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Pilot Study of Combination Chemotherapy of S-1, a Novel Oral DPD Inhibitor, and Interferon-α for Advanced Hepatocellular Carcinoma With Extrahepatic Metastasis

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BACKGROUND. To the authors' knowledge, there is no effective therapy for extrahepatic metastasis of hepatocellular carcinoma (HCC). In a pilot study, the results of combination therapy of S-1, a novel oral dehydropyrimidine dehydrogenase (DPD) inhibitor, and interferon-alpha (IFN-α) are reported for HCC patients with extrahepatic metastasis.

METHODS. Twelve patients with extrahepatic metastasis of HCC were enrolled in the pilot study. S-1 was administered orally at a dose based on body surface area, twice daily after a meal, for 4 weeks. IFN-α was injected subcutaneously on Days 1, 3, and 5 of each week. One course consisted of consecutive administration for 28 days followed by 14 days rest.

RESULTS. An objective response was observed in 3 (25%) of 12 patients. The overall 1-year survival rate was 61.7%. Grade 3 leukocytopenia was observed in 1 patient (8.3%). No severe toxicity or treatment-related deaths were observed.

CONCLUSIONS. The combination therapy of S-1 and IFN-α appears to be highly efficacious, with low toxicity in patients with extrahepatic metastases of HCC. The combination chemotherapy of oral S-1 and subcutaneous IFN-α is a potentially promising treatment strategy for advanced HCC with extrahepatic metastasis. *Cancer* **2008;112:1765–71.** © *2008 American Cancer Society.*

KEYWORDS: advanced hepatocellular carcinoma, treatment, combination therapy, dehydropyrimidine dehydrogenase inhibitor, interferon.

With over 600,000 new cancer cases reported per year, hepatocellular carcinoma (HCC) is the sixth most common cancer in the world.[1] In the U.S., cirrhosis is expected to develop in 20% to 30% of approximately 3 million carriers of hepatitis C virus (HCV), and HCC is likely to develop in 3% to 5% each year in the latter group.[2] Recent progress in diagnostic modalities and several effective locoregional treatments can control intrahepatic recurrences and improve survival, such as repeated hepatectomy, transcatheter arterial embolization (TAE), percutaneous ethanol injection therapy, microwave coagulation therapy, and radiofrequency ablation.[3–8] However, longer survival may lead to increased incidence of extrahepatic metastasis; once extrahepatic metastasis occurs the prognosis is limited to extremely poor.[9–11] Many clinicians do not routinely offer chemotherapy for metastatic patients because nothing has definitively been demonstrated to improve survival in this setting; several investigators consider that any extrahepatic metastasis of HCC is a contraindication for further treatment and prefer to use

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palliative treatment only.[11,12] In selected patients, surgical resection for metastatic lesions might be beneficial.[13,14] Unfortunately, however, most patients with extrahepatic metastases of HCC are not candidates for surgery due to multiple tumor spreading and/or poor liver function caused by underlying chronic liver disease. Although chemotherapy is often used for such advanced-stage solid neoplasms, a large number of controlled and uncontrolled studies have reported that the response rates were low and the response duration was typically short for HCC over a long time.[15,16] At the 2007 American Society of Clinical Oncology meeting, the result of the Sorafenib HCC Assessment Randomized Protocol (SHARP) study was reported by Dr. Josep Llovet; the patients who received sorafenib demonstrated a 3-month benefit in overall survival for those with advanced HCC without any severe toxicity. To our knowledge, this study reported the first systemic therapy proven to demonstrate a large survival benefit in HCC.[17]

Conversely, recently we and others reported the clinical effects of combination chemotherapy of the intra-arterial infusion of 5-fluorouracil (5-FU) and subcutaneous interferon-alpha (IFN-α) injection for HCC with portal vein tumor thrombosis (PVTT).[18–22] However, this combined treatment would not be expected to have a clinical effect on extrahepatic metastasis because 5-FU was given through the hepatic artery. In this study, we tried the systemic combination therapy of S-1, a novel oral combination anticancer drug that consists of tegafur and 2 modulators, and IFN-α for HCC patients with extrahepatic metastasis as a pilot trial.

MATERIALS AND METHODS

Eligibility Criteria

Patients between 20 and 75 years of age with a radiologic or histopathologic diagnosis of extrahepatic metastasis of HCC were eligible. The diagnosis was based on serum α-fetoprotein (AFP) and serum protein induced by vitamin K absence or antagonist-II (PIVKA-II) and imaging techniques including a computed tomography (CT) scan and magnetic resonance imaging (MRI). Cases with PVTT and/or hepatic vein tumor thrombosis were excluded. The patients who had history of psychologic disease were excluded to avoid severe depression because of the side effects of IFN in this study. Other inclusion criteria were 1) an Eastern Cooperative Oncology Group performance status (PS) ≤2; 2) a life expectancy of ≥12 weeks; 3) measurable or assessable disease; 4) no prior therapy at least 28 days before registration; 5) adequate bone marrow function (hemoglobin ≥8.0 g/dL, leukocyte count between 2500 and 12,000/μL, platelet count ≥80,000/μL); and 6) adequate hepatic and renal reserve (total bilirubin ≤1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, blood urea nitrogen ≤30 mg/dL, and serum creatinine ≤1.5 mg/dL). All patients signed informed consent approved by the Institutional Review Board attesting to the finding that they were aware of the investigational nature of the study and were willing to try the combination therapy.

Treatment Regimen

S-1 (Taiho Pharmaceutical, Tokyo, Japan) was administered orally twice daily after a meal at a total dose of 80 mg/m^2. Three initial doses of S-1 were established according to body surface area (BSA) as follows: <1.25 m^2, 80 mg/day; ≥1.25 to <1.5 m^2, 100 mg/day; and ≥1.5 m^2, 120 mg/day. IFN-α (OIF, Otsuka Pharmaceutical, Tokyo, Japan; at a dose of 5 × 10^6 U [5 MU]/body) was injected subcutaneously on Days 1, 3, and 5 of each week. One course consisted of consecutive administration for 28 days followed by at least 14 days of rest. Diclofenac sodium, a nonsteroidal antiinflammatory drug, was administered before IFN-α injection to alleviate fever, which is a common adverse effect of IFN-α.

Assessment of Toxicity

Blood counts and biochemical profiles were performed at least once every 2 weeks. We monitored patients for the occurrence of nonhematologic toxicities such as general fatigue, fever, nausea/vomiting, stomatitis, diarrhea, skin pigmentation, eczema, hand-foot syndrome, and especially depression. Toxicity during each course was evaluated according to the National Cancer Institute-Common Toxicity Criteria (vesion 2.0).

Assessment of Response

Lesions before and after treatment and once every 3 months thereafter were measured or evaluated by CT and/or MRI. Objective responses were classified according to World Health Organziation (WHO) criteria[23] into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). In addition to serum chemistry, tumor markers such as α-fetoprotein and protein induced by vitamin K antagonist or absence (PIVKA-II) were measured at least once every 4 weeks.

