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Yau-Tong You
Chung-Rong Changchien
Jen-Seng Huang
Koon-Kwan Ng

Combining systemic chemotherapy with chemoembolization in the treatment of unresectable hepatic metastases from colorectal cancer

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Y.-T. You (✉) · C.-R. Changchien
Division of Colon and Rectal Surgery,
Chang Gung Memorial Hospital,
5, Fu-Hsing St., Kuei-Shan,
Tao-Yuan, Taiwan
e-mail: proct@adm.cgmh.org.tw
Tel.: +886-3-3281200
Fax: +886-3-3278355

J.-S. Huang
Department of Oncology,
Chang Gung Memorial Hospital,
Tao-Yuan, Taiwan

K.-K. Ng
Department of Radiology,
Chang Gung Memorial Hospital,
Tao-Yuan, Taiwan

Abstract Treatment of liver metastases from colorectal cancer include surgical resection, radiation, hepatic chemoembolization, immunotherapy and intravenous chemotherapy. Complete surgical resection of liver metastases is feasible only for solitary or unilobar metastasis. Unresectable hepatic metastases of colorectal origin are resistant to radiation and immunotherapy, and the unsatisfactory results of systemic chemotherapy and chemoembolization have led to more aggressive treatment. A new method that combines systemic chemotherapy and chemoembolization is proposed. In this study, data from a total of 40 patients with unresectable hepatic metastasis from colorectal cancer were collected. All of these patients received combined chemoembolization and systemic chemotherapy. Embolization was performed by the selective cannulation of right and left hepatic artery. Equal amounts of a mixture of 10 ml lipiodol, 1,500 mg 5-fluorouracil (5-FU) and 15 mg leucovorin was deployed selectively in equal parts into the main right and left hepatic artery. Two weeks following chemoembolization, patients underwent systemic chemotherapy with 2,600 mg/m^2 5-FU continuous infusion for 24 h and received 150 mg leucovorin intravenous bolus. The course of chemotherapy was repeated weekly for 24 weeks. The median follow-up period was 27 months (range 10–36 months). Following the intention-to-treat principle, the objective tumor response rate was 47.5%. The median disease-free interval was 12 months and the median survival time was 16 months. Most of the patients (73%) died of hepatic failure, while the second largest group died of abdominal carcinomatosis. In conclusion, the results of this study are of sufficient interest to justify future randomized trials.

Keywords Systemic chemotherapy · Chemoembolization

Introduction

Liver metastasis is the main cause of death in patients with colorectal cancer. It presented in 18% of patients at diagnosis of their primary tumor and in 60% [1] of patients who develop the advanced disease associated with colorectal cancer. Two important factors influence survival: (1) the extent of the disease presented and (2) the histological grade of the cancer. Many patients would benefit from an effective treatment of hepatic metastasis. Treatment of these patients presents a difficult but common clinical problem. Surgery [2] is the preferred treatment when the tumor is confined to a resectable segment or lobe. Past and present therapies in unresectable cases include intravenous chemotherapy, trans-portal vein or hepatic artery infusion chemotherapy, external beam irradiation, selective chemoembolization, etc. The survival rate of patients receiving therapy has been claimed to be higher than that of untreated patients. Systemic and arterial chemotherapy have been shown to be increasingly successful in eliminating or at

least retarding the growth of metastatic colorectal liver lesions. However, only 30% [3] of patients have objective responses, and their median period of survival is under 12 months [4, 5]. Chemoembolization [6] using an emulsion of a chemotherapeutic agent and lipiodal has also been proposed and appears to promote antitumor activity in patients with colorectal cancer and bulky liver metastasis. A measure of success is revealed by a median survival period of 10 months [7]. The unsatisfactory results obtained using the above two therapies have led to the development of more aggressive treatments. An alternative treatment that combines chemoembolization and systemic chemotherapy is feasible for patients with unresectable hepatic metastasis from colorectal cancer. The aim of this study was to determine the response and survival rates of patients who undergo combined chemoembolization and systemic chemotherapy for unresectable hepatic metastasis from colorectal cancer. Morbidity and toxicity were also evaluated.

