Neoadjuvant Chemotherapy and Radiotherapy in Locally Advanced Rectal Carcinoma

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Abstract

Background:

Neoadjuvant chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. Neoadjuvant chemoradiotherapy not only can reduce tumor size and recurrence, but also increase the tumor resection rate and anus retention rate with very slight side effect. Comparing with preoperative chemotherapy alone, preoperative chemoradiotherapy can further reduce the local recurrence rate and downstage. Middle and low rectal cancers can benefit more from neoadjuvant chemradiotherapy than high rectal cancer.

Aim of the work:

1- Selection of suitable neoadjuvant chemoradiotherapy method with less acute and late toxicity effect.

2- Discover which drug or combination of drugs have better results in terms of local recurrence and survival .

3- Selection of appropriate patients and irradiation modes for neoadjuvant chemoradiotherapy.

Methods:

Three major databases (PubMed,MEDLINE and Cochrane library).

The review included articles published in English in NCCN Journal and ASCO Journal fromJanuary 2012 t0 march 2018.

Conclusion:

Preoperative chemoradiotherapy has been recommended as the standard treatment for locally advanced middle and low rectal cancer.

Introduction

Colorectal cancer is the fourth most common cancer worldwide, the etiology of colorectal cancer involves multiple genes and three possible pathways: chromosomal instability, mismatch repair (MMR) and the hypermethylation of the promoter of the MLH1 gene **(*Hwang K,et al 2015*)**

Preoperative or neoadjuvant therapy has been accepted as atreatment for increasing resectability ,decreaing the rate of locoregional recurrence,and potentially improving survival in locally advanced rectal patients**(*Glimelius B et al;2012*).**

Neoadjuvant chemoradiotherapy has become the standard of care for stages II and III rectal cancer since the CAO/ARO/AIO trial however efforts have been made in order to discover which drug or combination of drugs have better results in terms of local recurrence and survival (***Sauer et al, 2004***).

Combined treatment reduces loco-regional recurrences but the overall survival rate has not been remarkably improved. With better staging, better surgery technique, and incorporation of radiotherapy, slightly better 5-year

survival rate has been reported in several large randomized trials **(*Lemmens et al;2007*).**

The most important prognostic factor for overall survival rate is the pathologic extent of disease (TNM stage), lymphatic invasion, vascular invasion, pathologic type, circumferential resection margin and the type of surgical technique (the length of the cutting edge and degree of lymph node dissection). Downstage effect of neoadjuvant radiochemotherapy (nCRT) is also considered as a risk factor**(*Hwang K,et al 2015*)**

The loco-regional recurrence rate of resectable stage II ~ III rectal cancer patients was 15% to 65%. Even with the total mesorectal excision (TME), local regional recurrence rate of stage III patients is up to about 20% ~ 30%. To improve the local control rate and long-term survival rate, it is necessary for resectable stage II ~ III patients to receive neoadjuvant therapy before surgery. Preoperative concurrent radiochemotherapy (nCRT) have become the standard treatment for resectable stage II ~ III patients. For unresectable locally advanced rectal cancer, preoperative concurrent chemoradiotherapy is the only standerd treatment

(Glimelius B et al;2012).

1- Neoadjuvant radiotherapy for rectal cancer:

Total mesorectal excision (TME) is now the standard of care for rectal cancer surgery,permitting en bloc removal of intact tumor with its lymphatic and vascular supply resulting in a negative circumferential margin and lower local relapse rates. In this setting, two large studies have explored the role of preoperative RT and demonstrated their superiority.

The Dutch Colorectal Cancer Group randomly assigned 1861 patients with rectal cancer either to preoperative RT (5 Gy x 5) followed by TME or to TME alone. They concluded that short-term preoperative radiotherapy reduces the risk of local recurrence at 2 years (2.4% vs 8.2%, p<0.001) in patients with rectal cancer who undergo a TME. However, neoadjuvant RT did not have any impact on distant relapse or overall survival.