Statistical Analysis

Survival curves were constructed using the Kaplan-Meier method[24] and compared using the log-rank test. Significance was interpreted as $P < .05$.

RESULTS

Patient Characteristics

Twelve patients with extrahepatic metastasis of HCC were enrolled in this pilot study between January 2003 and September 2006. Table 1 lists the patient characteristics. Patient age ranged from 22 to 71 years. Ten of the 12 patients had viral hepatitis. Eleven patients had received prior therapies: combination chemotherapy of intra-arterial 5-FU infusion and subcutaneous IFN-α injection (IFN-α/5-FU) in 7 patients, TAE in 4 patients, oral tegafur-uracil (UFT) in 2 patients, combination of interferon-β and doxorubicin (Adriamycin) (ADR/IFN-β) in 1 patient, and radiotherapy in 1 patient. These therapies were stopped at least 28 days before treatment. All patients had undergone surgery for HCC. The mean number of treatment cycles was 3 (range, 2–12 cycles).

Clinical Response

The effect of combination therapy was evaluated in all 12 patients. Table 2 lists the overall and site-specific responses to the treatment classified according to WHO criteria. Three of the 12 patients (25%) demonstrated objective response, whereas another 3 patients were found to have SD over 6 months. With respect to survival, the overall 1-year survival was 61.7% (Fig. 1). Change in tumor markers before and after 2 treatment courses are listed in Table 3. All patients who showed PD were positive for several tumor markers.

Adverse Effects

All 12 patients were assessable for toxicity (Table 4). With regard to the hematologic toxicity, toxicity greater than grade 3 was observed in only 1 patient (8.3%), and grade 3 leukocytopenia did not require withdrawal or reduction of the dose of either drug. None of the patients required treatment with granulocyte–colony-stimulating factor or other similar therapies. Thrombocytopenia was the most frequent adverse effect but it was grade 1 in all 3 patients. Severe nonhematologic toxicities, including adverse effects greater than grade 3, were not observed. Grade 1 fever was noted in 4 patients (33.3%), but it was well controlled with antipyretic agents. There was no need for discontinuation of the combination therapy because of adverse effect and no treatment-related deaths were reported during this study.

DISCUSSION

In the present study, combination therapy of the oral administration of a novel DPD inhibitory agent, S-1,

TABLE 1
Patient Characteristics

Case No.	Age, years	Gender	Hepatitis	Metastatic lesions	Previous surgery	Previous treatment	Leukocyte count, /μL	Hemoglobin, g/dL	Platelet count, /μL	Total bilirubin, mg/dL	AST, IU/L	ALT, IU/L	Child score
1*	56	Man	HCV	Liver, lung	Extended left lobectomy, VP	IFN-α/5-FU	7520	13.6	10.8	0.7	40	37	A
2*	55	Man	HBV	Liver, lung, spleen	Extended left lobectomy, VP	IFN-α/5-FU	6840	12.3	24	0.7	31	24	A
3	58	Man	None	Liver, lung	Extended posterir segmentectomy, VV, RA, VP	ADR/β, IFN-α/5-FU	4470	13.6	14.7	0.8	32	32	A
4	39	Woman	HBV	Lung, adrenal grand	Right lobectomy	TAE	4090	14.3	18.8	0.7	36	62	A
5	53	Man	HBV	Lung	Right lobectomy, VP	IFN-α/5-FU	3150	12.7	11.8	0.8	26	30	A
6	58	Man	HBV	Lymph nodes	Posterior segmentectomy	TAE	4990	14	13	0.7	57	73	A
7	22	Woman	None	Lymph nodes	Anterior lobectomy and partial resection	TAE, RT, UFT	2910	9.7	8.2	1.3	18	16	B
8	57	Man	HBV	Lymph nodes	Extended posterior segmentectomy, VV, RA	ADR/β	6230	10.5	21.2	0.5	28	14	A
9	67	Man	HCV	Lung	Extended left lobectomy, VV, RA	(–)	3580	13.9	8.2	0.9	76	77	A
10	70	Man	HCV	Liver, RA	Extended posterior segmentectomy, VP	IFN-α/5-FU	2500	10.7	11	0.5	24	10	A
11	49	Man	HCV	Liver, peritineal, brain	Lateral segmentectomy and partial resection	IFN-α/5-FU	3920	13.3	16.5	1.2	19	13	A
12	71	Man	HCV	Lymph nodes	Extended right lobectomy, VP	TAE, IFN-α/5-FU, UFT	3790	13.2	15.2	0.6	29	17	A

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; VP, reduction of tumor thrombus in main trunk of portal vein; IFN-α/5-FU, combination chemotherapy of intraarterial 5-fluorouracil infusion and subcutaneous interferon-α injection; HBV, hepatitis B virus; VV, reduction of tumor thrombus in hepatic vein; RA, tumor thrombus in the right atrium; ADR/β, combination chemotherapy of intraarterial infusion of doxorubicin (adriamycin) and interferon-β; TAE, transarterial chemoembolization; RT, radiotherapy; UFT, tegafur-uracil.

* Cases 1 and 2 were quoted from Nakamura 2005[47] and Nakamura 2006,[48] respectively.

TABLE 2
Overall and Site-specific Responses* to Treatment (n = 12)

	CR	PR	SD	PD	RR (%)
Overall	0	3	3	6	25
Liver	2	0	1	3	33.3
Lung	1	2	3	0	50
Spleen	1	0	0	0	100
Lymph nodes	0	0	3	2	0
Peritoneal	0	0	0	1	0

CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate.
* Objective responses were classified according to World Health Organization criteria.

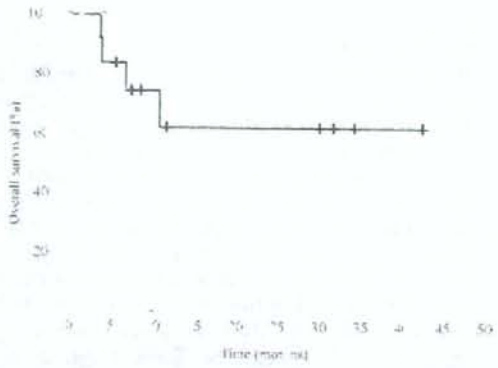

FIGURE 1. Overall survival curve of 12 patients with extrahepatic metastasis after administration of S-1/interferon-α.

and subcutaneous injection of IFN-α was applied for advanced HCC with distant metastasis. Recently, we and others reported the clinical effects of combination chemotherapy of intra-arterial infusion of 5-FU and subcutaneous IFN-α injection for HCC with PVTT.[18–22] In HCC, PVTT can cause liver failure and most patients die within several months after diagnosis; no treatment is available for these patients. IFN-α/5-FU therapy demonstrated excellent clinical effect, with an approximately 50% response rate. However, patients with extrahepatic metastasis of HCC were not included in the indication of this combination therapy because they were not expected to respond to such treatment. With regard to extrahepatic metastasis of HCC, we previously reported a case with uncontrollable multiple lung and bone metastases that demonstrated nearly complete regression after treatment with UFT and IFN-α; the patient remained alive for 7 years after the first occurrence of extrahepatic metastasis.[25] UFT is a combination drug of 1M of 1-(2-tetrahydrofuryl)-5-FU (Tegafur, a prodrug of 5-FU) and 4M uracil, an inhibitor of DPD.[26] DPD is a metabolic enzyme of 5-FU and DPD inhibitors are expected to result in long-term elevation of serum and tissue 5-FU concentrations and a rise in the antitumor effect of 5-FU by RNA dysfunction and damage to DNA synthesis.

