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Evaluation of efficacy and toxicity of systemic chemotherapy of combined epirubicin, cisplatin and bolus 5-fluorouracil for hepatobiliary tumors

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ABSTRACT

We aimed to search the efficacy and toxicity of epirubicin, cisplatin, bolus 5-fluorouracil regimen in hepatobiliary tumors. Twelve patients, (8 with biliary tumors, 4 with hepatocellular carcinoma) were included. All patients were inoperable or metastatic. 5- Fluorouracil 500 mg/m^2 i.v. bolus (day 1-5), cisplatin 60 mg/m^2 i.v. (day 1), epirubicin 50 mg/m^2 i.v. (day 1) chemotherapy was given every 21 days. The patients were evaluated after median 4 cycles. There was partial response in 3 (37.5%), stable disease in 2 (25%) and progression in 3 (37.5%) patients with biliary tumor. One patient showed partial response (25%), 1 had stable disease (25%) and 2 patients had progression (50%) in hepatocellular carcinoma group. Grade 3/4 side effects were thrombocytopenia in 2 patients (17%), neutropenia in 2 patients (17%), emesis in 1 patient (8%) and alopecia in 4 patients (33%). Treatment of hepatobiliary tumors with this regimen was well tolerated. More definite results with further studies including homogeneous groups of patients must be performed. [Turk J Cancer 2006;36(2):69-74].

KEY WORDS:

Hepatobiliary tumors, 5-fluorouracil, systemic chemotherapy

INTRODUCTION

Hepatobiliary tumors are a heterogeneous group of tumors which are usually diagnosed lately and definitive treatment is generally difficult. Biliary system tumors are uncommon cancers, which are seen at old ages especially between fifth and seventh decades. The difficulties of treatment are; their de novo resistance to chemotherapy agents, the difficulty of optimum surgery because of localization and their advanced stages at the time of diagnosis. The disease usually progresses rapidly and median survival time is six months (1). Curative surgery is rarely possible because the symptoms are indolent and appear lately. Pyrimidine analogues constitute the most effective group of agents for chemotherapy choice. In some monotherapy studies with 5-fluorouracil (5-FU), response rates change between 10% and 24% (2). Among combination therapies, FAM (5-FU, Doxorubicin, Mitomycin C) is the most prevalent combination and its response rates are approximately 29% (3).

Hepatocellular carcinomas (HCC) are the tenth leading cause of cancers in the world (4). HCC is a type of tumor that is resistant to therapies because it develops from a

cirrhotic background and remains asymptomatic for a long time until intrabiliary spreading begins (5). The role of systemic chemotherapy in the treatment of HCC is very limited. Doxorubicin is the most popular agent that was used in the studies. Response rates are less than 20% in mono or combining therapies. Median survival time is shorter than four months (6). Another frequently used agent is 5-FU and its response rates change between 10% and 75% (7,8). Combined chemotherapy regimens with doxorubicin or 5-FU show higher response rates but survival is not different from untreated patients (2,9). In this study, we searched the efficacy and toxicity of combined chemotherapy with bolus 5-FU, cisplatin, and epiribucin for hepatobiliary tumors.

MATERIALS AND METHODS

All of the 12 patients were either inoperable or metastatic in this study and all had histopathologically confirmed adenocarcinoma. Their glomerular filtration rate was more than 40 ml/min, WHO performance status between 0-1 and all had adequate liver, renal functions as well as normal cardiac functions. 5- Fluorouracil 500 mg/m^2 intravenously (i.v.) bolus (day 1-5), cisplatin 60 mg/m^2 i.v. day (given in 4 hours, with adequate hydration), epirubicin 50 mg/m^2 i.v. infusion (given in an hour, day 1) given every 21 days. We monitored complete blood count and serum chemistry analysis before each cycle and Computed Tomography (CT) scans were performed after two or three cycles. Patients were assessed according to standard WHO criteria prior to each treatment for response and toxicity (10). After chemotherapy cycles, evaluations were done with abdominal CT. Patients were accepted as having partial response if the size of tumor diminished more than 50%. Patients with regression between 25% and 50% were considered as stable. If new tumors developed or response rates were less than 25%, the disease was accepted as progressive (WHO criteria). Side effects clinically expressed within 21 days following each treatment were recorded as acute side effects.

