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Clinical paper

Weekly 24 h infusion of high-dose 5-fluorouracil and leucovorin in patients with biliary tract carcinomas

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From October 1995 to June 1997, 19 chemotherapy-naive patients with pathology-proven locally advanced or metastatic biliary tract carcinomas (BTC) were enrolled. The regimen consisted of 5-fluorouracil (5-FU) 2600 mg/m^2 and leucovorin (LV) 150 mg by weekly 24 h infusion for 6 weeks and followed by a 2 week break. The treatment was terminated if disease progressed, the patient refused or unacceptable toxicity occurred. All patients required a Port-A catheter insertion and were treated at outpatient clinics by portable infusion pumps. There were 12 males and seven females with a median age of 62 years (range 45–77). The primary tumor sites were nine intrahepatic cholangiocarcinomas (CC), three perihilar CC, one distal BTC and six gallbladder cancers. A total of 179 chemotherapy sessions were given with a mean of 9.5 (range 2–18). Eighteen patients were evaluable for response. The response rates were: 33% (six of 18) partial response (PR), 39% (seven of 18) stable disease (SD) and 28% (five of 18) progressive disease (PD). All of the patients were evaluable for toxicity. The most common toxicities were mild fatigue (nine of 19, 47%), loss of appetite (nine of 19, 47%), skin hyperpigmentation (five of 19, 26%) and diarrhea (two of 19, 11%). Only one patient had grade IV myelotoxicity with sepsis but without treatment-related death. The median time to progression was 4 months. The overall median survival time was 7.0 months. The median survival time of the PR was not reached, SD was 8.0 months and PD 3.5 months. In conclusion, weekly high-dose 5-FU with LV by 24 h infusion in an outpatient setting for patients with BTC is effective, only mildly toxic and deserves further study. [© 1998 Lippincott-Raven Publishers.]

Key words: Biliary tract carcinoma, high-dose fluorouracil, infusion pump, leucovorin.

Introduction

The results of treatment of locally unresected or disseminated biliary tract cancer (BTC) to date have been discouraging, possibly due to its rarity. The agent with the greatest reported experience is 5-fluorouracil (5-FU), administered by a variety of schedules or with other cytotoxic agents, with a response rate of only 0–20%.[1–5] Thus, new treatment strategies must be evaluated. Over the past 10 years, a number of preclinical studies and clinical trials indicating enhancement of 5-FU anti-tumor activity by addition of leucovorin (LV) have been performed. An excess of intracellular reduced folates appears to be necessary for optimal inhibition of thymidylate synthesase by fluorinated pyrimidines. Multiple controlled clinical trials from Roswell Park Institute,[6] City of Hope,[7] Princess Margaret Hospital[8] and the review of the Advanced Colorectal Cancer Meta-Analysis Project[9] have confirmed a statistically significant increase in objective tumor response rates in patients with metastatic colorectal cancer with 5-FU and LV compared with 5-FU alone. Ardalan *et al.*, using a weekly 24 h infusion of high-dose 5-FU (2600 mg/m^2) and LV (500 mg/m^2) for metastatic colorectal cancer, reported a high response rate and low toxicity in pretreated and untreated patients in 1991.[10] Their study differs from the other studies using 5-FU/LV in the following: (i) the maximum-tolerated dose (MTD) of 5-FU as a single agent was not compromised when a modulator was co-administered, (ii) unlike other 5-FU/LV studies, toxicity was minimal and acceptable, (iii) responses were seen in patients who had failed 5-FU/LV administered by other methods, and (iv) survival of chemotherapy-naive patients greater than 22 months was reported. Since 5-FU remains the most common agent for patients with BTC, we suggest that a regimen similar to that of Ardalan can be applied to patients with BTC. It was reported from the Ardalan series and our pilot study experience that many implanted central venous catheters were becoming blocked by calcium-LV stones when 5-FU and high-dose LV

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(500 mg/m^2) were infused in the same bag. In addition, the optimal dose for LV as a bio-modulator of 5-FU has not been determined. Therefore, we decided to perform a clinical trial to use weekly 5-FU 2600 mg/m^2 and LV 150 mg infused concomitantly through a portable infusion pump for chemotherapy-naive patients with BTC. Here, we present the results of this phase II trial.