S-1 is a novel oral combination anticancer drug that consists of tegafur and 2 modulators, 5-chloro-2, 4 dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molecular ratio of 1:0.4:1.[27] CDHP is a more effective DPD inhibitor than uracil (reported approximately 200 times in vitro), and strongly blocks 5-FU metabolites.[28] Oxo is a reversible competitive inhibitor of orotate phosphoribosyltransferase and is reported to concentrate selectively in gastrointestinal tissues after oral administration and suppresses gastrointestinal toxicity induced by phosphoribosylation of 5-FU in the gastrointestinal tract without reducing antitumor activity.[29,30] These features provide S-1 with high efficacy and low toxicity.[30] Moreover, S-1 is an oral anticancer agent, thus having a great advantage for administration without the need for hospitalization. In Japan, S-1 is widely used for the treatment of gastric cancer, colorectal cancer, pancreatic cancer, neck cancer, cervical cancer, nonsmall cell lung cancer, and breast cancer, and excellent antitumor activity has been reported.[32,33]

In the current study, 25% of the patients responded to S-1/IFN-α combination therapy and another 25% of patients demonstrated SD over 6 months. All patients who demonstrated PR/SD survived greater than 1 year, including 2 SDs achieved over 30 months. These survival rates and times were higher and longer than the other results previously reported.[10,11] The response rate and survival rate to doxorubicin, a major anticancer agent for solid tumors, were 3.3% and 10.6 weeks, respectively, whereas those to capecitabine, another oral chemotherapeutic agent, were 11%.[34,35] The reported response rate in phase 2 studies of other systemic chemotherapies, such as CPT-11, paclitaxel, and gemcitabine were 7%, 0%, and 0%, respectively.[36–38] Other therapies including combination chemotherapy were also considered ineffective or minimally and of uncertain effectiveness.[15,16,39] A clinical response rate was not negligible, which might lead patients to take a chance to receive further therapies, such as a surgical procedure; these further therapies might play a role in prolonging survival.

The exact mechanism of the excellent clinical efficacy of the combination chemotherapy of S-1/IFN-α for HCC is not clear at present. First, the combination of fluorouracil, which is an antitumor component of S-1, and IFN-α demonstrated the strongest

TABLE 3
Clinical Outcome of Patients

Case no.	Treatment cycles	Adverse effect (NCI-CTC)	Overall response	Response 1	Response 2	Response 3	AFP, ng/mL		PIVKA-II, mAU/mL		Adjuvant therapy	OS, months	Outcomes
							Pre	Post	Pre	Post			
1*	7	Grade 1 thrombocytopenia	PR	Liver: CR	Lung: PR		5>	5>	40>	40>		34	Alive
2*	12	Grade 1 fever increase, fatigue	PR	Liver: CR	Spleen: CR	Lung: PR	28	18	47,806	2986	Surgery	29.8	Alive
3	5	Grade 1 fever increase	PR	Lung: CR	Liver: SD		97	78	708	1112	Planning surgery	11.5	Alive
4	12		SD	Lung: SD	LN: SD		439	377	15	19	ADR/β	42.3	Alive
5	2	Grade 3 leukocytopenia, Grade 1 thrombocytopenia, Grade 1 increase in bilirubin	SD	Lung: SD			5>	8	60	214	Surgery	31.5	Alive
6	2		SD	LN: SD			23	24	40>	40>		8.4	Alive
7	2	Grade 2 anemia, Grade 2 increase in bilirubin	PD	LN: PD	New lesion in liver and spleen		5>	5>	1080	2083	ADR/β	10.7	Died
8	3		PD	LN: SD	New lesion in lung and bone		116	731	40>	41	RT	7.2	Alive
9	2	Grade 1 thrombocytopenia, Grade 1 fever increase, dermatitis	PD	Lung: SD	Liver: PD		206	3519	3170	5150	TAE	6.6	Died
10	3		PD	Liver: PD	TT: PD		82	351	6510	7258	BSC	5.4	Alive
11	2		PD	Liver: PD	Peritoneal: PD		18,690	732,000	1849	21,401	BSC	3.7	Died
12	2	Grade 1 fever increase	PD	LN: PD			34,500	91,300	110	1082	BSC	3.3	Died

NCI-CTC indicates National Cancer Institute-Common Toxicity Criteria (version 2.0); AFP, α-fetoprotein; PIVKA-II, serum protein induced by vitamin K absence or antagonist-II; OS, overall survival; Pre, before 2 treatment courses; Post, after 2 treatment courses; PR, partial response; CR, complete response; SD, stable disease; LN, lymph nodes; ADR/β, combination chemotherapy of intraarterial infusion of doxorubicin (adriamycin) and interferon-β; PD, progressive disease; RT, radiotherapy; TAE, transarterial chemoembolization; TT, tumor thrombosis; BSC, best supportive care.
* Cases 1 and 2 were quoted from Nakamura 2006[48] and Llovet 2000[49], respectively.

TABLE 4
Adverse Effects Encountered in the Current Study*

(n = 12)	NCI-CTC grade 1	2	3	4	%	Grade 3/4 (%)
Leukocytopenia	0	0	1	0	8.3	8.3
Anemia	0	1	0	0	8.3	0
Thrombocytopenia	3	0	0	0	25	0
Increase in bilirubin	1	1	0	0	16.7	0
Fever increase	4	0	0	0	33.3	0
Fatigue	1	0	0	0	8.3	0
Dermatitis	1	0	0	0	8.3	0
Depression	0	0	0	0	0	0

NCI-CTC indicates National Cancer Institute Common Toxicity Criteria.
* Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

synergistic antitumor effect in vitro among several combinations of chemotherapies.[40] Moreover, the synergistic antitumor effect of fluorouracil and IFN-α most likely involves several mechanisms such as direct cell arrest effect, apoptosis, and immunomodulatory effect via TRAIL/TRAIL receptor or Fas/FasL system.[41–44] We also performed molecular analysis to predict the clinical antitumor effect.[45] In addition, we have reported that the expression level of IFN receptor is important for the clinical effect of IFN-α-related therapy.[22,46] In this regard the expression level of the IFN receptor is higher in HCC cells than in other gastrointestinal cancers.[47] Finally, the concentrations of fluorouracil in peripheral circulation and tumor tissue might be increased with the effect of a strong DPD inhibitor, CDHP. In Cases 1 and 2, the

lesions in the remnant liver demonstrated complete remission with S-1 and IFN-α, although both cases were resistant to the combination treatment of intra-arterial infusion of 5-FU and IFN-α.[48,49] These observations suggest that orally administered S-1 could maintain higher 5-FU concentrations than intra-arterial infusion of 5-FU alone.

