gy/25 fractions/5 weeks regimen. Although the aim of the study was to intensify radiation and chemotherapy, fewer patients received the full dose of radiation and chemotherapy in the CAPOX 50 arm.

Table. Summary of phase III clinical trials using oxaliplatin.*

	ACCORD 12[23]	STAR-01[24]	NSABP R-04[14]	CAO/ARO/AIO-04[25]
No. of patients	598	747	1608	1236
Primary endpoint	ypCR	OS	LRR	DFS
Study design	RT 50 Gy + Cap 1600 mg/m^2 daily for 5 days/week + Oxa 50 mg/m^2 weekly during RT vs. 45 Gy + Cap 1600 mg/m^2 daily 5 days/week during RT	50.4 Gy + 5-FU 225 mg/m^2 daily + Oxa 60 mg/m^2 once/week during RT vs. 50.4 Gy + 5-FU 225 mg/m^2 daily during RT	50.4 Gy + Cap 1650 mg/m^2 daily 5 days/week with or without Oxa 50 mg/m^2 once/week during RT vs. 50.4 Gy + 5-FU 225 mg/m^2 daily with or without Oxa 50 mg/m^2 once/week during RT	50.4 Gy + 5-FU 250 mg/m^2 daily plus Oxa 50 mg/m^2 once in weeks 1,2,4, and 5 of RT vs. 50.4 Gy + 5-FU 1000 mg/m^2 in weeks 1 and 5 of RT
Total dose of chemotherapy	Cap 40,000 mg/m^2 with or without Oxa 250 mg/m^2	5-FU 8550 mg/m^2 with or without Oxa 360 mg/m^2	5-FU 8550 mg/m^2, Cap 46,200-51,150 mg/m^2 with or without Oxa 250 mg/m^2	5-FU 7000 mg/m^2 with Oxa 200 mg/m^2 vs 5-FU 10,000 mg/m^2
Compliance with chemotherapy	Oxa: 87%	5-FU: 69% vs. 84% Oxa: 66%	Not reported	85% vs. 79%
Total dose of RT	50 Gy/25 fractions and 45 Gy/25 fractions	50.4 Gy/28 fractions	45 Gy/25 fractions + 5.4 Gy/3 fractions for non-fixed tumours or 10.8 Gy/6 fractions for fixed tumours	50.4 Gy/28 fractions
Compliance with RT	87% vs. 100%	84% vs. 92%	Not reported	94% vs. 96%
Grade 3/4 diarrhoea	12.6% vs. 3.2%†	15% vs. 4%†	15.4% vs. 6.6%†	12% vs. 8%
Grade 3/4 neuropathy	0.8% vs. 0%	1% vs. 0%	Not reported	11% vs. 2%
Timing of surgery	6 Weeks after CTRT	6-8 Weeks after CTRT	Not reported	5-6 Weeks after CTRT
Rate of ypCR	19.2% vs. 13.9%	16% vs. 16%	21% vs. 19%	17% vs. 13%†
Rate of metastasis	2.8% vs. 4.2% (intra-abdominal)	0.5% vs. 2.9%† (intra-abdominal)	Not reported	4% vs. 6%
Adjuvant chemotherapy	No specific recommendation	5-FU–based	Not mandatory but strongly encouraged	Oxaliplatin-based vs. 5-FU–based

Abbreviations: Cap = capecitabine; Oxa = oxaliplatin; CTRT = chemoirradiation; DFS = disease-free survival; 5-FU = 5-fluorouracil; LRR = locoregional relapse; OS = overall survival; RT = radiotherapy; ypCR = pathologically complete response.

* All comparisons are in the form of: (with oxaliplatin) vs (without oxaliplatin).

† Denotes statistical significance.

In another study, known as the Studio Terapia Adiuvante Retto (STAR)-01 trial, 747 patients with locally advanced (cT3-4 and/or cN1-2) adenocarcinoma of the mid-low rectum were randomised.[24] Continuous infusion of 5-FU 225 mg/m^2/day was used in the control arm while oxaliplatin 60 mg/m^2 weekly for six doses was combined with 5-FU in the experimental arm. The radiation dose was 50.4 Gy in 28 daily fractions given from Monday to Friday. The primary endpoint was OS and the study was designed to detect a 30% reduction in mortality rates. Moreover, an 8% absolute difference in ypCR rates could be detected with a statistical power of 80%.

