Cancer Chemother Pharmacol (1989) 23 (Suppl): S 9–S 12

Cancer Chemotherapy and Pharmacology

Randomized controlled study of mitomycin C/carboquone/5-fluorouracil/OK-432 (MQ-F-OK) therapy and mitomycin C/5-fluorouracil/doxorubicin (FAM) therapy against advanced liver cancer

Yuh Sakata, Yoshihiko Komatsu, Shinya Takagi, Soh Saitoh, Tohru Itoh, Hidekazu Suzuki, Kenichi Tsushima, Daisuke Sasaki, and Yutaka Yoshida

Hirosaki Cooperative Study Group of Cancer Chemotherapy, First Department of Internal Medicine, Hirosaki University School of Medicine, Hirosaki 036 Japan

Summary. We have previously reported that the combination of mitomycin C, carboquone, 5-fluorouracil and OK-432, including the intra-arterial administration of mitomycin C and carboquone (MQ-F-OK therapy), was effective in the treatment of advanced liver cancer. The Cooperative Study Group conducted a controlled study on MQ-F-OK therapy and the combination of mitomycin C, 5-fluorouracil and doxorubicin, including the intra-arterial administration of mitomycin C and doxorubicin (FAM therapy), against advanced liver cancer. Forty patients with advanced primary or secondary liver cancer were enrolled in this study and randomized into the MQ-F-OK group and the FAM group. Seventeen of the 21 cases in the MQ-F-OK group and 16 of the 19 cases in the FAM group were eligible for response evaluation in accordance with the criteria of the Japan Society for Cancer Therapy. There was no significant difference in the patient characteristics between the two groups. Three cases in the MQ-F-OK group and two in the FAM group showed partial response. There was, however, no significant difference in the response rates and the prolongation of life between the two groups. As for the side-effects, only anemia was observed more frequently in the FAM group than in the MQ-F-OK group. In conclusion, we could not preferentially recommend either MQ-F-OK therapy or FAM therapy for advanced liver cancer. The performance status of the patient was one of the most important factors in the treatment of advanced liver cancer because patients with poor performance status showed poorer results.

Introduction

In spite of the recent progress in diagnostic imaging for liver cancer, such as ultrasonography and computed tomography, cases of advanced and inoperable liver cancer are still found [7]. We have treated such patients with advanced liver cancer either with chemotherapy or with embolization [23]. The application of embolization is limited by the general condition of the patient, and the size and type of tumor [21]. At present, we have not standard effective therapy for the patients who are ineligible for surgical resection or embolization. It therefore remains necessary to find more effective protocols of chemotherapy for such patients through continued clinical research.

Offprint requests to: Yuh Sakata

We have previously reported that the combination of mitomycin C carboquone, 5-fluorouracil and OK-432 (MQ-F-OK therapy), including the intra-arterial administration of mitomycin C and carboquone, was beneficial for the treatment of advanced liver cancer 21). There have already been many reports about the intra-arterial administration of doxorubicin [9, 22] and several combination regimens including this drug [3, 4, 11]. Among them, the combination of mytomycin C, doxorubicin and 5-fluorouracil (FAM) [1, 10, 13, 24] was one of the best regimens reported. In this paper we present the results of a controlled clinical trial comparing the effectiveness of MQ-F-OK and FAM therapies on advanced liver cancer.

Materials and methods

Patients with the final diagnosis of progressive primary and/or secondary liver cancer were assessed by objective measurements in this study. The final diagnosis was confirmed by celiac angiography and/or histology of a biopsy specimen. The eligibility requirements for this trial included individuals under 75 years of age who were expected to survive more than one month, a performance status of 3 or better in accordance with the criteria of the Japan Society for Cancer Therapy (JSCT) [6], a minimum white blood cell count of 2000/cmm, a minimum platelet count of 50000/cmm, a serum creatinine level of under 2 mg/dl and a bilirubin value of under 2.5 mg/dl, with no prior chemotherapy within two weeks for biological-response-modifier therapy and antimetabolites or within four weeks for other therapy.

The patients were randomized into the MQ-F-OK group and the FAM group. Objective disease measurements were made using ultrasonography, computed tomography, liver scans using 99m-Tc and angiography.