The combination therapy was associated with tolerable adverse effects despite the underlying chronic liver disease. The myelosuppressive effects of chemotherapy are particularly important in HCC. This is not only because thrombocytopenia and/or leukocytopenia are often present before the initiation of anticancer therapy, but also because treatment often has to be discontinued because of these side effects. In the present study, only 1 patient was found to have grade 3 leukocytopenia but it was well controlled without any treatment. Severe thrombocytopenia was not observed in these 12 patients, although nearly all patients had liver dysfunction. Thrombocytopenia was most likely the result of the use of IFN-α. Previous studies reported that nonhematologic toxicity, fever, chilliness, and a flu-like syndrome were observed in 50% to 100% of patients receiving IFN-α-related chemotherapy, and was 1 of the reasons for treatment discontinuation.[22,50] In our study, such toxicities were well controlled with nonsteroidal anti-inflammatory drugs administration before IFN-α injection. Other side effects were also well controlled by conventional treatment. Depression due to IFN-α is a very critical adverse effect because it could lead to suicide, but it was not observed in our patients. The relatively mild nature of the observed side effects allowed continuation of treatment, and may enhance the marked clinical effect because treatment was never interrupted because of adverse effects. All patients could maintain their social life while receiving S-1/IFN-α therapy.

All 12 patients enrolled in this study had undergone surgery and had preserved liver function; it is difficult to determine whether this regimen would work as well in those with more compromised liver function. Because this study was experimental and a pilot application, and patient safety must be promised, we set strict exclusion criteria, including liver function, for the eligibility criteria. There was no need for discontinuation of the combination therapy because of adverse effects and no treatment-related deaths in this study. To set the exact and appropriate inclusion criteria, a phase 1 clinical trial is necessary.

In conclusion, the combination chemotherapy of oral S-1 and subcutaneous IFN-α is a potentially promising strategy for patients with advanced HCC with extrahepatic metastasis.

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肝がん

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はじめに

肝細胞がんに対する化学療法の適応は，肝切除やradiofrequency ablation(RFA)等の局所治療による治療効果が期待しえない進行肝がんや，肝外転移病巣変とされる。しかしながら，肝細胞がんは一般的に抗がん剤の感受性が低く[1]，併存する肝障害によって十分量の抗がん剤が投与できないという問題点もある。このため，標準治療としての肝細胞がんに対する化学療法における標準的治療はいまだ確立されていない[2]。その一方で，肝細胞がんは，肝切除によって肉眼的治癒切除し得たとしても，高率に肝内再発をきたすため，さらなる肝細胞がんの切除成績向上のためには，術後の肝内転移再発を制御することが極めて重要である。切除後肝内再発の抑制を目的として，術前肝動脈(化学)塞栓術(Transcatheter Arterial(Chemo)Embolization：TAE/TACE)や術後補助化学療法などの治療が試みられてきた。

本稿では，肝細胞がんに対する化学療法の現況を，外科の立場から，①肝切除術後再発巣に対する化学療法，②術前肝動脈化学塞栓術，③術後補助化学療法の3項目について概説する。

1. 肝切除術後再発巣に対する化学療法

1)肝動注化学療法

再発肝細胞がんのうち，TAE/TACEが効を奏さない門脈内腫瘍栓を有する症例や広範囲にわたる多発肝内転移症例などを対象に，肝動注化学療法が施行されてきた。最近の肝細胞がんに対する肝動注化学療法の使用薬剤とその治療成績を表1に示した。肝動注化学療法における投与方法は，One-shot動注および持続動注がある。One-shot動注においては，濃度依存性の高いdoxorubicin(ADR)やcisplatin(CDDP)などが適している。一方，持続動注では時間依存性の高い5-fluorouracil(5-FU)を機軸とし，CDDPの間欠的投与が中心となっている。単剤投与における奏効率は15～60%と単純には比較できないが，全身化学療法より良好な成績であると考えられる[3]。また，多剤併用による肝動注化学療法の奏効率は，7～51%であると報告されている。

最近では，肝動注化学療法にInterferon(IFN)-αを併用することで，良好な治療成績が報告されている。IFNは生体内サイトカインの1種であり，生体内においてさまざまな生物学的作用を持つ。抗がん剤の作用を増強させるmodulatorの作用に加えて，自身が抗腫瘍効果を有している。Kanekoらの報告では，門脈内腫瘍栓を伴った進行肝細胞がん29例に対して，5-FU，CDDP，methotrexate(MTX)の3剤による肝動注投与とIFN-αとLV(leucovorin)の全身投与を併用し，奏効率45%と良好な結果を示している[4]。また，IFN-αと5-FU持続肝動注化学療法は，門脈内腫瘍栓を伴った進行肝細胞がん症例を対象として，8例のComplete Response(CR)症例を含めて，奏効率が48%と極めて良好な結果[5-7]が報告されている。さらに，その後の他施設における追試においても，ほぼ同程度の抗腫瘍効果を確認しており[8]，極めて有望な治療法と考えられる。

2)全身化学療法

切除後再発症例の中で，肺・副腎・リンパ節などの肝外病巣に対して全身化学療法が施行される。現在までの，肝細胞がんに対する単剤もしくは多剤併用による全身化学療法の治療成績を表2に示す。各種消化器がんと同様に，ADR，5-FU，CDDP，mitomycin C(MMC)などの薬剤が使用されているが，単剤での十分な効果は期待できない[9]。ADRは，もっとも肝細胞がんに感受性の高い薬剤であるが，ADRと他の薬剤との併用に関しては，

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表1　肝動注化学療法

報告者	使用薬剤	症例数	奏効率(%)
Olweny et al(1980)	ADR	10	60
Ikeda et al(1992)	ADR, CDDP, MMC	76	51
Nagasue et al(1986)	Epi-ADR	53	15
Takayasu et al(2000)	Epi-ADR, CDDP, VP-16	30	30
Onohara et al(1988)	CDDP	33	55
Ansfield et al(1971)	5-FU	11	27
Tanaka et al(2000)	5-FU, CDDP	77	45
Ando et al(2002)	5-FU, CDDP	58	43
Kaneko et al(2002)	IFN-α(sc.), 5-FU, CDDP, MTX, LV(i.v.)	29	45
Ota et al(2005)	IFN-α(sc.), 5-FU	55	48
Enjoji et al(2005)	IFN-α(sc.), 5-FU	28	57
Obi et al(2006)	IFN-α(sc.), 5-FU	116	52

ADR：doxorubicin, CDDP：cisplatin, MMC：mitomycin C, Epi-ADR：epirubicin, VP-16：etoposide
5-FU：5-fluorouracil, IFN：interferon, MTX：methotrexate, LV：leucovorin
sc.：subcutaneous infusion, i.v.：intra-venous infusion

