

RESEARCH ARTICLE

A Systemic Analysis of S-1 Regimens for Treatment of Patients with Colon Cancer

En Zhang*[&], Wei Cao[&], Chong Cheng, Bin-Liang Huo, Yong-Heng Wang

Abstract

Background: Fluorouracil-based regimens have been widely accepted and recommended in the guidelines for treating patients with early or advanced staged colon cancer, although results are controversial. Here we performed a systemic analysis to evaluate the impact of S-1 based regimens on response and survival of patients with colon cancer. **Methods:** Clinical studies evaluating the impact of S-1 based regimens on response and survival of patients with colon cancer were identified using a predefined search strategy. Summary response rates (RRs) to treatment were calculated. **Results:** Six clinical studies which including 227 patients with advanced colorectal cancer were considered eligible for inclusion. Two studies were conducted using combination of S-1 and Oxaliplatin, and four studies featured S-1 and irinotecan. Systemic analysis showed that, in all patients, pooled RRs was 43.17%. Major adverse effects were hematological toxicities, gastrointestinal disturbance, neurosensory toxicity. No treatment related death occurred. **Conclusion:** This systemic analysis suggests that S-1 based regimens, both with oxaliplatin or irinotecan are associated with acceptable response and toxicity in patients with colon cancer.

Keywords: Systemic analysis - S-1 - colon cancer

Asian Pac J Cancer Prev, 15 (5), 2191-2194

Introduction

At present, colorectal cancer remains one of the most common cancer in both genders. The rate of recurrence for stage III colorectal cancer is reported to be 30.8% (Watanabe et al., 2012; Chen et al., 2013; Fathallah et al., 2013; Suh et al., 2013; Tastan et al., 2013; Tong et al., 2014). Chemotherapy is important in treating patients with advanced cancer after curative resection. In Western countries, oxaliplatin (Ox)-based regimens in addition to fluorouracil (FU) and leucovorin (LV) (FOLFOX (Ox + FU + LV), FLOX (Ox + FU), or XELOX (Ox + capecitabine)) have been established as the gold standard chemotherapy for advanced colon cancer based on the results of three large randomized controlled phase III studies conducted after 2000 (André et al., 2004; Kuebler et al., 2007; Haller et al., 2011). But, favorable results using an FU-based regimen without Ox were reported in a randomized controlled study (Shimada et al., 2012). And, in this field, oral FU is an effective, better tolerated, and convenient chemotherapy regimen, as it does not require the use of a central infusion port system and less need to visit clinics. The equality of UFT/LV or capecitabine to 5-FU/LV has already been confirmed in large randomized trials (Twelves et al., 2005; Lembersky et al., 2006). However, S-1 that is an oral preparation evolved from UFT is not routinely ordered for patients with colorectal cancer. S-1

combines tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil). Two Japanese phase II trials of S-1 monotherapy for chemotherapy-naïve patients with metastatic colorectal cancer showed that the response rates were 35.5% and 39.5%, similar to the results from the joint study of UFT/LV in the United States and Japan (36.4% in Japan and 34.1% in the United States). In addition, the efficacy of S-1 in an adjuvant setting has been demonstrated in a Japanese phase III trial in patients with stage II or III gastric cancer (ACTS-GC trial) (Sakuramoto et al., 2007).

Based on these findings, we hypothesize that S-1 originated regimen could be established as an optimal schedule for patients with advanced colorectal cancer.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (colon) and (S-1 or TS-1). All clinical studies evaluating the impact of S-1 or TS-1 on the response or survival and side effects for colon cancer published in English prior to February 2014 were identified. If samples

of two studies overlap, only the newest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with oxaliplatin or irinotecan; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic and/or locally advanced colorectal cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, country of the first or corresponding author, the number of patients. Outcome measures presented in at least 3 studies were extracted for combined analysis.