Patients and methods

All patients were required to have known primary biliary tract adenocarcinoma beyond the hope of cure. There had to be histologic proof of residual primary, recurrent or metastatic disease. Eligibility criteria included histologically confirmed and radiologically measurable or evaluable unresectable cancer of BTC without prior chemotherapy, performance status of 3 or less on the Zubrod scale, absolute granulocyte count greater than 1500/μl, platelet count greater than 100 000/μl, serum creatinine concentration 2 mg/dl or less and serum bilirubin 5.0 mg/dl or less. Jaundiced patients with evidence of biliary tract obstruction whose biliary tract could be adequately decompressed by a stent placed during endoscopic procedures, operation or percutaneous transhepatic approach with a subsequent reduction in the bilirubin level to 5.0 mg/dl or less were eligible for this study. Prior radiotherapy was allowed.

Before the initiation of therapy, all patients were required to have a Port-A catheter via the subclavian vein in order to accommodate protracted infusion of the compounds and allow the patients to be treated at an outpatient setting. Therapy consisted of 5-FU 2600 mg/m^2 admixed with LV 150 mg in the same bag and portable infusion pump over 24 h. Treatment was repeated every week for 6 weeks. After a therapy-free interval of 2 weeks, the second course was administered. No dose escalation was allowed for either 5-FU or LV. However, if grade 3 hematologic or gastrointestinal toxicities were observed in any course of the therapy, the dose of 5-FU was lowered by level 1, 2000 mg/m^2. Chemotherapy was continued until there was objective evidence of disease progression or unacceptable toxicity, or the patient refused further therapy.

Response was assessed by repeating preterite radiological studies at 8 weekly intervals. In instances of clinical suspicion of progressive disease (PD) during treatment, response to therapy was evaluated immediately. In the presence of PD or stable disease (SD) without improvement of the patient's condition, therapy was stopped. Complete response (CR) was defined as disappearance of all measurable disease based on the radiological studies. Partial response (PR) was defined as 50% or greater decrease in the sum of the products of the largest perpendicular diameters of all the measurable lesions at least 4 weeks without progression of any lesion or the appearance of new lesions. SD was defined as a decrease of the lesion for at least 4 weeks which did not reach the criteria of PR or a less than 25% increase of lesions. PD was defined as a 25% or greater increase in the size of one or more measurable lesions or the appearance of the new lesions. The time to disease progression for both CR and PR patients was calculated from the day of the first time of chemotherapy to the day of the first documented evidence suggestive of disease progression or the start of additional anticancer therapy. Survival time was calculated from the start of the therapy to death and was established by the Kaplan-Meier method. Factors of independent prognostic value were determined by the log-rank test.

Results

Nineteen patients were enrolled in this study between October 1995 and June 1997. The clinical data of the 19 patients are summarized in Table 1. There were 12 males and seven females with a median age of 62 years (range 45–77 years). The median performance status was 1. Five patients had a history of biliary stones. Six patients had tubal drainage for biliary obstruction prior to this trial. The sites of primary tumor included nine intrahepatic cholangiocarcinomas (CC), six gallbladder cancers (GB), three perihilar CC and one distal BTC. Seven patients had one disease site, nine had two and three had three. A total of 179 chemotherapy sessions with a mean of 9.4 (range 2–18) were administered to the 19 patients.

One patient developed recurrent biliary tract infection after the third dose of chemotherapy, so the chemotherapy was aborted due to intractable infection; he was excluded from assessment of response. The other 18 patients were all evaluable for response. There were six PR (33%) (95% CI: 14–57%), seven SD (39%) and five PD (28%). The median time to progression was 4 months. The overall median survival time was 7.0 months (1.5–24 months). The median survival time of the PR was not reached, SD was 8.0 months and PD was 3.5 months. There were no survival differences in terms of sex, tumor site, performance status, number of disease sites, stone history and tubal drainage by the log-rank test.

All of the patients were evaluable for toxicity by the NCI/SWOG criteria (Table 2). The most common toxicities were fatigue (nine of 19, 47%), loss of appetite (nine of 19, 47%), skin hyperpigmentation (five of 19, 26%) and diarrhea (two of 19, 11%). Most of the toxicities were grade I–II and well tolerated. No patient needed to be admitted for supportive care. Only one grade IV myelotoxicity with sepsis was observed and the patient recovered after parenteral antibiotics. One had grade III vomiting, but did not require parenteral nutrition. There was no treatment-related death.