The responses were defined according to the criteria of JSCT [6], which closely resemble the criteria of WHO: complete response (CR), absence of any detectable tumor mass for more than 4 weeks; partial response (PR), a decrease of over 50% in the product of two perpendicular diameters of the tumor or a decrease of over 30% of one diameter for than 4 weeks; no change (NC), a decrease of under 50% or a 25% increase in the product of two perpendicular diameters of the tumor or a decrease of under 30% of one diameter; progressive disease (PD), an increase of over 25% in the product of two perpendicular diameters of the tumor or the appearance of new lesions. In the assess-

Table 1. Regimens of MO-F-OK and FAM therapies

Therapy	Drug[a]	Dose (mg/m^2)	Application	Frequency
MQ-F-OK	MMC	10–20	i.a.	
	CQ	2–4	i.a.	// q. 2–4 weeks
	5-FUra or its analogs	300–600	p.o.	daily
	OK-432	0.2 KE up to the febrile reaction or 5 KE		
			s.c.	every other day
FAM	MMC	10	i.a.	
	DX	20	i.a.	// q. 4 weeks
	5-FUra	300	i.v.	once a week

[a] MMC, mitomycin, C; CQ, carboquone; 5-FUra, 5-fluorouracil; DX, doxorubicin

ment of no change, a case estimated with a tumor decrease of under 50% to over 25% or a 50% decrease for less than 4 weeks was estimated as having a minor response (MR).

MQ-F-OK therapy was performed according to our original protocol [21]: 10–20 mg/m^2 mitomycin C and 2–4 mg/m^2 carboquone were given intra-arterially as a single injection at the time of angiography using Seldinger's method every 2–4 weeks, and 5-fluorouracil tablets or one of its analogs, such as tegafur, was administered orally in a dose of 300–600 mg/patient every day. OK-432 [12, 14], the biological response modifier (produced in Japan), was subcutaneously injected every other day beginning with an initial dose of 0.2 KE and gradually increasing it until a febrile reaction occurred or the dose reached 5 KE; the administration was continued as far as possible. With the FAM therapy protocol, 10 mg/m^2 mitomycin C and 20 mg/m^2 doxorubicin were given intra-arterially as a single injection at the time of angiography every 4 weeks, and 5-fluorouracil was administered intravenously at a dose of 300 mg/m^2 once a week. These administrations were repeated and continued in the absence of major toxicities, particularly bone marrow suppression, or disease progression during therapy (Table 1).

Results

Between July 1984 and December 1985, 40 patients were enrolled in this study. Of the 40 cases, 21 were assigned to MQ-F-OK therapy and 19 to FAM therapy. The patient characteristics are shown in Table 2. The MQ-F-OK group consisted of 18 men and 3 women with an average age of 57 years (ranging from 32 to 72). The performance status ranged from 0 to 4, and the clinical stage was 2–4. There were 17 cases of primary liver cancer and 4 of secondary cancer metastasized from gastric cancer or colorectal cancer. Four cases had received prior therapy, such as 5-fluorouracil and mitomycin C, and 17 had no prior chemotherapy. Ten cases were positive for more than one of the HB series (HBsAg, HBsAb, HBeAg, HBeAb and HBcAb). There were 14 cases of liver cirrhosis and 8 cases had a positive α-fetoprotein value of over 200 ng/ml. Of the 21 cases, 3 were withdrawn from the study because their performance status was 4 or because they had received prior chemotherapy within 4 weeks, while one case had no follow-up after treatment. In the end, 17 cases were eligible for response evaluation, and 18 for side-effects.

In the FAM group, the ratio of men to women was 14 to 5, while the average age was 56.3 years (ranging from 31 to 74). The performance status ranged from 0 to 3, with most patients having grade 3. Fifteen cases had primary liver cancer and four had secondary liver cancer. Three cases had received prior chemotherapy, such as 5-fluorouracil and its analogs, and 16 cases had no previous therapy. In 16 cases, α-fetoprotein was positive, and 5 cases were positive for any in the HB series. Twelve cases had liver cirrhosis. Of the 19 cases, 3 were excluded from the response evaluation because of the lack of examination after treatment. In the end, 16 cases were eligible for response evaluation and 17 for evaluation of side-effects. There was no significant difference in the background between the two groups statistically.