表2　全身化学療法

報告者	使用薬剤	症例数	奏効率(%)
Chlebowski et al(1984)	ADR	52	11
Al-Idrissi et al(1982)	ADR, 5-FU, MMC	40	13
Yang et al(2002)	ADR, GEM	28	12
Park et al(2006)	ADR, CDDP, Capecitabine	29	24
Hochster et al(1985)	Epi-ADR	18	17
Kim et al(2006)	Epi-ADR, CDDP, UFT, LV	53	17
Tetef et al(1995)	5-FU, LV	15	1
Lozano et al(2000)	Capecitabine	37	13
Ikeda et al(2004)	5-FU, CDDP, MIT	51	27
Nakamura et al(in press)	S-1, IFN-α	12	25
Chao et al(1998)	Paclitaxel	20	0
Hebbar et al(2006)	Docetaxel	15	7
O'Reilly et al(2001)	Irinotecan	14	7
Kim et al(2004)	GEM, Docetaxel	21	10
Taieb et al(2004)	GEM, Oxaliplatin	26	15
Zhu et al(2006)	GEM, Oxaliplatin, Bevacizumab	33	18
Philip et al(2005)	Erlotinib	38	8
Eckel et al(2005)	Imatinib	17	0
Abou-Alfa et al(2006)	Sorafenib	137	2
Llovet et al(2007)	Sorafenib	299	2

ADR：doxorubicin, 5-FU：5-fluorouracil, MMC：mitomycin C, GEM：gemcitabine, CDDP：cisplatin,
Epi-ADR：epirubicin, UFT：uracil-tegafur, LV：leucovorin, MIT：mitoxantrone, IFN：interferon

表3　術前肝動脈(化学)塞栓療法

報告者	使用薬剤	症例数	結　果
Imaoka et al(1989)	CDDP	37	有効(Ts10cm以下)
Monden et al(1989)	ADR	71	有意差なし
Adachi et al(1993)	ADR, MMC	46	有効(完全壊死例, Ts5cm以下)
Wu et al(1995)*	Epi-ADR	24	有害
Yamasaki et al(1996)*	なし	50	有意差なし
Harada et al(1996)	Epi-ADR, MMC	98	有効(完全壊死例)
Sugo et al(2003)	Epi-ADR	113	有効(StageⅢ, Ⅳ)

CDDP：cisplatin, ADR：doxorubicin, MMC：mitomycin C, Epi-ADR：epirubicin, Ts：Tumor Size
*：ランダム化比較試験

第Ⅱ相試験における奏効率は12～24%であり，今後はランダム化比較試験における検証が必要である。Epirubicin(Epi-ADR)は，単剤での全身投与における奏効率は，ADRを上回るものではなかった。5-FUも肝細胞がんに対して古くより使用されてきた抗がん剤の1つであるが，近年の第Ⅱ相試験において，5-FUとCDDP，mitoxantrone(MIT)の3剤併用により27%の奏効率が報告されている[10]。S-1は，5-FU系の薬剤であり，他の消化器がん(胃がん，大腸がん，膵がん等)において高い有効性を示すと報告されている。肝細胞がんについても，S-1とIFNの併用により，25%の奏効率が報告されている[11]。その他，paclitaxel，docetaxel，irinotecanなどについても臨床試験が実施されているが，有望とはいえない。gemcitabine(GEM)は当初，奏効率が18%と良好な結果が報告されたが，その後の追試ではその効果は確認されなかった。GEMとoxaliplatinとの併用が試みられたが，奏効率は20%以下であった。さらに，GEMとoxaliplatinに加えて，分子標的治療薬である抗血管内皮増殖因子(VEGF)レセプター抗体のbevacizumabの3剤併用投与の第Ⅱ相試験の結果は，bevacizumabの上乗せ効果は認められなかった[12]。化学療法とは厳密にはその定義から少し外れるが，その他の分子標的治療薬に関しては，RAFやVEGFレセプターなどを標的とするマルチキナーゼ阻害薬のsorafenibは第Ⅱ相試験における奏効率は2.2%であったが[13]，近年の第Ⅲ相試験(SHARP Trial)において，生存期間において対照群の7.9か月と比較して10.7か月と有意な延長が認められた[14]。sorafenib投与群における治療効果の内訳は，partial response(PR) 2.2%，stable disease(SD)71%，progression disease(PD)18%であった。本治療は肝細胞がんに対する分子標的治療の中で標準的治療となる可能性があるものの，sorafenib単独の奏効率は2.2%と低率であり，このことから，単剤では肝細胞がんの増殖を抑制し得ても根治し得ないと考えられる。肝細胞がん患者の予後向上のためには，他の抗がん剤との併用による抗腫瘍効果の改善が必要であろう。

2. 術前肝動脈化学塞栓術

現在，手術可能な肝細胞がんに対する術前治療の選択肢として，主にTAE/TACEが選択される。TAE/TACEは，栄養動脈より抗がん剤と塞栓物質を注入することにより，肝動脈末梢部を塞栓し腫瘍を壊死に陥らせる治療法である。本邦では，反復治療が可能であり，肝機能に及ぼす影響も比較的少ないため，肝内多発症例に対する標準的治療として位置づけられている[2]。術前にTAE/TACEを施行する目的は，肝切除施行時にすでに存在する肝内微小転移や術前の画像診断により描出できない病巣の治療および制御にある。これまでに，諸家により報告されている術前TAE/TACEの効果を表3に示す。それぞれの報告により，肝内再発抑制に有用である，再発予防効果は認めない，肝機

表4　術後補助化学療法

報告者	使用薬剤	治療期間	症例数	結　果
Izumi et al(1994)	動注ADR+MMC+Lip	1回のみ	23	有効(進行がん)
Lai et al(1998)	静注Epi-ADR+動注CDDP+Lip	4年	30	有害
Tanaka et al(2005)	動注CDDP+5-FU	1か月	7	有効(進行がん)
Hasegawa et al(2007)	経口UFT	1年	79	有害
Nagano et al(2007)	動注5-FU+皮下注IFN-α	3か月	15	有効(進行がん)

ADR：doxorubicin, MMC：mitomycin C, Lip：Lipiodol, Epi-ADR：epirubicin, CDDP：cisplatin, 5-FU：5-fluorouracil, UFT：uracil-tegafur, IFN：interferon

能障害により生存期間に負の影響を及ぼすなどさまざまであり，一定の見解は得られていない[16]。多くの報告は，Retrospective Studyであるが，肝細胞がんの中で肝切除の対象となる全症例に術前TAE/TACEを施行することは，有益ではないと考えられる。しかし，術前TAE/TACEの対象とする症例を選別することにより，目的とする肝内転移再発を抑制し，無再発生存期間や全生存期間の延長に寄与する可能性はあると思われる。今後は，術前TAE/TACEの方法，回数，使用薬剤の統一と標準化や対象症例を腫瘍径やStageなどにより選別したランダム化比較試験が必要である。

