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Report

Mitomycin C with weekly 24-h infusion of high-dose 5-fluorouracil and leucovorin in patients with biliary tract and periampullar carcinomas

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We have reported a 33% partial response rate with acceptable toxicity using weekly 24-h infusion of high-dose 5-fluorouracil (5-FU) and leucovorin (LV) in patients with far advanced biliary tract cancers (BTC). In this study, we added mitomycin (MMC) to 5-FU and LV in an attempt to improve the response rate and survival. From July 1997 to September 1999, 25 chemotherapy-naive patients with pathology-proven far advanced BTC and periampullar cancers were enrolled. The regimen consisted of MMC 10 mg/m^2 every 8 weeks combined with 5-FU 2600 mg/m^2 and LV 150 mg at a schedule of 24-h infusion weekly for 6 weeks followed by a 2 week break. There were 10 males and 15 females with a median age of 57 years (range 40–76). The sites of primary tumor were 15 intrahepatic cholangiocarcinomas (CC), one perihilar CCs, three distal BTC, three gallbladder cancers (GB) and three periampular cancers. A total of 148 sessions of chemotherapy were given with a mean of 8 (range 2–18). Nineteen patients were evaluable for response. The response rate was: 26% (five of 19) partial response, 42% (eight of 19) stable disease and 32% (six of 19) progressive disease. All of the patients were evaluable for toxicity. Toxicities more than grade III–IV were thrombocytopenia 16% (four of 25), leukopenia 12% (three of 25) and vomiting 4% (one of 25). There were four treatment-related deaths. The median time to disease progression was 3 months. The median survival was 6 months. A combination of MMC with weekly high-dose 5-FU and LV in patients with BTC did not improve the response rate, but produced more toxicity than weekly high-dose 5-FU and LV alone. [© 2001 Lippincott Williams & Wilkins.]

Key words: Biliary tract carcinoma, high-dose 5-fluorouracil, infusion pump, leucovorin, mitomycin, periampullar cancer.

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Introduction

The results of treatment of locally unresected or disseminated biliary tract cancer (BTC) to date have been discouraging, possibly due to the rarity of this disease. The most common single agent studied for systemic application in BTC is 5-fluorouracil (5-FU).[1] 5-FU administered either by a variety of schedules or with other cytotoxic agents yielded response rates from 0 to 20%,[2–5] and a randomized trial comparing FAM (5-FU, doxorubicin and mitomycin) with 5-FU alone demonstrated an equal response rate and survival.[6] To date, single 5-FU is still the mainstay for patients with advanced BTC. Over the past 10 years, a number of preclinical and clinical trials indicating enhancement of 5-FU antitumor activity by the addition of leucovorin (LV) have been published.[7] In an attempt to enhance the 5-FU antitumor activity against BTC, we have used a new dose schedule of weekly 24-h infusion of high-dose 5-FU admixed with LV in patients with far advanced BTC; 33% response rate with acceptable toxicity was observed in this case.[8] However, since no complete response was attained and the response duration was short, indicating the requirement of adding other active agents into this dose-schedule to overcome the potential drug-resistance, and improve the response rate and survival.

Mitomycin (MMC) is another extensively studied agent for BTC.[1] The rationale for applying MMC in BTC patients was provided by the pharmacokinetic studies in which biliary MMC levels were found to be as much as 8 times higher than relative plasma levels because of enterohepatic drug recycling.[9] An early clinical report of single MMC in BTC had an encouraging response rate of 47% in 15 patients.[10] However, the EORTC trial showed that MMC for advanced BTC had only a 10% response rate.[11] In

addition, based on the observation of clinical synergy between MMC and infusional 5-FU in colorectal cancer by Ross *et al.*[12] and Becker *et al.*[13] A combination of 5-FU, LV and MMC seems to be an interesting approach for BTC because of its non-cross toxicity and unique antitumor activity against BTC. In fact, several such trials have been performed. Polyzos *et al.*[14] utilized monthly MMC and 4-day bolus 5-FU modulated by LV for BTC and achieved a 23% response rate in 13 patients with BTC. Raderer *et al.*[15] used a similar monthly MMC, 5-FU and LV combination for BTC and the response rate was 25%, but with higher myelotoxicty. We have reported using weekly 24-h infusion of high-dose 5-FU and LV in patients with far advanced BTC that yielded a 33% response rate with minimal toxicity.[8] It seems reasonable to add MMC into our weekly 24-h infusion of high-dose 5-FU and LV regimen to test whether this would improve the response without increasing the toxicity profile for patients with BTC. Herein, we present the results of this phase II trial.