Table 3 shows the treatment cycle and the average dose of each antitumor agent in the two groups. There was no significant difference in the treatment cycles between the two groups.

Table 4 lists the response for each treatment group. In the MQ-F-OK group, 3 cases showed PR, 7 NC and 7 PD,

Table 2. Patient characteristics

Characteristic	MQ-F-OK group	FAM group
Patients entered	21	19
Age (years; average, range)	56.9 (32–72)	56.3 (31–74)
Sex (M/F)	18/3	14/5
Evaluable for response	17	16
Diagnosis		
Primary	17	15
Secondary	4	4
Performance status		
0–1	4	3
2–3	15	16
4	2	0
Prior chemotherapy		
(+)	4	3
(−)	17	16
Cirrhosis		
(+)	14	12
(−)	7	7
HB series		
(+)	10	5
(−)	8	11
N.D.[a]	3	2
α-Fetoprotein (200 ng/ml <)	8	6

[a] Not determined

Table 3. Treatment cycles and average dose of each drug

Treatment	Cycles			Drug[a]	Average dose (mg)
	1	2	3		
MQ-F-OK (18 cases)	10	8	3	MMC	33.3
				CQ	6.1
				5-FUra	2138.3
				OK-432	48.3 KE
FAM (19 cases)	8	10	1	MMC	18.3
				DX	43.1
				5-FUra	2844.7

[a] MMC, mitomycin C; CQ, carboquone; 5-FUra, 5-fluorouracil; DX, doxorubicin

Table 4. Response

Group	Evaluable Case	Response				Response rate (%)
		CR	PR	NC (MR)	PD	
MQ-F-OK	17	0	3	7 (0)	7	3/17 (17.6)
FAM	16	0	2	8 (3)	6	2/16 (12.5)

Table 5. Side-effects according to the criteria of JSCT

Side-effect	MQ-F-OK[a]	FAM[a]
Anemia (Hb decrease over 2 g/dl)	9	13[b]
Leukocytopenia	12	8
Thrombocytopenia	9	10
Liver damage	2	2
Nausea	5	3
Vomiting	2	3
Anorexia	5	7
General malaise	6	6
Fever	5	4
Alopecia	0	3
Stomatitis	1	2
Abdominal distress	1	1
Pain	2	3

[a] Evaluable cases: 18 for MQ-F-OK group; 17 for FAM group
[b] $P < 0.05$ significant difference

while in the FAM group, 2 cases showed PR, 8 NC (including 3 MR) and 6 PD. There was no significant difference in response rate between the two groups. The toxicity data, including 18 cases in the MQ-F-OK group and 19 in the FAM group, are presented in Table 5. Hematological toxicities, such as leukocytopenia and thrombocytopenia, appeared after two treatment courses. Of the hematological toxicities, anemia was observed more frequently in the FAM group than in the MQ-F-OK group. There was, however, no difference in the incidence of leukocytopenia or thrombocytopenia between the two groups. Alopecia was found only in the FAM group and was due to doxorubicin. Other side-effects, including anorexia, nausea and general malaise, were found with almost the same frequency in the two groups.

The survival curves of the two groups, constructed using Kaplan-Meier's method, are shown in Fig. 1. There

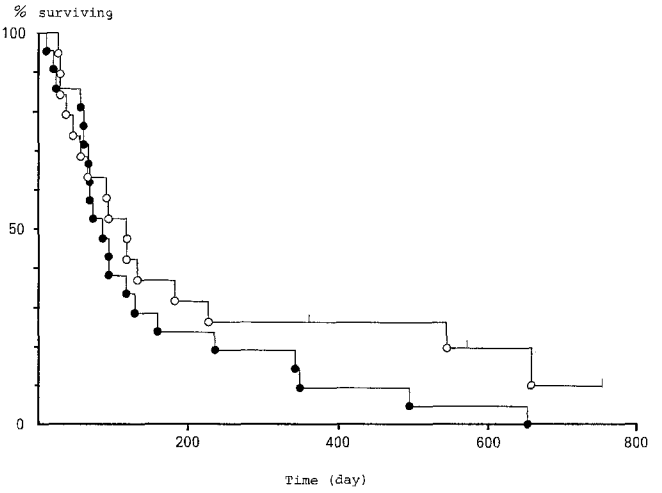

Fig. 1. Survival curves of the MQ-F-OK group (●——●) and FAM (○——○) group according to the Kaplan-Meier method. Median survival: MQ-F-OK group, 74 days; FAM group, 98 days. There is no significant difference between the two groups

was no significant survival advantage between the two groups. The median survival periods were 74 days for the MQ-F-OK group and 98 days for the FAM group.