Table 1. Clinical data of the 19 patients

Characteristic	No. of patients (%)
Median age	62 (45–77)
Gender (M/F)	12/7 (63/37)
Primary tumor	
intrahepatic	9 (47)
perihilar	3 (15)
distal	1 (5)
gallbladder	6 (32)
Performance status	
1	5
2	14
Sites of disease	
local disease	18
liver metastases	6
peritoneum	5
lymph node	3
ovary	1
hernia sac	1
No. of disease sites	
1	7
2	9
3	3
Tubal drainage for bile	
yes	6
no	13
Total bilirubin	
≤ 2	15
$>2, \leq 5$	4
Stone Hx	
yes	5
no	14

Discussion

At present, few reports exist on chemotherapy for advanced BTC. Most of the single-agent data have been generated with bolus 5-FU, while the remainder of the single-agent data is primarily anecdotal. The majority of previously reported trials comprised fewer than 10 patients and have frequently failed to separate patients with BTC from those with pancreatic cancer or hepatoma.[11] Although 5-FU has been used both as a single agent and in combination chemotherapy trials for the treatment of BTC, its impact on survival and response is limited. Combinations like FAM and 5-FU and doxorubicin and methyl-CCNU have produced minor improvements in response rate with little survival benefit.[1,2] A randomized trial comparing FAM with 5-FU alone did not demonstrate any benefit in terms of the response rate and survival.[5] Paclitaxel, a new promising agent in several solid tumors, has no activity in advanced BTC.[12] Therefore, single 5-FU is still the mainstay for patients with advanced BTC.

The modulation of 5-FU with LV has been widely documented in both biochemical and clinical studies in colorectal cancer, but 5-FU and LV were not commonly reported in the literature for patients with advanced BTC. The goal of this trial is to test the efficacy of biochemical modulation of high-dose 5-FU given on a weekly 24 h schedule adapted from the experience of patients with colorectal cancer.[10] The response rate and survival in this study are modest, and fall into the confidence ranges of other combination therapies for BTC. Kajanti *et al.*[13] reported epirubicin-sequential methotrexate with bolus infusion of conventional dose 5-FU/LV every 3 weeks and no objective tumor response was observed for extrahepatic BTC. Glimelius *et al.*[14] showed an

Table 2. Toxicity (NCI/SWOG) (n=19)

Toxicity	0	1	2	3	4
WBC	18 (95)	0	0	0	1 (5)
Stomatitis	15 (79)	2 (10.5)	2 (10.5)	0	0
Vomiting	12 (64)	5 (26)	1 (5)	1 (5)	0
Diarrhea	17 (89.5)	2 (10.5)	0	0	0
Loss of appetite	10 (53)	9 (47)	0	0	0
Skin hyperpigmentation	14 (74)	5 (26)	0	0	0
Fatigue	10 (53)	9 (47)	0	0	0

Percentages in parentheses.

improvement of survival and quality of life in advanced BTC by 3 day bolus infusion of 5-FU/LV with or without etoposide but the PR was only 8%. Polyzos *et al.*[15] demonstrated that monthly mitomycin with bolus of 5-FU and LV achieved a 23% response rate in 13 patients with BTC, but had higher incidence of stomatitis and diarrhea than our series. The weekly 24 h infusion of high-dose 5-FU and LV for patients with BTC yielded promising results in comparison with the conventional dose schedule of 5-FU/LV combination. We suggest that regimen deserves further confirmatory study for patients with BTC.

The toxicity of this regimen was mild and could be used in an outpatient clinic setting. The incidence and severity of stomatitis and myelotoxicity of this regimen were milder than conventional bolus of 5-FU.[6-8,13-15] The mechanism underlying the relatively high activity and surprisingly low toxicity of high-dose 5-FU and LV by 24 h weekly infusion, of which the dose intensity was almost four times those of the conventional bolus regimens, remains unclear. Some *in vitro* and *in vivo* studies have indicated that prolonged infusion of 5-FU and LV over 24 h may be critical for its maximal cytotoxic effect.[10,16,17] The negligibly low toxicity may be related to the optimal treatment and rest interval, which provides a 6 day rest after 24 h drug infusion, as well as the differential expression of the complex metabolizing enzymes of 5-FU in different organ systems.[10,18] Further studies are needed to clarify the mechanism underlying the beneficial effect of the high-dose 5-FU and LV regimen. However, since no complete response has been attained and the response was not durable, indicating the requirement of adding other agents such as cisplatin[19] or mitomycin[20] into this dose schedule to improve the response rate and survival. A phase II trial of weekly high-dose 5-FU and LV with mitomycin has been recently initiated in our institute.

