

MITOMYCIN C IN ADVANCED GALLBLADDER CARCINOMA

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Carcinoma of the gallbladder has an overall 5-year survival of about 5 per cent (WARREN et coll. 1968, NEVIN et coll. 1976, PERPETUO et coll. 1978). Prognosis is correlated mainly with the stage of invasion (NEVIN et coll.) and to some extent with the sex, age, and initial performance status (PERPETUO et coll.). Tumor growth in the mucosa only (stage I) or in the mucosa and muscularis (stage II), had a 5-year survival of about 65 per cent (NEVIN et coll.). Tumor spread through the wall of the gallbladder to the serosa (stage III) or to the regional lymph nodes (stage IV) had a 5-year survival of about 6 per cent (NEVIN et coll.). Patients with tumor spread beyond the regional lymph nodes (stage V) all died within one year. Gallbladder carcinoma treated with intravenous or intraarterial mitomycin C has shown objective remission (SHIRAHA 1968, GUERRO et coll. 1972, MOERTEL 1973, SHIGENAGA 1976). Patients with advanced gallbladder carcinoma have been treated with intravenous and intraarterial infusions of mitomycin C at this hospital and the results are now reported.

Material and Methods

Between 1977 and 1979, 10 patients (8 women and 2 men) with microscopically confirmed advanced gallbladder carcinoma were treated. Median age was 62 years (range 48–78) at the time of diagnosis. Six patients had performance status I, two patients had performance status II, and two patients had performance status III (ZUBROD et coll. 1960). Two patients had gallbladder carcinoma stage III, and 8

stage V. Cholecystectomy had been performed in 7 patients, explorative laparotomy in 3, ileocecal resection in one, regional lymph node extirpation in one, and choledochotomy in one. One patient was treated with melphalan and medroxy-progesterone acetate before mitomycin C. None of the patients had been irradiated. All patients had a measurable tumor, a leukocyte count above 4×10^9 cells/l and a platelet count above 125×10^9 /l at the beginning of the mitomycin C treatment (Table 1).

Before each course, Hb, white blood cell count, and platelet count were determined in all patients, and the patients were examined physically. Hepatic and renal function tests were carried out regularly, as well as scintigraphy of the liver and ultrasound examinations repeatedly to evaluate the response. The coeliac or the hepatic arteries were catheterized for the intraarterial infusions (Fig. 1). Seven patients were given 2 to 5 courses of mitomycin C intraarterially, with 10 to 24 days' interval. For infusion 10 mg mitomycin C was dissolved in 100 ml isotonic sodium chloride solution or 15 mg mitomycin C was dissolved in 150 ml isotonic sodium chloride solution. The infusion was given at a rate of 6 ml/min. After each infusion the catheter was withdrawn and the procedure was repeated for each intraarterial infusion. After the intraarterial treatment, 2 patients were given 5-fluoro-uracil 1000 mg/m^2 body surface intravenously in 6 hours on day 1 and day 2 and

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Fig. 1. Hypervascular carcinoma of the gallbladder. Case 10.

mitomycin C 6 mg/m² intravenously in 30 min on day 2, with 3 weeks' intervals. Two patients received a single intravenous infusion of mitomycin C.

All other courses were given intravenously in a dosage of 10 mg/m² with a median 3 weeks' interval (range 2–11). Mitomycin C was dissolved in 100 ml

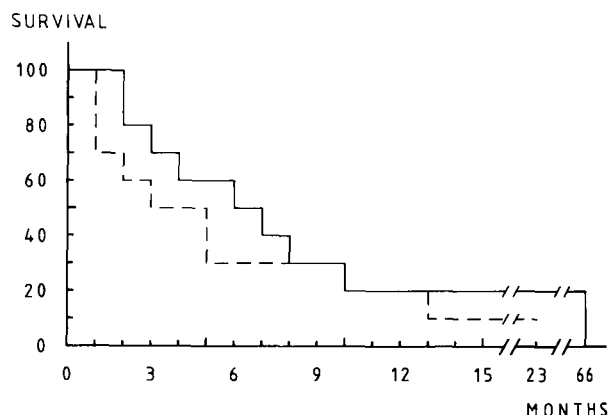


Fig. 2. Survival (in per cent) from time of diagnosis (—) and from beginning of mitomycin C treatment (---).

isotonic sodium chloride solution and infused in 20 to 30 min together with a fast running infusion of 300 ml isotonic sodium chloride solution. The dose was reduced according to myelosuppression (Table 2).

The response was assessed according to the following criteria: Stationary disease when the measurable tumor decreased or increased within 50 per cent of the initial size for at least one month, progressive disease when the tumor increased more than 50 per cent of the initial size or a new lesion appeared, and treatment failure when patients died after one course of mitomycin C.

Results

Stationary disease was obtained in 4 patients, progressive disease occurred in 4, and treatment

Table 1

Data of the cases before mitomycin C treatment

Case No.	Sex	Age	Performance status	Initial surgery	Stage of primary tumor
1	F	48	II	C+ICR	V
2	F	55	III	E	V
3	F	69	I	C	V
4	F	55	I	C	III
5	F	49	I	C+LNE	III
6	F	65	I	E	V
7	M	64	I	C+CD+GE	V
8	F	77	II	C	V
9	M	59	III	E	V
10	F	78	II	C+CDT	V

C=cholecystectomy. E=explorative laparotomy. ICR=ileocecal resection. LNE=lymph node extirpation. CDT=choledochotomy.