Materials and methods

This single-hospital retrospective study, conducted from 1995 to 2002, included a total of 40 patients with unresectable hepatic metastasis from colorectal cancer. Twelve patients had synchronous unresectable liver metastasis at the time of primary cancer diagnosis. All patients received resection of the primary tumor and entered this trial 3 weeks after surgery. The primary tumor was in the rectum in five patients and in the colon in seven. The other 28 patients had metachronous unresectable liver metastasis: primary tumor was located in the rectum and in the colon of 18 and ten subjects, respectively. All patients were assessed by physical examination, serum carcinoembryonic antigen assay (CEA) chest radiography, abdominal ultrasonography, computed tomographic imaging and colonoscopy. Unresectable colorectal metastasis was confirmed by histology, and the fraction hepatic replacement by the tumor was estimated by computed tomographic imaging. Patients were excluded if they had extrahepatic distant metastasis, or locally advanced recurrence in cases of metachronous hepatic metastasis, or unresectable primary tumor in cases of synchronous hepatic metastasis. Patients with extensive hepatic metastasis or combined liver cirrhosis who also had jaundice, ascites or hepatic replacement by the tumor of over 75% were also excluded. The 40 patients ranged in age from 45 to 86 years (average, 60 years). The subjects, consisting of 22 men and 18 women, gave written informed consent before receiving treatment. All patients received physical examination, a full blood count, a chest rontgenogram, a bone scan, a liver function test, abdominal computed tomography, and a test to determine plasma CEA level. The number and sites of the liver tumors and the total size of the liver were recorded by abdominal computed tomography. The performance status of the patients was evaluated using the Eastern Cooperative Oncology Group (ECOG) scale. Performance status was rated based on the following: 0=normal activity, 1=symptomatic and ambulatory, 2=ambulatory more than 50% of the time, 3=ambulatory 50% or less of the time, and 4=bedridden. All 40 patients in this study were ambulatory with performance status of 0, 1 or 2, and maintained oral intake. Patients with any of the following conditions were excluded from the study: WBC below 3,000 cells/μl, platelet count of less than 100,000 cells/μl, any elevation of serum creatinine level, or extrahepatic distant metastasis advanced local recurrence. All patients in this study received treatment of combined chemoembolization and systemic chemotherapy. Embolization was performed by selectively cannulating the right and left hepatic arteries. Equal amounts of an emulsion of 10 ml lipiodol, 1,500 mg 5-fluorouracil (5-FU) and 15 mg of leucovorin were deployed selectively to the main right and left hepatic arteries. Two weeks after chemoembolization, all 40 patients received intravenous systemic chemotherapy. The chemotherapy regimen was as follows. Each patient received a continuous infusion of 2,600 mg/m^2 5-FU for 24 h. A dose of 150 mg leucovorin was administered as an i.v. bolus and was immediately followed by 5-FU infusion. All procedures were repeated weekly for 24 weeks for all patients. Laboratory studies included a complete blood count, determination of coagulation parameters, and liver function tests. These studies were performed both 1 week before and 1 week after chemoembolization to assess the damage to and functional status of the liver. During systemic chemotherapy, toxicity [8–10] was recorded weekly according to the World Health Organization's grading scale. Therapy was stopped temporarily in patients who exhibited a grade 3 or higher toxicity. If unacceptable toxicity (grade ≥3) persisted for more than 2 weeks of treatment, the treatment was stopped. All of the patients in this study were clinically and biologically evaluated every 3 months. Evaluations included a physical examination, serum carcinoembryonic antigen assay, chest radiography, abdominal ultrasonography, computer tomography and colonoscopy. However, if patients developed symptoms and signs such as bloody stool, intestinal obstruction, tenesmus etc., in less than 3 months, clinical and biological evaluations were also performed immediately. The area of all lesions were measured via computed tomography. The criteria used to evaluate the objective response [11–13] were as follows. A complete response was defined as the total disappearance of all known lesion(s) confirmed at 4 weeks. Partial response was defined as a reduction of at least 50% of all known lesion(s) confirmed at 4 weeks. Stable disease was defined as neither partial response nor progressive disease criteria met. Progressive disease was defined as an increase of at least 25% of the overall measurable lesion or the appearance of a new neoplastic lesion. The period of survival was measured from the beginning of therapy. The duration of the response was defined as the time between the first record of the

response and the first recorded instance of disease progression. The disease progression-free interval was defined as the period between the beginning of treatment and the first recorded instance of disease progression. All patients were followed from the date of initial treatment. The overall survival rate, responses, disease-free interval and toxicities were assessed. The survival curve was estimated using the Kaplan–Meier method.