RESULTS

This chemotherapy regimen was given to 12 patients (8 biliary tumors and 4 with HCC). Ten patients were males and two were females. The demographics, biochemical features and previous treatments are shown in tables 1 and 2. Three of eight patients with biliary tumors had distant metastasis before our study (2 liver, 1 lung). After administration of a total of 48 cycles with a median of 4 (2-6) cycles, the results were examined. There was partial response in 3 patients (37.5%), progression in 3 patients (37.5%) and stable disease in 2 patients (25%). Median response duration was 7 months (min-max: 3-19). Median survival time was 15 months (min-max: 4-29). As to the four patients with HCC; one patient had partial response (25%), one patient remained stable (25%), and 2 patients' illness progressed despite medical therapy (50%). The median response duration and survival of the patient who showed partial response was 15 months, the median response duration and survival of stable patient was 16 months and median response duration of the patients who progressed despite the treatment was 4 and 3 months and their median survival time was 10 and 4 months, respectively. Durations of response, overall survival and rates of response to this regimen are shown in table 3. There was no difference in AFP (Alpha-feto protein) levels in the group of patient with partial response after chemotherapy. Overall tolerance was good. The complications (Grade 3/4 toxicities) were as follows: Thrombocytopenia in 2 patients (17%), neutropenia in 2 patients (17%), emesis in 1 patient (8%) and alopecia in 4 patients (33%) (Table 4). No febrile neutropenia or death was observed during chemotherapy and there was no need for dose modifications or delay during chemotherapy. All patients responded well to treatment, and there were no toxic neutropenic deaths.

Table 1
Demographic features of the patients

No	Age	Sex	PS	Diagnosis	Previous treatment
1	43	M	0	Klatskin tm.	Absent
2	59	M	0	Klatskin tm.	Absent
3	41	M	0	Klatskin tm.	Absent
4	64	M	1	Klatskin tm.	Absent
5	55	M	0	Klatskin tm.	Absent
6	61	F	0	Gallbladder	Cholecystectomy
7	41	F	0	Ampulla of vater	Absent
8	25	M	0	Ampulla of vater	Absent
9	64	M	1	HCC	Absent
10	57	M	1	HCC	Absent
11	70	M	1	HCC	Absent
12	56	M	0	HCC	Absent

PS: Performance status; tm.: tumor; HCC: Hepatocellular carcinoma

Table 2
The patients' renal and hepatic functions and tumor markers

No	AST (UI/L)	ALT (UI/L)	T. Bilirubin (mg/dl)	D. Bilirubin (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	CA 19-9 (U/ml)	AFP (U/ml)
1	76	110	4.4	2.5	36	0.4	179	3.5
2	29	25	4.2	2.6	35	0.8	40000	0.6
3	52	69	1.4	0.6	28	0.6	45.3	3
4	114	116	2.3	1.3	45	0.9	112	9.7
5	47	74	5.8	3.8	20	0.1	141	2.4
6	31	16	0.4	0.11	50	1.2	2.5	1.97
7	40	31	0.9	0.5	15	0.6	6.4	0.8
8	72	34	2.9	1.7	47	0.8	0.2	86.7
9	47	57	1.37	1.09	40	0.4	24.8	569
10	42	45	0.8	0.6	21	0.2	12	37
11	43	16	0.9	0.3	44	0.6	10.4	>30000
12	76	86	4.2	3.1	35	0.8	36.8	220

T. Bilirubin: Total Bilirubin; D. Bilirubin: Direct Bilirubin

Table 3
Response to treatment and survival rates

No	ECF (n)	Response	Duration response (months)	Survival (months)	Current status
1	6	PR	19	21	exitus
2	3	PR	5	5	alive
3	6	SD	12	20	alive
4	2	PD	3	4	exitus
5	6	PR	12	12	alive
6	6	PD	7	15	exitus
7	3	SD	7	24	alive
8	2	PD	4	29	exitus
9	6	PR	15	15	alive
10	2	PD	4	10	alive
11	2	PD	3	4	exitus
12	4	SD	16	16	alive

PR: partial response; SD: stable disease; PD: progressive disease

Table 4
Toxicity of the treatment

Grade 3/4 Toxicity	n (%)
Anemia	-
Neutropenia	2 (17%)
Thrombocytopenia	2 (17%)
Emesis	1 (8%)
Alopecia	4 (33%)

DISCUSSION

Many patients are first seen with advanced hepatobiliary tumors because of lack of early clinical symptoms and they usually do not have a chance for curative surgery. Debate still goes on about a standard chemotherapy regimen in patients with hepatobiliary tumors. In this report, we investigated the efficacy and toxicity of bolus 5-FU, cisplatin, and epiribucin regimen which was found useful for gastric cancers, in former studies (11).