Results

There were 52 papers relevant to the search words by the end of February 2014. Via steps of screening the title and reading the abstract, 6 studies were identified (Van den Brande et al., 2003; Kim et al., 2009; Yokoyama et al., 2009; Zang et al., 2009; Mizushima et al., 2013; Zhu et al., 2011). These studies had been carried out in China, Japan, Korea and Belgium. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities. Characteristics of studies included in the meta-analysis are presented as short-term outcomes: the response rate of Zhu et al. was 65.40% (CR 11.5%, PR 53.8%), of Yokoyama T et al. was 13.3%, of Kim SY et al. was 21.1%, of Mizushima T et al. was 47.7%, of Van den Brande J et al. was 24%, and of Zang et al. was 54%. Totally, 227 patients were enrolled and 98 patients achieved CR or PR, the pooled response rate thus was 98/227 (43.17%). Observation on toxicities: major adverse effects were hematological toxicities, gastrointestinal disturbance, and neurosensory toxicity.

Discussion

Previous study has indicated that in treating patients with advanced colorectal cancer, 5-FU continuous-

infusion is superior to bolus 5-FU administrations, both in terms of response and overall survival (Meta-analysis Group in Cancer, 1998). And improvements in response rates and survival were achieved with combinations of 5-FU/folinic acid and irinotecan or oxaliplatin (de Gramont et al, 2000; Douillard et al, 2000; Saltz et al, 2000). But the treatments are not easy to be conducted, necessitating vascular access devices and portable delivery systems. And grade 3-4 toxic effects such as diarrhoea are significantly more frequent in the combination treatment with irinotecan. Therefore, new and better treatments and ways of delivering them are necessary. Oral medication has the advantage of greater patient convenience and acceptance and potential cost savings (DeMario and Ratain, 1998; Borner et al, 2002). 5-Fluorouracil itself is not suitable for oral administration due to inability to achieve plasma concentrations of sufficient magnitude and the variability in oral bioavailability. Currently, there are several oral fluoropyrimidines in clinical practice for treating patients with colorectal cancer, eg., capecitabine and UFT (uracil plus tegafur), UFT/folinic acid (Orzel), and eniluracil. Capecitabine and UFT/folinic acid already proved to be as effective as intravenous bolus 5-FU/folinic acid regimens (Sharma et al, 2000; Pazdur et al, 1999; Hoff et al, 2001; Van Cutsem et al, 2001), achieving a response rates of 18.9-24.8 and 12%, respectively, with less toxicity than that with 5-FU containing regimens. S-1 is an oral fluorinated pyrimidine derivative, in which tegafur (FT) has been combined with two 5-FU modulators: 5-chloro-2, 4-dihydropyridine (gimostat (Gimeracils), CDHP), and potassium oxonate (otostat potassium (Oteracils), Oxo), at a ratio of FT : CDHP : Oxo^{1/4} : 0.4 : 1 (Shirasaka et al, 1996). Tegafur is a prodrug of 5-FU. After oral ingestion FT is well absorbed; in the patient it is gradually converted into 5-FU, mainly in the liver and in the tumoural cells (Kimura et al, 1980). CDHP inhibits the activity of dihydropyrimidine dehydrogenase (DPD), the initial and rate-limiting enzyme in the 5-FU metabolism, and thereby the degradation of 5-FU; in this respect CDHP is about 200-fold more active than uracil, which also is used in other oral combinations with FT (Tatsumi et al., 1987). Therefore, when 5-FU is combined with CDHP, this potentially results in the prolonged maintenance of concentrations of 5-FU, both in plasma and tumour. Potassium oxonate prevents intestinal phosphorylation of 5-FU by inhibiting the enzyme pyrimidine phosphoryl transferase (Shirasaka et al, 1993). After oral administration, it has the potential to reduce 5-FU-induced gastrointestinal side effects (Takechi et al, 1997). And another mechanism of S-1 is exerted by 5-FU. After transformation, the cytotoxic effects of 5-FU are mediated by inhibition of the enzyme thymidylate synthase interfering with DNA synthesis, incorporation of 5-fluorouridine-5-triphosphate (FdUTP) into RNA, and incorporation of 5-fluoro-20-deoxyuridine-50triphosphate (FdUTP) into DNA (Peters, 1995).