Results

Table 1 presents the characteristics of the 40 patients who enrolled in this study. All patients received the complete regimen. The median follow-up period was 27 months (10–36 months). Two of the 40 patients had left hepatic artery preclusion and one right hepatic artery preclusion during chemoembolization. The remaining 37 patients had successful right and left hepatic arteries chemoembolization. Two weeks after chemoembolization, all 40 patients received the systemic chemotherapy regimen. Post-embolization toxicity developed in most of the patients as follows. Thirty-one patients (77.5%) had right upper guardant abdominal pain for a period of 4–7 days. The pain was usually modest and resolved with an oral analgesic agent. Sixteen patients (40%) developed fever, while three had leukocytosis requiring antibiotics, which were intravenously administered. The fevers in the other 13 patients were transient and treated with salicylates. The fevers subsided within 4 days in all 16 patients. Twenty-five patients (62.5%) experienced some degree of nausea and/or vomiting. These symptoms were mild and resolved with conservative treatment. Analysis of liver function in 36 patients (90%) revealed a transient elevation of the levels of serum alkaline phosphatase and glutamic oxaloacetic transaminase, which returned to pre-embolization levels 2 weeks later. During chemotherapy, most toxicities that developed were moderate. Table 2 presents the major toxicities experienced by the treated patients. Seven of the 40 patients (17%) had various degrees of leukopenia and five displayed anemia (12%), one thrombocytopenia (3%), 35 (88%) diarrhea, 30 (75%) oral mucosities, 24 (60%) nausea and vomiting, eight (20%) dermitis and two (5%) infection. All four patients (10%) with grade 3 toxicity (two diarrhea, one oral mucosities, one nausea and vomiting) had to be admitted for supportive treatment and the chemotherapy regimen was immediately stopped. The toxicity symptoms subsided within 1 week and the chemotherapy regimen was restarted immediately. The patients with lower grade (1,2) toxicities received symptomatic treatment while following the chemotherapy regimen. No grade 4 toxicity was observed in the chemotherapy regimen treatment. All 40 patients completed the chemoembolization treatment and the full course of chemotherapy. No patient was lost during follow-up. The results of all those 40 patients were analyzed. No death due to chemotherapy toxicity or complication of chemoembolization occurred. No complete objective tumor response was observed in any of the 40 patients. Partial objective tumor responses were observed in 19 of 40 patients (47.5%). The tumor mass in these 19 patients decreased by more than 50% and serum CEA levels decreased to less than 100 ng/ml. The median response period of these 19 patients was 6 months (range 3–12 months). Seventeen of the 40 patients (42.5%) exhibited a minor response or disease stabilization for a period after the regimen. The remaining four patients had disease progression without tumor response during treatment. Three of the four nil-response patients had either right or left hepatic artery preclusion during chemoembolization and all four died within 12 months. Two of them survived for 10 months, the other two for 11 months. Although the diseases of all patients finally progressed, their intervals free of progression were prolonged. The median interval free of disease progression was 9 months (range 6–18 months). Among the patients, 100% survived for 9 months,

Table 1 Characteristics of the patients (*N*=40)

Characteristics	No. of patients
Median age (years)	60 (45–86)
Male/female	22:18
Median % liver replacement	35%
Median no. of liver metastatic masses	6 (4–12)
Serum CEA(ng/ml)	
200–500	3
>500	37
ECOG performance status	
0–1	31
2	9
Primary tumor site	
Colon	22
Rectum	18
Synchronous metastases	12
Metachronous metastases	28

Table 2 Toxicity of chemotherapy (*N*=40)

WHO grading				
Toxicity	0	1	2	3
Anemia no. (%)	35 (88)	3 (7)	2 (5)	0
Leukopenia no. (%)	33 (83)	3 (7)	4 (10)	0
Thrombocytopenia no. (%)	39 (97)	1 (3)	0	0
Anorexia no.(%)	36 (90)	4 (10)	0	0
Diarrhea no. (%)	5 (12)	22 (55)	11 (28)	2 (5)
Oral mucositis no. (%)	10 (25)	13 (32)	16 (40)	1 (3)
Nausea and vomiting no. (%)	16 (40)	15 (37)	8 (20)	1 (3)
Dermatitis no. (%)	32 (80)	6 (15)	2 (5)	0
Infection no. (%)	38 (95)	2 (5)	0	0