2-Neoadjuvant chemo-radiation for rectal cancer :

a- FU plus radiotherapy :

Currently, chemoradiation using 5-fluorouracil (5-FU) as a radiosensitizer is considered the common approach for rectal cancer in the neoadjuvant setting. There are a number of mechanisms by which 5-FU could increase radiation sensitivity at the cellular level. First is through the killing of S-phase cells which are relatively radioresistant. 5-FU has also a sensitizing effect related to enzyme thymidylate synthase inhibition and the ability to damage DNA. The primary toxicities of 5-FU include gastrointestinal symptoms including diarrhea, myelosupression, inflammation of mucosae, including the eyes, nose and urinary tract, neurotoxicity at high-dose levels, and rare cardiac toxicity ***(Zhu & Willett, 2003)***.

Capecitabine plus radiotherapy :b-

Capecitabine is an oral fluoropyrimidine carbamate prodrug of 5-FU designed to generate 5-flurouracil (5-FU) preferentially in tumor cells

Capecitabine is administered daily to mimic a continuous infusion of 5-FU. *(De Bruin et al, 2008)*. This continuous regimen is likely to have a more constant cytotoxic action, thereby limiting tumor regrowth. The side-effect profile of capecitabine is similar to that observed when 5-FU is given as a protracted infusion and consists mainly in diarrhea.The dose-limiting toxicity is the hand–foot syndrome,

occurring as the capecitabine dose reaches 1000 mg/m2 twice daily. Other toxicities were generally mild to moderate (Hoff et al, 2001).

C-UFT plus radiotherapy :

UFT is an oral combination of uracil and tegafur in a fixed 1:4 molar ratio (Hoff et al, 1998).

Tegafur is a prodrug converted to 5-FU by the hepatic microsomal system following intestinal absorption. Uracil competitively inhibits dihydropyrimidine dehydrogenase, the chief catabolic enzyme of 5-FU, which results in elevated and maintained concentrations of 5-FU for a prolonged period and thus simulates a continuous infusion of 5-FU to improve the absorption and bioavailability of tegafur. (Ho et al, 1998***)***

d-Oxaliplatin-based combination regimens :

Significant interest has arisen in the past several years in developing combinations of 5-FU,oxaliplatin, and RT in the neoadjuvant treatment of rectal cancer. This interest has been supported by the systemic synergistic activity between oxaliplatin and fluoropyrimidines and the added radiation-sensitizing activity of oxaliplatin ***(de Gramont et al, 2000)***

The mechanism of radiation sensitization appeared to be through cell-cycle

perturbations. It remains controversial whether oxaliplatin should be delivered before or after radiation to maximize its radiosensitizing activity. The main toxicities described are hematologic toxicity (neutropenia, trombocitopenia), nausea and/or vomiting, diarrhea,mucositis and neurologic toxicity which is dose limiting.

(Goldberg et al, 2004).

e-Oxaliplatin /capecitabine plus radiotherapy

The phase III trial ACCORD 12/0405 – Prodige 2 randomly assigned patients to receive 5 weeks of RT 45Gy/25 fractions with concurrent capecitabine 800 mg/m2 twice daily 5 days/week (CAP45) or RT 50Gy/25 fractions with same dose of capecitabine plus oxaliplatin 50 mg/m2 once weekly (CAPOX50). More preoperative grade 3 to 4 toxicity occurred in the CAPOX50 group (25% *vs* 1%, $p<0.001$). The ypCR rate was 13.9% with CAP45 and 19.2% with CAPOX50 ($p = 0.09$). In this trial, a benefit of Oxaliplatin was not demonstrated and they concluded that this drug should not be used with concurrent irradiation .***(Gerard et al, 2010)***

f-Irinotecan /5-FU plus radiotherapy

Irinotecan was investigated on a daily × 5 schedule in combination with a standardbolus 5-FU/LV-plus-RT regimen. A total of 59 patients were treated with RT (45 Gy),5-FU/LV (350/20 mg/m2/d) on days 1 to 5 and 29 to 33, and scalating doses of irinotecan (6, 8, 10, 12, 14, 16, 18, and 20 mg/m2/d) on days 1 to 5 and 29 to 33. Irinotecan at 18 mg/m2 was selected as the recommended dose for future studies. A pCR was observed in 24% patients and tumor downstaging in 41% of patients .***(Glynne-Jones et al, 2007)***

g-irinotecan / capecitabine plus radiotherapy :