3. 術後補助化学療法

肝細胞がん切除後の補助化学療法の目的は，術後の高頻度の肝内再発を抑制することである。肝細胞がん根治切除後の早期再発形式の大多数は，肝内転移に起因する残肝再発である[16]。表4に，これまでの主な補助化学療法の結果を示す。それぞれの報告によって，結果はさまざまであり，一定の見解は得られていない。また，統計学的な症例数の設定のもとに，十分な症例数を集積できた臨床試験は2件しかなく，この2件のいずれの報告においても，補助化学療法の有効性は示されていない[17,18]。よって，現時点で肝細胞がん切除後の補助化学療法として有効なレジメンはないと考えられる。しかしながら，この2件の臨床試験は両者とも，腫瘍の進展度に関して早期がんから進行がんまでのあらゆる症例を対象としているため，補助化学療法の有効性が示されなかった可能性もある。門脈内腫瘍栓や全肝に多発する肝内転移を有する進行がんを対象とした臨床試験においては，症例数が少ないながらも，補助化学療法の有効性が示されており[19-21]，今後の課題としては，多施設におけるランダム化比較試験などにより，臨床腫瘍統計上評価しうる症例数を十分に集積した上での検討が必要である。

おわりに

肝細胞がんの切除成績向上のためには，術後の肝内転移再発の抑制を目的とする術前・術後治療，および肝外転移病巣に対する全身化学療法の確立が急務である。これまで進行肝細胞がんに対するさまざまなレジメンが試みられており，その中でもIFN併用化学療法は高い奏効率を示すことが報告されており，極めて有望な治療法と考えられる。また，近年の分子生物学の進歩により，分子標的治療薬におけるsorafenib等の標準的治療となる可能性のある薬剤も開発されてきている。今後は，妥当性のある臨床試験において抗腫瘍効果を検証することが重要課題となる。

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Doxorubicin/IFN-β併用化学療法と肝切除術により長期生存し得た右心房内腫瘍栓を伴う進行肝細胞癌の1例

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A Case of Hepatocellular Carcinoma with Right Atrium Tumor Thrombus Treated with Combined Doxorubicin and Interferon-β/Intra-Arterial Injection Chemotherapy and Hepatectomy: Masahiro Murakami[*1], Hiroaki Nagano[*1], Takehiro Noda[*1], Hiroshi Wada[*1], Shogo Kobayashi[*1], Shigeru Marubashi[*1], Atsushi Miyamoto[*1], Yutaka Takeda[*1], Keizo Dono[*1], Koji Umeshita[*2] and Morito Monden[*1] ([*1]*Dept. of Surgery and* [*2]*Dept. of Health Science, Graduate School of Medicine, Osaka University*)

Summary

A-58-year-old male was admitted to Osaka University Hospital for advanced hepatocellular carcinoma in July 2005. The main tumor was located in the posterior segment and hepatic vein tumor thrombus extended to the right cardiac atrium. He felt of pressure in his chest and a serum total bilirubin level was beyond normal range because of the tumor progress. We started a doxorubicin and interferon-β combined chemotherapy. Although anti-tumor effect was NC, his symptom rather improved and a serum total bilirubin level went into the normal range. Consequently, we performed an extended posterior segmentectomy and tumor thrombectomy of IVC and right cardiac atrium. The patient survived for 13 months after the initial treatment, but he died of distant metastasis. It was suggested that the doxorubicin and interferon-β combined chemotherapy might be the promising modality for advanced hepatocellular carcinoma as one of the multimodel treatment. **Key words:** Hepatocellular carcinoma, Interferon-β, Doxorubicin

要旨 症例は58歳，男性。B型肝炎，多量飲酒歴あり。2005年4月疲労感などを主訴に近医を受診し，精査にて進行肝細胞癌と診断され当院へ紹介。7月精査加療目的で入院した。画像上，肝後区域の主腫瘍と肝部下大静脈から右心房内に至る腫瘍栓を認めた。入院時より胸部圧迫感や下腿浮腫などが出現，血清総ビリルビン値（T-Bil）は2.2 mg/dLと上昇し，腫瘍進展による肝不全徴候を認めた。doxorubicin/IFN-β併用化学療法の施行により，画像上の抗腫瘍効果はNCであったものの，症状の改善とT-Bilの正常化を認めたことより，10月肝拡大後区域切除，右心房内・下大静脈内腫瘍栓摘出術を施行した。術後経過は特に問題なく退院し，最終的に遠隔転移により癌死したが，初回治療より13か月の長期生存を得た。以上よりdoxorubicin/IFN-β併用化学療法は，進行肝細胞癌に対して集学的治療の有用な選択肢の一つとなり得ると思われた。

緒 言

今回われわれは肝部下大静脈をほぼ充満し，右心房内に至る広範な腫瘍栓を伴う進行肝細胞癌で腫瘍進展に伴う肝不全徴候の出現した症例に対して，doxorubicin/IFN-β併用化学療法を施行後に根治肝切除術を施行し，長期生存を得た症例を経験したので報告する。

I. 症 例

患者: 58歳，男性。HBs抗原陽性。

既往歴: 20年前より高血圧で内服中。

飲酒歴: 日本酒3合/日×38年と多量飲酒。

現病歴: 2005年4月疲労感および咳嗽を主訴に近医を受診し，心房細動を指摘。その時の腹部CT検査で進行肝細胞癌と診断され，7月精査加療目的にて入院した。入院時，胸部圧迫感や下腿浮腫などの右心房内腫瘍栓によると思われる症状が出現していた。

入院時血液検査: PT値76%と軽度低下，T-Bil 2.2 mg/dLと上昇し，腫瘍進展による肝不全徴候を認めた。腫瘍マーカーはAFP 4,014 ng/mLとPIVKA-II 56

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0385-0684/07/¥500/論文/JCLS

表 1 入院時血液検査所見

WBC	5,100/μL	APTT	30 sec
RBC	418×10⁴/μL	PT	76%
Hb	13.8 g/dL	HPT	76%
Hct	40.6%	ICG R_{15}	20%
Plt	14.6×10⁴/μL	HBs-Ag	(+)
TP	7.5 g/dL	HBs-Ab	(−)
Alb	3.8 g/dL	HBe-Ag	(−)
T-Bil	2.2 mg/dL	HBe-Ab	(+)
D-Bil	1.0 mg/dL	HBc-Ab	(+)
AST	37 IU/L	HCV-Ab	(−)
ALT	29 IU/L	AFP	4,014 ng/mL
γ-GTP	391 IU/L	L_3 分画	35.8%
ALP	366 IU/L	PIVKA-II	56 mAU/mL