Patients and methods

All patients were required to have known primary bilirary tract and periampullar adenocarcinoma beyond 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 and periampullar without prior chemotherapy, performance status $\leqslant 2$ on the Zubrod scale, absolute granulocyte count >1500/l, platelet count $>100\,000$/l, serum creatinine concentration $\leqslant 2$ mg/dl and serum bilirubin $\leqslant 5.0$ mg/dl. Jaundiced patients with evidence of biliary tract obstruction whose biliary tract could be adequately decompressed by a stent placed during endoscopic procedures, operation or a percutaneous transhepatic drainage approach with a subsequent reduction in the bilirubin level to $\leqslant 5.0$ mg/dl were eligible for this study. Prior radiotherapy was allowed.

Before the initiation of therapy, all patients were required to have a Port-A-Cath 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 MMC 10 mg/m^2 on day 1 every 8 weeks. 5-FU 2600 mg/m^2 was admixed with LV 150 mg in the same bag and delivered by the portable infusion pump over 24 h. 5-FU and LV were 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 preterit radiological studies at 8-weekly intervals and was classified according to WHO response criteria. When there was 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 for 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 that did not reach the criteria of PR or less than a 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 response rate of our previous study of 5-FU/LV alone in BTC was 33%; however, the 95% confidence (CI) interval was 14–57%.[8] Therefore, we hypothesized a 20% response rate of this study was reasonable. A Simon's two-stage optimal design was utilized for the first 10 evaluated patients; if there was more than one response then an additional 19 patients were to be enrolled. 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. Survival curves were established by the Kaplan–Meier method. Factors of independent prognostic value were determined by log-rank test. Toxicity was classified according to WHO criteria.

Results

Twenty-five patients were enrolled in this study between July 1997 and September 1999. The clinical data of the 25 patients are summarized in Table 1. There were 10 males and 15 females with a median age of 57 years (range 40–76 years). The median performance status was 1. Seven patients had a history

Table 1. Clinical data of the 25 patients

Characteristic	No. of patients (%)
Median age	57 (40–76)
Gender (M/F)	10/15 (40%/60%)
Primary tumor	
intrahepatic	15 (60%)
perihilar	1 (4%)
distal	3 (12%)
gallbladder	3 (12%)
periampular vater	3 (12%)
Performance status	
0	1
1	15
2	9
Tubal drainage for bile	
yes	12
no	13
Stone history	
yes	7
no	18

of biliary stones. Twelve patients had tubal drainage for biliary obstruction prior to treatment. The sites of primary tumor included 15 intrahepatic cholangiocarcinomas (CC, one), one perihilar CCs, three gallbladder cancers (GB), three distal BTC and three periampullar cancers. A total of 148 sessions of chemotherapy [mean=8 (range 2–18)] were administered to these 25 patients. Six patients were excluded for response evaluation due to toxicity and lost to follow-up. Nineteen patients were evaluable for response. There were five PRs, but no CRs. The overall response rate was 26% (95% CI 14–57%). In addition, there were eight SDs (42%) and four PDs (32%), respectively. The median time to disease progression was 3 months. The overall median survival was 6 months. There were no survival differences in terms of sex, tumor site, performance status, stone history and tubal drainage by the log-rank test.

All of the patients were eligible for toxicity evaluation by the WHO criteria (Table 2). The major grade III/VI toxicities were thrombocytopenia 16% (four of 25), neutropenia 12% (three of 25) and vomiting 4% (one of 25). Stomatitis and diarrhea were minimal. Four patients suffered treatment-related deaths; three patients with percutaneous transhepatic drainage died of neutropenic sepsis in the early course of treatment, and one patient died of acute endocarditis without myelotoxicity and history of valvular heart disease. One female patient dropped out due to recurrent peptic ulcer bleeding after the second session of chemotherapy, but she did not have oral mucositis or stomatitis. One patient was lost to follow-up after 3 sessions of chemotherapy without any adverse effects. Because the treatment-related deaths exceeded 10% of the initial 25 patients, we terminated this study early.