No adequately powered head-to-head studies have compared irinotecan- or oxaliplatin-based neoadjuvant chemoradiation studies. In a small neoadjuvant randomized phase II study,similar downstaging was seen for both apecitabine/oxaliplatin– and capecitabine/irinotecan–based

neoadjuvant radiation. The irinotecan-based combination was associated with increased diarrhea and chemoradiation-induced fibrosis. ***(Privitera et al, 2006).***

h-Bevacizumab/5-fu plus radiotherapy

The safety of bevacizumab in the neoadjuvant chemoradiation setting

was established in a phase I/II study. A total of 22 patients received bevacizumab (5 or 10 mg/kg) every 2 weeks, continuous-infusion 5-FU (225 mg/m2/24 h), and RT (50.4 Gy), followed by surgery in 7 to 9 weeks. Two of the five patients in the cohort receiving bevacizumab at 10 mg/Kg with 5-FU plus RT experienced grade 3/4 dose-limiting diarrhea and colitis during treatment. This regimen showed significant downstaging (55%) with a 22% pCR rate.Bevacizumab at 5 mg/kg every 2 weeks in combination with RT plus 5-FU yielded promising results and did not show any dose-limiting toxicity or perioperative morbidity/mortality. ***(Willett et al, 2007)***

i-Bevacizumab/capecitabine plus radiotherapy:

Torino et al presented the results of a phase II study of neoadjuvant antiangiogenic therapy (intravenous infusion of bevacizumab 5 mg/Kg each two weeks for 4 courses, the first administration 2 weeks before chemoradiotherapy) combined with capecitabine (825 mg/m2 twice daily) and RT (50.4 Gy / 28 fractions) in patients with locally advanced rectal cancer. The authors concluded this is a feasible and safe regimen with a tumor downstaging rate of 6.9%, a pCR rate of 9.3% and conservative surgery in 72.5% patients. ***(Torino et al, 2008)***

j-Bevacizumab plus xeliri/-xelox plus radiotherapy

Bevacizumab was also evaluated with capecitabine and either oxaliplatin or irinotecan in a pilot feasibility study. A total of 11 patients with advanced rectal cancer received bevacizumab (5 mg/Kg) every 2 weeks with capecitabine (1000 mg/m2 twice daily on days 1 to 14 before the chemoradiation phase and then 825 mg/m2 twice daily during RT on days 22 to 55) plus irinotecan at 180 mg/m2 (XELIRI) or oxaliplatin at 130 mg/m2 (XELOX) on days 1, 22, 43, and concurrent radiotherapy (54 Gy). Surgery was carried out 8 weeks after the completion of chemoradiation. Only one patient had grade 3 diarrhea and was unable to complete the planned chemotherapy. In combination with XELIRI/-XELOX plus RT, bevacizumab neither increased the treatment toxicity profile nor provoked any surgical delay or modifications. ***(Privitera et al, 2007)***

k-Cetuximab/5-FU plus radiotherapy :

A pilot study conducted at Memorial Sloan-Kettering Cancer Center investigated the safety of cetuximab in combination with standard neoadjuvant 5-FU and RT in patients with locally advanced or locally recurrent rectal cancer. A total of 20 patients received cetuximab at 400 mg/m2 on day 1 followed by 250 mg/m2/wk × 4, continuous-infusion 5-FU at 225 mg/m2/d over 5.5 weeks, and concurrent pelvic RT (50.4 Gy). Of the 20 patients enrolled,12% of patients had a pCR. Grade 3 diarrhea was seen in 10% of patients. ***(Chung, 2006)***

l-Cetuximab/capecitabine plus radiotherapy :

A Belgian phase I/II trial evaluated a regimen of cetuximab, capecitabine, and RT in 40 patients with endoscopically staged locally advanced rectal cancer. Patients were treated with a loading dose of cetuximab at 400 mg/m2 the first week followed by 250 mg/m2/wk × 5,escalating doses of capecitabine twice daily, and concurrent RT (45 Gy in 25 fractions). The recommended regimen consisted of capecitabine, 825 mg/m2 twice daily, in combination with cetuximab and RT. This dose level was investigated in 30 patients. Only 2 patients (5%) experienced a pCR. Grade 3 diarrhea occurred in 15% of patients. ***(Machiels, 2007)*****m-**