Commonly used chemotherapeutic agents in treatment of inoperable biliary tumors are 5- FU and mitomycin C (MMC). Adding alkylating agents to 5-FU chemotherapy had been tried in the past, but it was showed that it did not change survival and quality of life (2). In one study, only cisplatin was administered to nine patients with biliary tumors and no benefit with cisplatin monotherapy was shown (12). Generally, response rates with monotherapies are partial and less than 20%. Although response could be achieved with monotherapies, response times are too short and have no affect on survival. Other than monotherapies, FAM is one of the commonly used combined chemotherapy regimens. In one study where FAM (5-FU, Doxorubicin, MMC) was used every 4 weeks, the objective response rate was 31% (3). We observed better response rates than the old FAM regimen in our study. Ellis et al. (13) used ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, 5 FU 200 mg/m^2 i.v. continuous infusion) for biliary tumors in their study. The objective response rate was 40% (8 of 25 patients) and median duration of response was 10 months (5-22 months). In despite of the administration of 5-FU as i.v. bolus in our study, our response rate was 37.5% and median duration of response was 7 months. When our study was compared with the study of Ellis et al.'s, the response rates

and median duration of response were similar although our administration of 5-FU was bolus instead of continuous infusion. Di Lauro l et al. (14) used epirubicin 60 mg/m^2, cisplatin 75 mg/m^2, 5-FU 500 mg/m^2 i.v. continuous chemotherapy to 15 patients with unresectable tumors (6 gallbladder, 5 cholangiocarcinoma and 4 biliary duct carcinoma). They observed complete response in one patient, partial response in four patients and overall response rate was found as 33% (14). The response rate was better in our study compared to Di Lauro's study, though administration of 5-FU was as bolus.

The role of chemotherapy and which regimen should be used for HCC still remain controversial. Doxorubicin is the most frequently used drug and thought to be the most effective agent (15,16). Monotherapy studies were commonly done with doxorubicin and response rates were found approximately 11-15% (17). In the other monotherapy studies, 5-FU and cisplatin also were used and response rates were found in the range of 10-11% and 8.5% (6,18). While response rates were low in the monotherapies with 5-FU or doxorubicin, the response rates were higher in our ECF regimen (37.5%). Generally, higher response rates were found with combined chemotherapy regimens especially including 5-FU or doxorubicin but when their results are compared with untreated patients, improvement on survival cannot be shown with any combined regimen (9). Ellis et al. (13) reported partial response in 2 of 7 patients (%29) by using the ECF chemotherapy regimen. The response rate in our study was similar to Ellis et al.'s study, despite the administration of bolus 5-FU. Boucher et al. (19) administered ECF regimen to 21 patients with HCC (locally advanced or metastatic) and found a 14.5% response rate and median survival as 10 months. The low response rate in this study could be explained as the tumor development was seen in cirrhotic liver, in most of the cases, and the patient group was not homogeneous. This regimen was extremely well tolerated by the patients. Our study didn't have any neutropenia fever case while there were four cases in Ellis et al.'s study. Major hematological toxicity was minimal and the rate was equal to Ellis et al.'s study (Leukopenia 17%, Thrombocytopenia 17%). In our study, the most seen adverse effect was alopecia.

In conclusion, 5-FU and doxorubicin are the most commonly used and effective agents in hepatobiliary tumors. With this regimen, which is a combination of these drugs, objective response rates could be achieved but the most active combination chemotherapy regimens could not be developed yet. It seems that it is wiser to administer 5-FU continuously. It is likely that further studies with larger and homogeneous groups of patients will help to find an answer for more definite results.

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