Discussion

On the basis of the best result of the experimental examination using the ascitic tumor of Hirosaki tetraploid sarcoma [16], AH-7974 and AH-130 [15], we designed an intravenous MQF-OK therapy and applied it in clinical practice [17]. We concluded that this MQF-OK therapy was exceedingly beneficial in the treatment of advanced gastric cancer from the result of a randomized controlled study [18]. Subsequently we modified the MQ-F-OK protocol to include the intra-arterial administration of mitomycin C and carboquone for advanced liver cancer [21]. As for FAM therapy, since MacDonald et al. [8] reported the efficacy of this regimen in the treatment of advanced gastric cancer, many researchers have evaluated its therapeutic potential for various tumors in clinical practice [2, 5].

In this comparative study of MQ-F-OK and FAM therapies against liver cancer, we could not find any differences in terms of the antitumor effect or the prolongation of life between the two groups, and yet the response rates were 17% in the MQ-F-OK group and 12.5% in the FAM group. Comparing the side-effects, only anemia was observed in the FAM group more frequently than in the MQ-F-OK group. This side-effect, however, was rectified by blood transfusion and did not impede the continuance of the treatment. In the FAM group, however, three cases showed minor response in contrast to no response in the MQ-F-OK group. This result suggested that a higher dosage of agents and/or shorter intervals between administrations in the FAM regimen might be beneficial in the treatment of advanced liver cancer.

Incidentally, most cases in this trial had a performance status of 3, and it was difficult to administer more than two cycles because of the patients' rapidly deteriorating clinical condition. We have previously reported [19] that the better the performance status the better the response. The poor response in both groups studied might be asso-

ciated with the poorer performance status of the patients. The choice of which kind of regimen is optimal for patients with liver cancer [7] and the question of how to treat patients with a poor performance status remain unanswered, but it seemed to be of value to try sequential treatment from FAM therapy to MQ-F-OK therapy because of the similarity of tumor responsiveness as well as toxicity tolerance.

In conclusion, from this comparative study we could not preferentially recommend either MQ-F-OK therapy or FAM therapy in the treatment of advanced liver cancer because their effectiveness and side-effects were similar. The patient's performance status was one of the most important factors in the treatment of advanced liver cancer because a patient with a poor performance status will show poorer results. The greatest need is to find an early detection method for liver tumors and to discover new and more effective antitumor agents for this particular cancer.

Acknowledgement. We are greatful to Dr. H. Yodono, Department of Radiology, Hirosaki University School of Medicine, for his cooperation in the intra-arterial administration of antitumor agents.