Cetuximab/capecitabine/oxaliplatin plus radiotherapy :

Cetuximab was also investigated in combination with oxaliplatin, capecitabine, and concurrent RT. Rodel et al conducted a phase I/II trial of cetuximab (400 mg/m2 loading dose followed by 250 mg/m2/wk × 5), oxaliplatin 50 mg/m2 weekly, escalating doses of capecitabine (days 1 to 14 and days 22 to 35), and RT (50.4 Gy). The phase II dose was identified at a capecitabine dose level of 1650 mg/m2/d on days 1 to 14 and 22 to 35. A total of 48 patients were enrolled on the phase II trial. Tumor downstaging was observed in 47% patients with pCR in 9% patients. Grade 3-4 diarrhea was seen in 19% patients. This combination is feasible and safe and the addition of cetuximab did not compromise chemotherapy doses and did not lead to higher toxicity. However, the addition of cetuximab produced a relatively low rate of pathologic responses and underachieved the assumptions.Further preclinical and clinical research is necessary to clarify the mechanism and define the reason of this phenomenon. ***(Rödel C, 2007)***

n-Cetuximab/irinotecan/capecitabine plus radiotherapy:

Cetuximab has been similarly investigated in Irinotecan-based neoadjuvant rectal cancer trials. A German phase I trial investigated a combination of cetuximab, irinotecan, and capecitabine in 20 patients with rectal cancer. Cetuximab was given weekly (400 mg/m2 loading dose followed by 250 mg/m2 on days 8, 15, 22, and 29) and escalating doses of irinotecan and capecitabine with pelvic RT (50.4 Gy). Irinotecan at 40 mg/m2 and capecitabine at 500 mg/m2 twice daily were determined as the recommended doses for future studies. About 7% of patients with T3 disease and 80% with T2 disease achieved a pCR. ***(Hofheinz, 2006)***

o-Gemcitabine plus Radiotherapy :

Gemcitabine is a chemotherapy drug that works by killing any cells that are dividing *(UK Electronic Medicines Compendium et al; 2017)* Cancer cells divide rapidly and so are targeted at higher rates by gemcitabine, but many essential cells divide rapidly as well, including cells in skin, the scalp, the lining of the stomach, and bone marrow, resulting in adverse effects (***Rachel Airley et al; 2009***).

Common adverse effects (occurring in 1–10% of people) include fever, loss of appetite, headache, difficulty sleeping, tiredness, cough, runny nose, diarrhea, mouth and lip sores, sweating, back pain, and muscle pain ***(UK Electronic Medicines Compendium et al; 2017)*** .

3-**Evaluation criteria for the efficacy of neoadjuvant therapy for rectal cancer:**

How to evaluate the efficacy of preoperative concurrent chemoradiotherapy for local advanced rectal cancer? The criteria are very important. Evaluation methods include clinical symptoms, serum biomarkers and imagings including transrectal ultrasound (ERUs), computer tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)**(*Belluco C,et al;2011)* .**

4- Interval time between neoadjuvant therapy and surger:

The interval time of 4~6 weeks after the neoadjuvant chemoradiotherapy before surgery is recommended(***Lim S, Choi H,2008*****).**

Conclusion

- Preoperative chemoradiotherapy has been recommended as the standard treatment for locally advanced middle and low rectal cancer.
- Preoperative chemoradiotherapy can reduce the tumor mass, block

the tumor invasion, increase the tumor resection rate, and anus retention rate, reduce iatrogenic dissemination during operation, and reduce the local recurrence rate.

- This article summarized the progress of the preoperative chemoradiotherapy for rectal cancer.
- Long duration preoperative concurrent chemo-radiotherapy is preferable than short duration.
- The most effective combination of drugs ,optimal mode of administration, and sequence of radiation and chemotherapy still needed to be determined.

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