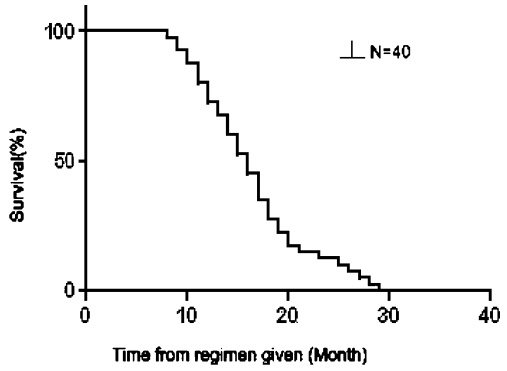

Fig. 1 Overall survival distributions in 40 patients treated with regimen

36 (90%) for 12 months, 27 (67%) for 15 months, 16 (40%) for 18 months, 11 (27%) for 21 months, six (15%) for 24 months, two (5%) for 27 months and one (3%) for 32 months. The median survival period was 16 months. Figure 1 plots the distribution of survival periods. Extrahepatic progression developed in 11 patients, including eight cases of abdominal carcinomatosis, two cases of lung metastasis and one case of brain metastasis. Most of the patients (29/40) died of hepatic failure; the next largest group died of abdominal carcinomatosis (8/40). Two of the other three cases died of respiratory failure due to lung metastasis and one died of brain metastasis.

Discussion

Hepatic involvement frequently determines the prognosis in patients with metatastic colorectal cancer. Between 15 and 35% of such patients have liver metastasis at the time of their first laparotomy, whereas two thirds of patients will have liver metastasis at the time of their death. The median survival period of untreated patients is 6 months. Systemic chemotherapy has been proven to be increasingly successful in eradicating or at least retarding the growth of metastatic colorectal liver lesion. However, systemic chemotherapy to treat unresectable hepatic metastasis from colorectal cancer rarely yields a response rate of above 30%. The median survival period in this study was 12 months. Chemoembolization in patients with colorectal metastases to the liver concentrates and prolongs the retention of the chemotherapeutic agent in the tumor. The median survival period following chemoembolization in treating unresectable hepatic metastases from colorectal cancer is 10 months. Separate systemic chemotherapy or chemoembolization in treating unresectable hepatic metastases from colorectal cancer is of limited efficacy. However, combining systemic chemotherapy with chemoembolization in treating unresectable hepatic metastases from colorectal cancer may be more effective because the mechanisms of these two treatments differ. Chemoembolization acts mainly in the metastatic areas of the liver, while systemic chemotherapy may include hepatic and other distant metastasis at the same time. The toxicity rates of chemoembolization in this regimen are similar to another study [14]. In our regimen, the median survival time (16 months) and response rate (47.5%) were both obviously better than chemoembolization alone (10 months, 25%) [15] or systemic chemotherapy alone (5-FU plus leucovorin) (12 months, 38%) [16]. In recent studies, new agents such as irinotecan [17] and oxaliplatin have been used in combination with 5-FU and leucovorin, respectively, as a new regimen of systemic chemotherapy. In these studies, the median survival time and response rate of the regimen of irinotecan plus 5-FU and leucovorin [18–22] (18.5 months, 49%) or oxaliplatin plus 5-FU and leucovorin [23–25] (19.2 months, 50%) may be somewhat higher than the results obtained in our study. However, the severity of disease in our subjects was greater than that found in patients covered by these studies (unresectable liver metastasis vs metastatic colorectal cancer). There is a need for further randomized phase III study to compare the results. At the same time, the incidences of grade 3–4 toxicities in both regimens mentioned ranged from 22 to 43%, which is obviously worse than the incidence of main chemotherapy toxicities (grade 3–4) in our regimen (10%). The overall toxicities encountered in this study were low and manageable. The treatment of unresectable liver metastases from colorectal cancer is only a palliative treatment. Although the efficacy of the regimen is a major end-point, its toxic effects should be as low as possible. The quality of life of the treated patients should also be maintained. The proposed regimen met these two requirements. Based on the results of this study, combining chemoembolization and systemic chemotherapy in treating unresectable liver metastasis from colorectal cancer are of sufficient interest to justify future randomized trials. Many factors including performance status, age, grade of anaplasia and tumor burden may also affect the response rate or survival period. More randomized studies are needed to evaluate the efficacy and toxicity of this combination therapy before it can be used as an alternative method in treating unresectable liver metastasis from colorectal cancer. Moreover, future studies focusing on the combination of chemoembolization with irinotecan plus 5-FU and leuocovorin or oxaliplatin plus 5-FU and leucovorin may also be of interest to obtain extraordinary results in treating unresectable hepatic metastasis from colorectal cancer.