References

1. Al-Idrissi HY, Ibrahim EM, Abdel Satir A, Satti MB, Al-Kasem S, Al-Qurain A (1985) Primary hepatocellular carcinoma in the eastern province of Saudi Arabia: treatment with combination chemotherapy using 5-fluorouracil, adriamycin and mitomycin C. Hepatogastoroenterology 32: 8–10
2. Aoyama M, Hirose H, Adachi N, Udo K, Oshima K, Kobayashi S (1981) Comparison of combination therapy of 5-fluorouracil, mitomycin C and adriamycin (FAM) and mitomycin C, 5-fluorouracil, and cytosine arabinoside (MFC) for advanced gastric cancer. Jpn J Cancer Chemother 8: 757–762
3. Falk RE, Greig P, Makowaka L, et al. (1982) Intermittent percutaneous infusion into the hepatic artery of cytotoxic drugs for hepatic tumours. Can J Surg 25: 47–50
4. Friedman MA, Vorbelding PA, Cassidy MJ, et al. (1979) Therapy for hepatocellular cancer with intrahepatic arterial adriamycin and 5-fluorouracil combined with whole liver irradiation: a Northern California Oncology Group study. Cancer Treat Rep 63: 1885–1888
5. Heim N, Epelbaum R, Cohen Y, Robinson E (1984) Further studies on the treatment of advanced gastric cancer by 5-fluorouracil, adriamycin (doxorubicin), and mitomycin C (modified FAM). Cancer 54: 1999–2002
6. Japan Society for Cancer Therapy (1986) J Jpn Soc Cancer Ther 21: 929–942
7. Kubo Y, Shirai K, Hirai H, Abe M (1986) Present status of chemotherapy on hepatocellular carcinoma. Saishin Igaku 41: 594–599
8. MacDonald JS, Schein PS, Woolley PV, et al. (1980) 5-Fluorouracil, doxorubicin, and mitomycin C (FAM) combination chemotherapy for advanced gastric cancer. Ann Intern Med 93: 533–536
9. Melia WM, Johnson PJ, William R (1983) Induction of remission in hepatocellular carcinoma. Cancer 51: 206–210
10. Miyamoto H, Ogawa M, Inagaki J, et al. (1982) Arterial infusion of combination chemotherapy using adriamycin and mitomycin C for hepatoma and metastatic tumors of the liver. Jpn J Cancer Chemother 9: 1955–1960
11. Morstyn G, Bunn PA, Ihde DC, Eddy JL, Cohen MH, Minna JD (1983) Combination chemotherapy of hepatocellular carcinoma with doxorubicin and streptozotocin. Am J Clin Oncol 6: 547–551
12. Natsu-ume Sasaki S, Ryoyama K, Koshimura S, Migita S (1976) Studies on the properties of a streptococcal preparation OK-432 (NSC-B-116209) as an immunopotentiator. Jpn J Exp Med 46: 123–133
13. Ogawa M, Ito Y (1986) Chemotherapy for hepatoma. Sogo Rinsho 35: 1937–1939
14. Okamoto H, Shoin S, Koshimura S, et al. (1967) Studies on the anticancer and streptolysin S-forming abilities of hemolytic streptococci (a review) Jpn J Microbiol 11: 323–336
15. Sakata Y (1978) Effect of new trial MQF combination therapy against ascitic hepatic tumor cells- AH 7974, AH 130. Proc Jpn Cancer Ass 37th Annu Meet 1978, Tokyo, p 624
16. Sakata Y, Nishimura S, Komatsu Y, et al. (1979) The effect of the combination chemotherapy of mitomycin C, carboquone and 5-fluorouracil on the life span of the Hirosaki tetraploid sarcoma. Jpn J Cancer Clin 25: 1481–1482
17. Sakata Y, Sugawara K, Komatsu Y, Yoshida Y, Nishimura S, Kikuchi H (1979) Combination Chemotherapy of mitomycin C, carboquone, 5-fluorouracil and OK-432 for inoperable gastric cancer. J Jpn Soc Cancer Ther 14: 978–987
18. Sakata Y, Yoshida Y, Komatsu Y, et al. (1982) Studies on MQF-OK therapy against inoperable gastric cancer-Comparison with MFC therapy. Jpn J Cancer Chemother 9: 109–115
19. Sakata Y, Tsushima K, Suzuki H, et al. (1987) Prognostic factors prior to chemotherapy in patients with inoperable liver cancer. Hirosaki Med J 39: 395–399
20. Tanikawa K, Hirai K, Kawazoe Y, Yamashita K, Kumagai M, Abe M (1985) One-shot therapy and transcatheter arterial embolization (TAE) therapy for unresectable hepatocellular carcinoma. Jpn J Cancer Chemother 12: 1930–1937
21. Tsushima K, Sakata Y, Suzuki H, et al. (1984) The combination chemotherapy of mitomycin C, carboquone, 5-fluorouracil and OK-432 against inoperable liver cancer – including the method of intraarterial administration of MMC and CQ. Hirosaki Med J 36: 590–599
22. Ueoka H, Kuroda S, Ohnoshi T, et al. (1984) Intraarterial adriamycin for patients with hepatocellular carcinoma and metastatic liver carcinoma. Jpn J Cancer Chemother 11: 2579–2584
23. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S (1983) Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 148: 397–401
24. Wils J, Schalngen J, Naus A (1986) Phase II of hepatic artery Infusion with 5-fluorouracil, adriamycin, and mitomycin C (FAM) in liver metastases from colorectal carcinoma. Recent Results Cancer Res 100: 157–162