Table 2. Drug toxic effects (WHO) (*n*=25)

	Toxicity				
	0	1	2	3	4
WBC	18 (72%)	1 (4%)	3 (12%)	0	3 (12%)[a]
Platelet	18 (72%)	1 (4%)	2 (8%)	2 (8%)	2 (8%)
Stomatitis	21 (84%)	1 (4%)	3 (12%)	0	0
Vomiting	18 (72%)	2 (8%)	4 (16%)	0	1 (4%)
Diarrhea	23 (92%)	2 (8%)	0	0	0

[a]Three patients had percutaneous transhepatic drainage.

Discussion

At present, the number of studies on chemotherapy for advanced BTC is low. Most of the single-agent data have been generated with bolus 5-FU, while the rest of the single-agent data were primarily anecdotal. 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, doxorubicin and methyl-CCNU have produced only minor improvements in response rates with little survival benefit.[3,4] A randomized trial comparing FAM with 5-FU alone did not demonstrate any benefit in terms of the response rate and survival.[6] Paclitaxel, a promising agent in several solid tumors, has no effect on advanced BTC.[16] 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,[7] but 5-FU and LV was not commonly reported in the literature for patients with advanced BTC. Kajanti *et al.*[17] reported that epirubicin–sequential methotrexate with bolus infusion of conventional dose 5-FU/LV every 3 weeks did not give any objective tumor response for extrahepatic BTC. Glimelius *et al.*[18] showed an improvement of survival and quality of life in advanced BTC by 3-day bolus infusion of 5-FU/LV with or without etoposide; however, the response rate was only 8%. Recently, a cisplatin and 5-day 5-FU infusion without LV has showed a 25% response rate in 25 patients with BTC.[19] The major adverse effects were over 30% grade III/IV neutropenia and vomiting in this series. Sanz-Altmira *et al.*[20] presented a schedule of 4-day 5-FU with LV and carboplatin monthly for patients with BTC. The response rate was 21.4% with 57% febrile neutropenia.

We had reported a unique schedule of weekly 24-h infusion of high-dose 5-FU and LV for patients with BTC in 1998.[8] The response rate was 33% and the median survival was 7 months with less than 10% major toxicity. This dose schedule was superior to others in terms of its relatively low toxicity. However, there were no CRs and the response duration as well as survival was not longer than other studies. Therefore, a combination regimen consisting of weekly high-dose 5-FU and LV with other active agents against BTC is worthy of study.

The MMC has an 8 times higher level in the biliary tree than the relative plasma level because of enterohepatic drug recycling.[9] The toxicity of MMC is not crossed with 5-FU. Therefore, the 5-FU and MMC combination is worthy of exploration for advanced BTC. The present study reported a 26% response rate. The major toxicities of this study were neutropenia and thrombocytopenia. A monthly MMC schedule with a 4-day bolus of 5-FU and LV by Polyzos *et al.*[14] achieved a 23% response rate in 13 patients with BTC, but the incidence of stomatitis and diarrhea was higher than in our study. Raderer *et al.*[15] showed a similar schedule of monthly MMC with a 4-day bolus of 5-FU and LV in patients with BTC. The response rate was 25% with 15% severe thrombocytopenia. Our study and others suggested that MMC with different schedules of 5-FU and LV yielded similar response rates with equal toxicity. There is no evidence that adding MMC to 5-FU/LV improves the response rate and survival.

The rationale of adding MMC to a 5-FU-based regimen is the enterhepatic circulation. However, a great majority of patients with BTC had some degree of biliary tract obstruction and required biliary drainage. In this study, three patients that died of neutropenia sepsis had percutaneous transhepatic drainage. It is obvious that the effect of hepatobiliary circulation on such patients might be less or lost, particular on patients with total biliary tract obstruction. This may partially explain why MMC in combination with 5-FU did not increase the efficacy of treatment and gave serious neutropenia sepsis on patients with percutaneous transhepatic drainage. Therefore, we need to modify the eligibility criteria in any subsequent study for jaundiced patients with biliary tract drainage; reducing the bilirubin level from 5.0 to less than 3.0 mg/dl and the tube position needs to be reconfirmed by a radiologist before the chemotherapy.

Conclusion

This schedule is less effective with higher toxicity than weekly 24-h infusion of high-dose 5-FU and LV in patients with far advanced BTC. The 5-FU/LV-based schedule is still an interesting regimen for further exploration; we have initiated a study with oral tegafur–uracil and LV for more convenience and lower toxicity to patients with BTC and periampullar cancer.

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