References

1. Kemeny N, Daly J, Reichman B et al (1987) Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma: a randomized trial. Ann Intern Med 107:459–465
2. Wagner JS, Adson MA, Van Hearden JA et al (1984) The natural history of hepatic metastases from colorectal cancer: a comparison with resective treatment. Ann Surg 5:502–508
3. Kemeny N, Cohen A, Bertino JR (1989) Continuous intrahepatic infusion of floxuridine and leucovorin through an implantable pump for the treatment of hepatic metastases from colorectal carcinoma. Cancer 65:2446–2450
4. Machover D (1997) A comprehensive review of 5-fluorouracil and leucovorin in patients with metastatic colorectal carcinoma. Cancer 80:1179–1187
5. Kemeny N, Niedzwiecki D, Shurgot B et al (1989) Prognostic variables in patients with hepatic metastases from colorectal cancer: importance of medical assessment of liver involvement. Cancer 63:742–747
6. Sanz-Altamira PM, Spence LD, Huberman MS et al (1997) Selective chemoembolization in the management of hepatic metastases in refractory colorectal carcinoma: a phase II trial. Dis Colon Rectum 40:770–775
7. Hunt TM, Flowerdew ADS, Birch ST et al (1990) Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases. Br J Surg 77:779–782
8. Erlichman C, Fine S, Wong A et al (1988) A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. J Clin Oncol 6:469–475
9. Poon MA, O'connell MJ, Wieand HS et al (1991) Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J Clin Oncol 9:1967–1972
10. Gramont AD, Bosset JF, Milan C et al (1997) Randomized trail comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 15:808–815
11. Buroker TR, O'Connell MJ, Wieand HS et al (1994) Randomized comparison of two schedules of fluoreouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 12:14–20
12. Stagg RJ, Lewis BJ, Friedman MA et al (1984) Hepatic arterial chemotherapy for colorectal cancer metastatic to the liver. Ann Intern Med 100:736–743
13. Jager E, Heike M, Bernhard H et al (1996) Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. J Clin Oncol 14:2274–2279
14. Lang EK, Brown CL (1993) Colorectal metastases to the liver: selective chemoembolization. Radiology 189:417–422
15. Martinelli DJ, Wadler S, Bakal CW et al (1994) Utility of embolization or chemoembolization as second-line treatment in patients with advanced or recurrent colorectal carcinoma. Cancer 74:1706–1712
16. Becouarn YH, Brunet RC, Rouhier MLP et al (1995) High dose folinic acid and 5-fluorouracil bolus and continuous infusion for patients with advanced colorectal cancer. Cancer 76:1126–1131
17. Ychou M, Raoul JL, Desseigne F et al (2002) High-dose, single-agent irinotecan as first-line therapy in the treatment of metastatic colorectal cancer. Cancer Chemother Pharmacol 50:383–391
18. Rosati G, Rossi A, Reggiardo G et al (2002) A phase II study of irinotecan alternated with a weekly schedule of high dose leucovorin and 48-hour 5- fluorouracil infusion in patients with metastatic colorectal cancer. Oncology 62:209–215
19. Saltz LB, Cox JV, Blanke C et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905–914
20. Cunningham D, Pyrhonen S, James RD et al (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413–1418
21. Rougier P, Van Cutsem E, Bajetta E et al (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407–1412
22. Doulliard 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 355:1041–1047
23. Moehler M, Hoffmann T, Hildner K et al (2003) Weekly oxaliplatin, high-dose folinic acid and 24 h 5-fluorouracil (FUFOX) as salvage therapy in metastatic colorectal cancer patients pretreated with irinotecan and folinic acid/5-fluorouracil regimens. Z Gastroenterol 40:957–964
24. Recchia F, Rea S, Nuzzo A et al (2004) Oxaliplatin fractionated over two days with bimonthly leucovorin and 5-fluorouracil in metastatic colorectal cancer. Anticancer Res 24:1935–1940
25. Levi F, Zidani R, Misset JL et al (1997) International Organization for Cancer Chronotherapy: randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. Lancet 350:681–686