While the OS data are pending, the analysis of the ypCR rates has been reported. In line with the results of the ACCORD 12 study[23] and NSABP R-04 study,[14] the ypCR rates were the same in both study groups and grade 3/4 adverse events were more common with the addition of oxaliplatin (24% vs. 8%; $p < 0.001$). Again, the increase in the rate of grade 3/4 diarrhoea was the major contributor to the adverse events profile (15% vs. 4%; $p < 0.001$). Another important finding of this study is that the rate of intra-abdominal metastasis found intra-operatively was significantly lower in the oxaliplatin arm (2.9% vs. 0.5%; $p = 0.014$). The ability to reduce early metastasis is consistent with oxaliplatin's activity in the adjuvant setting. A numerical survival benefit as a result of reduced metastasis is anticipated, but whether this will be statistically significant with this sample size and statistical power is questionable.

The results of the NSABP R-04 study were reported at the American Society for Clinical Oncology Annual Meeting in 2011.[14] A total of 1608 patients were enrolled in this four-arm study that compared continuous infusion of 5-FU 225 mg/m^2 for 5 days/week with capecitabine 825 mg/m^2 twice daily for 5 days/week, and the same fluoropyrimidine-based chemotherapy with or without oxaliplatin 50 mg/m^2 per week for 5 weeks in stage II or III rectal cancer patients undergoing neoadjuvant chemoirradiation. The dose of radiotherapy was 50.4 to 55.8 Gy at 1.8 Gy per fraction. Neither capecitabine nor the addition of oxaliplatin increased the rate of ypCR, sphincter-saving surgery, or surgical downstaging. Grade 3/4 diarrhoea was more common with the addition of oxaliplatin (15.4% vs. 6.6%; $p < 0.0001$).

The CAO/ARO/AIO 04 study was the only phase III study that showed positive results with the addition of oxaliplatin to neoadjuvant chemoirradiation.[25] A total of 1265 patients were enrolled and patients received either bolus 5-FU 1000 mg/m^2 on days 1-5 and 29-33 or infusional 5-FU 250 mg/m^2 on days 1-14 and 22-35 with oxaliplatin 50 mg/m^2 on days 1, 8, 22, and 29. In both arms, the dose of radiotherapy was 50.4 Gy in 28 fractions. The primary endpoint was disease-free survival, but mature data will not be available until the end of 2013. Only the results for the secondary endpoints, including toxicity and early efficacy, have been published. The rate of ypCR was 17% in the oxaliplatin arm and 13% in the 5-FU arm (odds ratio = 1.4; $p = 0.038$). The rate of grade 3/4 diarrhoea was also higher for patients in the oxaliplatin arm (12% vs. 8%).

The results should be interpreted with caution. First, as stated by the author, no formal equivalence margins were specified for the secondary endpoints so the results were descriptive rather than statistically significant. Second, the different 5-FU regimens used in both arms may confound the benefit seen with oxaliplatin.

In summary, the best level of evidence today does not support the routine use of oxaliplatin with neoadjuvant fluoropyrimidine-based chemoirradiation. Nevertheless, there are lessons learnt from these studies. The results of the CAO/ARO/AIO 04 study suggest that an intentional chemotherapy break during radiotherapy may improve the toxicity profile which, in turn, may improve treatment compliance as well as treatment efficacy.[25] The STAR-01 study also showed early promise for oxaliplatin to reduce metastasis.[24] The failure to improve short-term clinical outcomes is not equivalent to an inability to achieve long-term clinical benefit. Mature survival data from the above clinical trials are eagerly awaited.

ADDITION OF CETUXIMAB

Cetuximab is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody that has been shown to improve clinical outcomes of patients with metastatic colorectal cancer.[26] KRAS mutation status is the most powerful predictive factor for response to anti-EGFR antibody treatment. The combination of cetuximab and radiotherapy was supported by the significant improvement in survival in advanced head and neck cancer.[27]

A number of phase I/II studies have been performed to evaluate the efficacy of adding cetuximab to neoadjuvant chemoirradiation in locally advanced

rectal cancer. In unselected patients, the rate of ypCR ranges from 5% to 23% for cetuximab added to fluoropyrimidine-based chemoirradiation.[28] The triplet combination of cetuximab, capecitabine, and irinotecan or oxaliplatin achieved rates of ypCR 8-25% and 8-17%, respectively. The rate of G3/4 diarrhoea was mostly around 10-20%.[29]