S-1 has already undergone phase I and II testing. The dose-limiting toxicity was myelosuppression in a Japanese (Taguchi et al, 1997), and diarrhoea in a European and a North-American phase I study (Hoff et al, 1999; van Groenigen et al, 2000). The plasma pharmacokinetics

of 5-FU after oral administration of S-1 were linear and almost similar to that of continuous intravenous infusion of 5-FU (Hirata et al, 1999). A statistically significant relation was observed between the severity of diarrhoea and pharmacokinetic parameters of 5-FU (van Groeningen et al, 2000).

This systemic analysis suggests that S-1 is active for patients with advanced colorectal cancer, response rate could be around 43%. Main adverse effects were hematological toxicities, gastrointestinal disturbance, and neurosensory toxicity. No treatment related death occurred. These could be related to Oxo (potassium oxonate, otastat (Oteracils)), which has the potential to reduce 5-FU-induced gastrointestinal side effects (Shirasaka et al, 1993), clearly decreased risk of gastrointestinal disturbance.

In conclusion, this systemic analysis suggests that S-1 based regimens, both with oxaliplatin or irinotecan are associated with acceptable response and toxicities for treating patients with colon cancer. However, in the future, S-1 will have to be compared to other products in randomised studies to determine which oral fluoropyrimidine has best results and the least toxicities.

References

- André T, Boni C, Mounedji-Boudiaf L, et al (2004). Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*, **350**, 2343-51.
- Borner MM, Schoffski P, de Wit R, et al (2002). Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin. A randomised crossover trial in advanced colorectal cancer. *Eur J Cancer*, **38**, 349-58.
- Chen YS, Xu SX, Ding YB, et al (2013). Colorectal cancer screening in high-risk populations: a survey of cognition among medical professionals in Jiangsu, China. *Asian Pac J Cancer Prev*, **14**, 6487-91.
- de Gramont A, Figer A, Seymour M, et al (2000). Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*, **18**, 2938-47.
- DeMario MD, Ratain MJ (1998) Oral chemotherapy: rationale and future directions. *J Clin Oncol*, **16**, 2557-67.
- Douillard JY, Cunningham D, Roth AD, et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*, **355**, 1041-7.
- Fathallah RM, Dajani R (2013). Comparison of population based cancer incidence rates among Circassians, Chechans and Arabs in Jordan (1996-2005). *Asian Pac J Cancer Prev*, **14**, 6035-40.
- Haller DG, Tabernero J, Maroun J, et al (2011). Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*. **29**, 1465-71.
- Hoff PM, Ansari R, Batist G, et al (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol*, **19**, 2282-92.
- Kim SY, Hong YS, Kim BC, et al (2009). A phase II study of S-1 plus irinotecan and oxaliplatin in heavily-treated patients with metastatic colorectal cancer. *Invest New Drugs*, **27**, 269-74.
- Kimura K, Suga S, Shimaji T, et al (1980) Clinical basis of chemotherapy for gastric cancer with uracil and 1-(20-tetrahydrofuryl)-5-fluorouracil. *Gastroenterol Jpn*, **15**, 324-9.
- Kuebler JP, Wieand HS, O'Connell MJ, et al (2007). Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol*, **25**, 2198-204.
- Lembersky BC, Wieand HS, Petrelli NJ, et al (2006). Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol*, **24**, 2059-64.
- Meta-analysis Group In Cancer (1998) Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol*, **16**, 301-8.
- Mizushima T, Ide Y, Murata K, et al (2013). A phase II study of combined chemotherapy with 5-week cycles of S-1 and CPT-11 plus bevacizumab in patients with metastatic colon cancer. *Oncology*, **85**, 317-22.
- Pazdur R, Douillard JY, Skillings JR, et al (1999) Multicenter phase III study of 5-fluorouracil (5-FU) or UFTTM in combination with leucovorin (LV) in patients with metastatic colorectal cancer. *Proc Annu Meet Am Soc Clin Oncol*, **18**, A1009.
- Peters GJ (1995) Antimetabolites. In: Oxford Textbook of Oncology, Vol 1, Peckham M, Pinedo HM, Veronesi U (eds), pp 530-534. Oxford, New York, Tokyo: Oxford University Press.
- Sakuramoto S, Sasako M, Yamaguchi T, et al (2007). ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*, **357**, 1810-20.
- Saltz LB, Cox JV, Blanke C, et al (2000). Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med*, **343**, 905-14.
- Sharma S, Saltz LB (2000). Oral chemotherapeutic agents for colorectal cancer. *Oncologist*, **5**, 99-107.
- Shimada Y, Hamaguchi T, Moriya Y, et al (2012). Randomized phase III study of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofofolinate in patients with stage III colon cancer: Final results of Japan Clinical Oncology Group study (JCOG0205). *J Clin Oncol*, **30**, abstr 3524.
- Shirasaka T, Shimamoto Y, Fukushima M (1993). Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res*, **53**, 4004-9.
- Shirasaka T, Shimamoto Y, Ohshimo H, et al (1996). Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs*, **7**, 548-57.
- Suh M, Choi KS, Lee YY, et al (2013). Cancer screening in Korea, 2012: results from the Korean National Cancer Screening Survey. *Asian Pac J Cancer Prev*, **14**, 6459-63.
- Takechi T, Nakano K, Uchida J, et al (1997). Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. *Cancer Chemother Pharmacol*, **39**, 205-11
- Tguchi T, Inuyama Y, Kanamaru R, et al (1997) Phase I study of S-1. S-1 Study Group. *Gan To Kagaku Ryoho*, **24**, 2253-64.
- Tatsumi K, Fukushima M, Shirasaka T, et al (1987) Inhibitory

effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res*, **78**, 748-55

- Tong GX, Chai J, Cheng J, et al (2014). Diagnostic value of rectal bleeding in predicting colorectal cancer: a systematic review. *Asian Pac J Cancer Prev*, **15**, 1015-21.
- Tastan S, Andsoy II, Iyigun E (2013). Evaluation of the knowledge, behavior and health beliefs of individuals over 50 regarding colorectal cancer screening. *Asian Pac J Cancer Prev*, **14**, 5157-63.
- Twelves C, Wong A, Nowacki MP, et al (2005). Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med*, **352**, 2696-704.
- Van Cutsem E, Twelves C, Cassidy J, et al (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol*, **19**, 4097-106.
- Van den Brande JI, Schöffski P, Schellens JH, et al (2003). EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. *Br J Cancer*, **88**, 648-53.
- van Groeningen CJ, Peters GJ, Schornagel JH, et al (2000). Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. *J Clin Oncol*, **18**, 2772-9.
- Watanabe T, Itabashi M, Shimada Y, et al (2012). Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol*, **17**, 1-29.
- Yokoyama T, Tokuhara H, Egawa T, et al (2009). The efficacy of S-1 monotherapy as a 2nd/3rd-line therapy for unresectable recurrent colon cancer: Kanagawa conference of clinical oncology (KCCO). *Gan To Kagaku Ryoho*, **36**, 1667-70.
- Zang DY, Lee BH, Park HC, et al (2009). Phase II study with oxaliplatin and S-1 for patients with metastatic colorectal cancer. *Ann Oncol*, **20**, 892-6.
- Zhu QC, Jin ZM (2011). Efficacy and side effects of combination therapy of oxaliplatin and S-1 for colorectal cancer. *Zhonghua Zhong Liu Za Zhi*, **33**, 388-90.