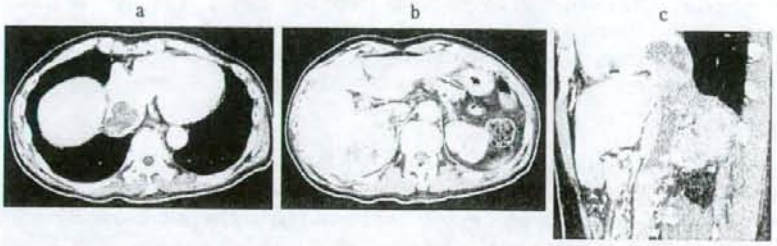

図 1 腹部 CT 検査 (a, b, c)
肝後区域の主腫瘍と肝部下大静脈から右心房内へ進展する腫瘍栓を認める。

図 2 術中所見
肝切除施行後，肝部下大静脈を切開し，右心房内・下大静脈内腫瘍栓を摘出した。

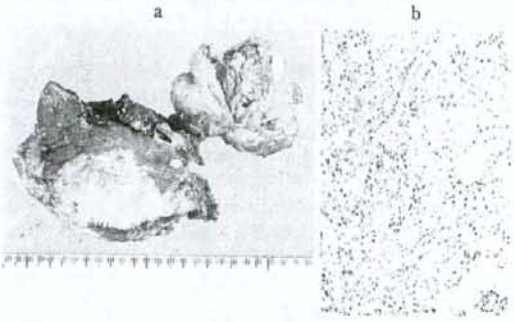

図 3
a: 摘出標本
最大腫瘍径 8 cm，白色の充実性腫瘍で下大静脈内に腫瘍進展を認めた。
b: 病理組織学的所見
HE 染色。低分化型，Edmondson III 型の肝細胞癌の所見であった。

mAU/mL の上昇を認めた（表 1）。

腹部 CT 検査: 肝後区域中心に径 7 cm の主腫瘍と肝部下大静脈をほぼ充満し，さらには右心房内へ進展する腫瘍栓を認めた（図 1）。また右副腎腫大も認め，転移が疑われた。

以上より右心房内腫瘍栓を伴う進行肝細胞癌と診断。2005 年 7 月肝動脈リザーバー留置術の後，doxorubicin/IFN-β 併用化学療法（プロトコールは doxorubicin 10 mg/body + IFN-β 300 万単位/回の肝動脈内注入を週 3 回，計 4 週間[1]）を 1 クール施行した。抗腫瘍効果は NC であったが，胸部圧迫感などの症状は改善し T-Bil が正常範囲内に復したことより，10 月 17 日に肝拡大後区域切除，右心房内・下大静脈内腫瘍栓摘出，右副腎・横隔膜合併切除，胆嚢摘出術を施行した（図 2）。

摘出標本: 切除肝重量は 442.2 g。原発巣の割面は白色の充実性腫瘍で，最大腫瘍径は 8 cm。原発性肝癌取扱い規約[2]に基づく術後診断は，Ig，Fc (−)，Sf (+)，massive，S2，N0，Vp2，Vv3，Va0，B0，IM0，P1，SM (−)，CH で T3N0M0，Stage III であった（図 3a）。

病理組織学的所見: 術後の病理学的検索では低分化型, Edmondson III型の肝細胞癌で, vp2, vv3, va0, s2, b1, p1, sm(−)(図3b)。背景肝に硬変像はなく, HAI score は Grade 1, Stage 3 であった。

術後経過は特に問題なく退院し, 社会復帰した。外来通院中の2006年1月より肺や骨, リンパ節への遠隔転移を来したため, S-1/IFN-α 療法[3,4] を施行したが, 治療効果を認めず, 初回治療から13か月後に癌死した。

II. 考 察

脈管侵襲を伴う肝細胞癌は極めて予後不良である。教室ではこのような進行肝細胞癌に対して, 5-FU の肝動注に IFN-α の皮下投与を併用した化学療法(FU arterial infusion and IFN therapy: FAIT)を機軸とした集学的治療を行い, その良好な成績について報告してきた[5-8]。しかしながら, 過度の腫瘍進展により黄疸や腹水などの肝不全徴候を来したため, 治療適応外となり, 残念ながら緩和医療へと移行せざるを得ない症例も少なからず存在する。このような症例に対しても治療を断念することなく, 予後の改善を図るためには肝不全徴候下にあっても施行し得る何らかの抗腫瘍治療が必要である。

教室では, これまでに *in vitro* で IFN-β と各種抗癌剤の併用による抗腫瘍効果の有用性を報告し[9,10], さらにはパイロットスタディとして, doxorubicin/IFN-β 併用化学療法を T-Bil が上昇しているような進行肝細胞癌を対象としてこれまで11例に施行した[1]。本療法においては既報のごとく, たとえ T-Bil の上昇があっても肝不全徴候を増強することなく治療の完遂が可能であり, さらにほとんどの症例において T-Bil の低下など肝機能の改善が得られ, 中間生存期間が12か月と予後の向上を認めた。そこで本症例においてもまず, doxorubicin/IFN-β 併用化学療法を施行, 腫瘍進展を抑制し, さらには肝不全徴候の改善後に根治切除を施行することで長期生存を得た。

以上, 既報のパイロットスタディと本症例での経験より, doxorubicin/IFN-β 併用化学療法は進行肝細胞癌に対する neoadjuvant としての可能性を含めた, 集学的治療の有用な選択肢の一つとなり得ると考える。

本論文の要旨は第29回日本癌局所療法研究会において発表した。

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5FUとインターフェロン

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索引用語：肝細胞癌，インターフェロン，化学療法，外科手術

要旨：肝細胞癌に対するインターフェロンの抗腫瘍効果は，IFN単剤では否定的であるが，抗癌剤との併用療法，特に5-FUとの併用についてはその有用性が期待される．たとえば，門脈内腫瘍栓を伴う難治性進行肝細胞癌には有効な治療法は皆無であったが，最近では諸家の報告より，IFN/5-FU併用化学療法により有意な抗腫瘍効果と生存率の改善を認めることが明らかになってきた．また，その作用機序としては，p27Kip1による細胞周期調節，IFNARからのシグナル伝達の関与，TRAIL/TRAIL-receptor pathwayやFas-FasLなどの免疫学的機序や抗血管新生作用などの関与が推察されている．

1 はじめに

門脈内腫瘍栓を伴う難治性進行肝細胞癌症例は既存の治療法が無効で極めて予後不良であり，有効な治療が施されなければ，ほぼ1年以内に癌死する[1,2]．このような場合は，一般的に化学療法が選択されるが，肝細胞癌は抗癌剤の感受性が低く，その奏効率は20%以下とその抗腫瘍効果については期待しがたい[3]．最近このような難治性進行肝癌に対するインターフェロン(以下IFN)と種々の抗癌剤との併用療法により有意な抗腫瘍効果と生存率の著明な改善が認められることが明らかになってきた[4-7]．本稿では，これら抗癌剤の中でIFN-αと5-FUの併用療法(IFN/5-FU併用化学療法)による進行肝細胞癌に対する抗腫瘍効果における，作用機序，適応と投与方法，治療成績，副作用について概説する．