A retrospective translational analysis of 130 specimens from patients enrolled in four European phase I/II studies of cetuximab concurrent with chemoirradiation suggested that *KRAS* mutation status was also predictive for treatment response.[30] Subsequently, the Eloxatin (oxaliplatin) Xeloda (capecitabine) Pre-operative Radiotherapy – Cetuximab (EXPERT-C) study demonstrated a slightly different result.[31] A total of 165 patients with magnetic resonance imaging (MRI)–defined high-risk rectal cancer were randomised to four cycles of capecitabine 850 mg/m^2 twice daily on day 1 to 14 and oxaliplatin 130 mg/m^2 on day 1 every 21 days (CAPOX) followed by capecitabine chemoirradiation, surgery, and adjuvant CAPOX with or without cetuximab. Data on patients with *KRAS* or *BRAF* wild-type tumours have been presented. Interestingly, the rate of ypCR (11% vs. 9%; p = 1.0) and progression-free survival (hazard ratio [HR] = 0.65; p = 0.363) were similar, but the improvement in response rate (71% vs. 51%; p = 0.038) and OS (HR = 0.27; p = 0.034) both reached statistical significance. The validity of *KRAS* mutation status was again questioned in a pooled analysis of two Korean phase II studies using capecitabine and irinotecan concurrent chemoirradiation.[32] It was shown that, in *KRAS* wild-type tumours, the pathological response rate, disease-free survival, and pathological stage did not differ significantly with the addition of cetuximab.

So far, the evidence for the addition of cetuximab to neoadjuvant chemoirradiation is disappointing. While selection of patients may explain part of the observation, the main culprit may lie in the radiobiology principle. It is postulated that cetuximab reduces the fractions of cells in the G2/M phase and thus reduces the tumour's sensitivity to both chemotherapy and radiotherapy.[33]

INDUCTION CHEMOTHERAPY

The introduction of total mesorectal excision (TME) and neoadjuvant chemoirradiation has resulted in a local recurrence rate of below 10% for locoregionally advanced rectal cancer; however, around 30% of patients will eventually develop distant metastasis. Extrapolation of the benefit for adjuvant chemotherapy in colon cancer may suggest a similar benefit of chemotherapy in patients who have received neoadjuvant chemoirradiation. However, compliance with adjuvant chemotherapy has been consistently low and this makes induction chemotherapy an attractive option.[2,3]

In the EXPERT study, 105 patients with MRI-defined high-risk rectal adenocarcinoma (low-lying T3 tumour, T4 tumour, N2, tumour <1 mm from or through the mesorectal fascia, or tumour invading >5 mm into the perirectal fat) were enrolled to investigate the efficacy of induction chemotherapy with capecitabine 1000 mg/m^2 twice daily on days 1-14 every 21 days and oxaliplatin 130 mg/m^2 on day 1 every 21 days (CAPOX) followed by capecitabine chemoirradiation and adjuvant capecitabine after TME.[34] Following this intensive treatment, the rate of ypCR was 20%, and the three-year progression-free survival and OS were 68% and 83%, respectively. The results were promising for high-risk patients, but toxicity was a concern since clinically significant cardiotoxic events mandated protocol amendment.

Another Spanish phase II study randomised 108 patients with locally advanced rectal cancer to four cycles of CAPOX either before or after CAPOX chemoirradiation and surgery.[35] The rate of ypCR, downstaging, tumour regression, and R0 resection were not different between the two arms of study, but treatment compliance and exposure were improved in the induction arm. Only the 18-month failure-free survival (82% vs. 76%) and OS (89% vs. 91%) were published.

Induction chemotherapy may overcome the drawback of adjuvant chemotherapy, but patient selection and toxicity remain the major concerns. Long-term survival data are lacking and further phase III studies are warranted.

CONCLUSION

The treatment of locally advanced rectal cancer is evolving. Capecitabine is now the preferred agent for use concurrently with radiotherapy. The addition of oxaliplatin will not be completely excluded until long-term survival data are available. Cetuximab in this setting remains investigational and further translational research is warranted to aid patient selection and pharmacodynamics study needed to define the optimal sequence with chemoirradiation. Induction

chemotherapy is a promising strategy to improve treatment compliance and thus intensify treatment, especially in patients at high risk of recurrence. Nevertheless, phase III studies of the above approaches are eagerly awaited to define the best strategy that will survive in the evolution of neoadjuvant chemoirradiation of rectal cancer.

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