Table 2*Scheme for dose modification of mitomycin C*

Leukocytes ($\times 10^9$ cells/l)	Platelets ($\times 10^9$ /l)	Per cent of planned dose
3.1-3.5	71-100	50
2.1-3.0		25
≤ 2.0	≤ 70	0

failure in 2 patients. Eight patients with gallbladder carcinoma stage V survived for a median 3 months after mitomycin C treatment, 2 with stage III survived 13 and 23+ months, respectively (Table 3, Fig. 2).

After the intraarterial infusions, one patient had a local hematoma in the groin, 5 patients had a mild leukopenia, and one had a longlasting thrombocytopenia. Otherwise, no severe side effects of the intraarterial treatment occurred.

After intravenous mitomycin C treatment 4 patients had a mild leukopenia for a short time, and 4 patients had thrombocytopenia, extreme and longlasting in one of these. Nausea, diarrhea, and extensive alopecia occurred in one patient, and severe gastrointestinal bleeding in one. No side effects from other organ systems were noted. No drug-related deaths occurred.

Discussion

Mitomycin C has proved to be effective in several cases of gallbladder carcinoma (SHIRAHA, GUERRO et coll., MOERTEL, SHIGENAGA). However, in the present series, no objective remission occurred in 10 cases of advanced gallbladder carcinoma. The result was statistically significantly lower ($p=0.002$, binomial test) than the 47 per cent objective remission rate in a compiled review of cases published by CROOKE & BRADNER (1976; 7 patients with objective remission of 15). The present result did not differ ($p=0.31$, binomial test) from another series of cases with an 11 per cent objective remission rate (3 cases of 27; SHIRAHA).

In 2 cases, myelosuppression was so severe that the mitomycin C treatment was discontinued. This corresponds to previous reports (CROOKE & BRADNER). No drug-related deaths occurred. Thromboembolism was not encountered in any case, which is in accordance with previous experiences of intraarterial mitomycin C treatment at this hospital (MATTSSON et coll. 1977, HELLEKANT & SVANBERG 1978, HELLEKANT et col. 1978). This may be due to the duration of infusion; in long-term intraarterial infusions thromboembolism was frequent (CLOUSE et coll. 1977).

Patients with advanced gallbladder carcinoma have an extremely poor prognosis. Radical surgery does not improve survival compared with cholecys-

Table 3*Doses and results of mitomycin C in gallbladder carcinoma*

Case No.	Mitomycin C treatment				Overall total dose (mg/m ²)	Response	Survival (in months)	
	Intraarterially		Intravenously				After diagnosis	After mitomycin C
	No. of courses	Total dose (mg/m ²)	No. of courses	Total dose (mg/m ²)				
1	-	-	1	10	10	TF	7	1
2	-	-	1	10	10	TF	2	1
3	3	28	7	52	80	NC	10	10
4	3	32	5	33	65	NC	35+	23+
5	3	27	15	62	89	NC	66	13
6	3	30	-	-	30	PD	4	3
7	3	17	3	13	30	NC	6	5
8	-	-	6	53	53	PD	8	5
9	2	16	-	-	16	NC	2	1
10	5	41	-	-	41	PD	3	2

NC=stationary disease. PD=progressive disease. TF=treatment failure.

tectomy (DOWDY 1969). Single drug chemotherapy with 5-fluoro-uracil has proved to be of no use (MOERTEL, PERPETUO et coll.). High voltage irradiation has given alleviation (MOERTEL, SMORON 1977, KOPELSON et coll. 1977), combination chemotherapy with 5-fluorouracil and nitrosourea or adriamycin has given objective remission (PERPETUO et coll.), in small series of patients.

The median survival in the present series was longer than in previous reports. Thus, 8 patients with carcinoma stage V survived for a median 5 months after diagnosis. In other series of all stages of gallbladder carcinoma treated with or without chemotherapy, median survival was 3 to 5 months (MOERTEL, PERPETUO et coll.). Two patients with carcinoma stage III who had a relapse after nonradical surgery survived longer after mitomycin C treatment (13 and 23+ months) than the patients with stage V (median survival 3 months). The prolonged survival may be due to less extensive or less malignant tumor or to a better effect of mitomycin C. No objective remission occurred in the present series but the survival was prolonged compared with previous reports. Therefore, further trials with mitomycin C in gallbladder carcinoma are indicated.

SUMMARY

Seven patients with advanced gallbladder carcinoma were given intraarterial infusions of 10 to 15 mg mitomycin C with 10 to 24 days' interval, 3 received intravenous infusion (10 mg/m²) with median 3 weeks' interval. Stationary disease was obtained in 4 patients, progressive disease in 4, and treatment failures in 2. The median survival after mitomycin C treatment was 4 months (range 1-23+). Irreversible thrombocytopenia occurred in 2 patients and a severe gastrointestinal bleeding episode in one.

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