We conclude that this schedule is an effective and safe regimen for patients with BTC, which can be used in outpatient treatment. Further comparative studies to validate this schedule with the bolus dose schedule are warranted.

References

1. Hall SH, Benjamin RS, Murphy WK, Valdivieso M, Bodey GP. Adriamycin, BCNU, ftorafur chemotherapy of pancreatic and biliary tract cancer. *Cancer* 1979; **44**: 2008–13.
2. Harvey JH, Smith FP, Schein PS. 5-Fluorouracil, mitomycin, and doxorubicin (FAM) in carcinoma of the biliary tract. *J Clin Oncol* 1984; **2**: 1245–8.
3. Falkson G, MacIntrne JM, Moertel CG. Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. *Cancer* 1984; **54**: 965–9.
4. Haskell CM, Lavey RS, Ramming KP. Neoplasms of the gastrointestinal system, In: Haskell CM, Berek JS, eds. *Cancer treatment*, 4th edn. Philadelphia, PA: Saunders 1995: 502–29.
5. Takada T, Kato H, Matsushiro T, Nimura Y, Nagakawa T, Nakayama T. Comparison of 5-fluorouracil, doxorubicin and mitomycin C with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinoma. *Oncology* 1994; **51**: 396–400.
6. Petrelli N, Herrera L, Rustum Y, *et al.* A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. *J Clin Oncol* 1987; **5**: 1559–65.
7. Doroshow JH, Multhauf P, Leong L, *et al.* Prospective randomized trial comparing 5-fluorouracil versus 5-fluorouracil and high dose folinic acid for treatment of advanced colorectal cancer. *J Clin Oncol* 1990; **8**: 495–501.
8. Erlichman C, Fine S, Wong A, Elhakim T. A comparison of 5-fluorouraciand folinic acid in patients with metastatic colorectal carcinoma (MCC). *J Clin Oncol* 1988; **6**: 469–75.
9. The Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; **10**: 896–903.
10. Ardalan B, Chua L, Tian EM, *et al.* A phase II study of weekly 24-hour infusion with high-dose 5-fluorouracil with leucovorin in colorectal carcinoma. *J Clin Oncol* 1991; **9**: 625–30.
11. Oberfield RA, Rossi RL. The role of chemotherapy in the treatment of bile duct cancer. *World J Surg* 1988; **12**: 105–8.
12. Jones DV, Lozano R, Hoque A, Markowitz A, Patt YZ. Phase II study of paclitaxel therapy for unrectable biliary tree carcinomas. *J Clin Oncol* 1996; **14**: 2306–10.
13. Kajanti M, Pyrhonen S. Epirubicin-sequential methothrexate-5-flouorouracil-leucovorin treatment in advanced cancer of the extrahepatic biliary system. *Am J Clin Oncol* 1994; **17**: 223–6.
14. Glimelius B, Hoffman K, Sjoden PO, *et al.* Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996; **7**: 593–600.
15. Polyzos A, Nikou G, Giannopoulos A, *et al.* Chemotherapy of biliary tract cancer with mitomycin-C and 5-fluorouracil biologically modulated by folinic acid. A phase II study. *Ann Oncol* 1996; **7**: 644–5.
16. Houghton JA, Williams LG, DeGraff SSN, *et al.* Relationship between dose rate of (6*RS*) leucovorin administration, plasma concentrations of reduced folates, and pools of 5,10-methylene-tetrahydrafolates in human colon adenocarcinoma xenografts. *Cancer Res* 1990; **50**: 3493–502.
17. Harris BE, Song R, Soong SJ, Diasio RB. Relationship between hydropyridamidine dehydrogenase activity and plasma 5-fluorouracil levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. *Cancer Res* 1990; **50**: 197–201.

18. Hsu CH, Heh KH, Chen LT, *et al.* Weekly 24-hour infusion of high-dose of 5-fluorouracil and leucovorin in the treatment of advanced gastric cancer. *Oncology* 1997; **54**: 275-80.
19. Okada S, Ishii H, Nose H, *et al.* A phase II study of cisplatin in patients with biliary tract carcinoma. *Oncology* 1994; **51**: 515-7.
20. Taal BG, Audisio RA, Bleiberg H, *et al.* Phase II trial of mitomycin in advanced gall bladder and biliary tree carcinoma. An EORTC gastrointestinal tract cancer cooperative group study. *Ann Oncol* 1993; **4**: 607-9.

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