2 IFN/5-FU併用化学療法—作用機序に関する基礎的検討—

IFN-αは単剤でも抗腫瘍効果があるとされ，その機序は癌細胞への直接的な抗腫瘍効果(直接作用)と免疫担当細胞を介した間接的抗腫瘍効果(間接作用)とに大別できる．直接作用としては細胞障害作用[8]，細胞周期遅延作用[9]，癌抗原の発現上昇[10]などが報告されており，間接作用としてはNK細胞の活性化[11]，マクロファージ系の活性化[12]，T細胞

Hiroaki NAGANO et al: Combiud chemotherapy for HCC, IFN and 5FU
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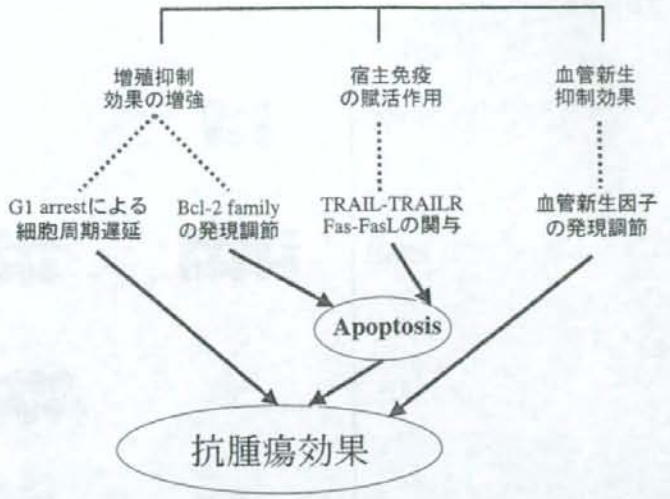

図1　IFN併用化学療法の作用機序に関する仮説

系の活性化[13]などが報告されている．ただし，現在までの臨床例での肝細胞癌に対する成績[14]を考えると，単独での効果は期待しがたく，IFN-αと5-FUの相加・相乗効果[15]による抗腫瘍効果が必須であると考えられる．この効果については，IFN-αとの併用による5-FUの中間代謝物質である5-fluoro-2'-deoxyuridine 5-monophosphate（FdUMP）の細胞内濃度[16]とthymidylate synthetase（TS）阻害率の上昇効果[17]やDPD活性に対する影響[18]などの報告や，腫瘍細胞のapoptosisの増加[19,20]，cell cycleの遅延[21]などがその機序として報告されている．

教室ではこれらの報告をふまえて，その作用機序について，①IFN-αと5-FUの直接的増殖抑制効果の増強，②IFN-αと5-FUの免疫担当細胞を介した間接的抗腫瘍効果・宿主免疫の賦活作用，③IFN-αと5-FUの併用による血管新生抑制作用，が関与しているのではないかと推察している（図1）．

①については，両薬剤併用による細胞周期遅延やapoptosisの誘導による増殖抑制効果についての検討より，ヒト肝癌細胞株を用いた併用治療により，G0/G1期での細胞集積による細胞増殖遅延と細胞周期関連蛋白であるp27Kip1の発現増強を伴うことを見出した[22]．また，この増殖抑制効果はインタフェロンレセプター（IFN-α/β receptor; IFNR）の発現[23]が強い細胞株で顕著に認められ，IFNRの発現強度とシグナル伝達の重要性，特にSTAT1（signal transducer and activator of transcription）のリン酸化による活性化，apoptosisの頻度およびapoptosis関連蛋白であるBcl-2 familyの発現調節との相関を確認した[24-26]．この点については，他施設からもIFNRの遺伝子発現が併用療法の抗腫瘍効果に対して重要であると報告されている[27]．また，IFNARの発現とFAITの抗腫瘍効果との相関は，臨床検体を用いた検討においても確認された[28-30]（図2）．

次に，②の宿主免疫賦活効果として，IFN-α投与により進行肝細胞癌患者の末梢血中の単核球にTRAIL（Tumor necrosis factor-related apoptosis-induced ligand）mRNAの発現が誘導され，*in vitro*においてIFN-α添加によるTRAIL mRNAの発現を確認した．

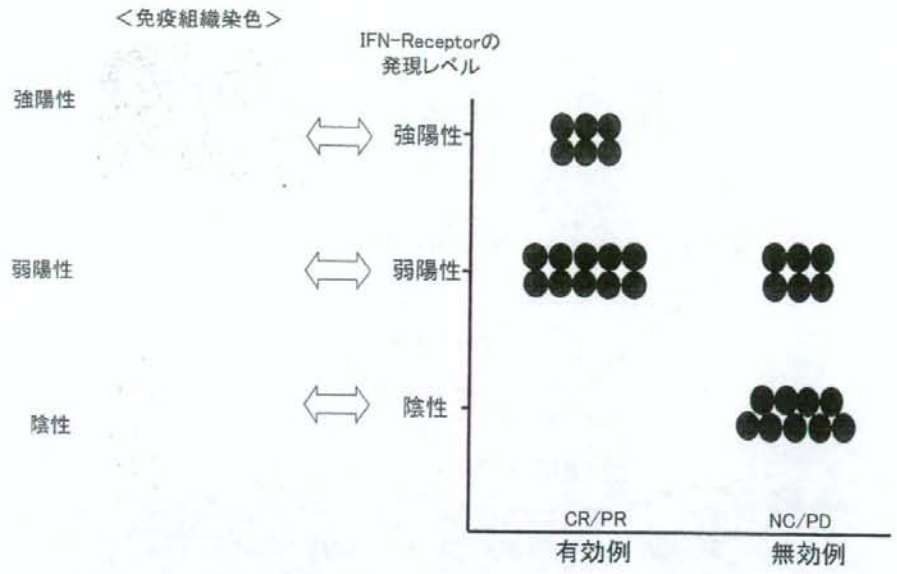

図2　IFNRの発現と臨床例での抗腫瘍効果との関係

さらに末梢血単核球の肝細胞癌株に対する細胞障害活性は，末梢血単核球にIFN-αの前刺激を加えることにより有意に増加し，TRAIL中和抗体によってその活性は阻害されることと，5-FUは肝癌細胞上のTRAILRの発現増強を促すことから，TRAIL-TRAILRを介している[31]．また，Fas/FasL系においても，IFN/5FUの併用によりNK細胞を免疫担当細胞とする間接的抗腫瘍効果が示され，Caspase-3, -8, -9とapoptptic-factorとしてFLIP, BCL-xL, Baxの関与が示され，Fas-FasLの関与についても明らかにした[32]．

最後に③の血管新生抑制作用については，先の肝細胞癌細胞増殖抑制実験で用いた培養液中の血管新生因子(VEGF)の発現量を測定したところ，IFN-αと5FUの併用によりその発現が減弱することを確認した[33]（図3）．さらにヌードマウスを用いたモデルにより，MVDやVEGF，Ang-1，Ang-2，の各種血管新生因子の発現強度の関与について報告した[34]．

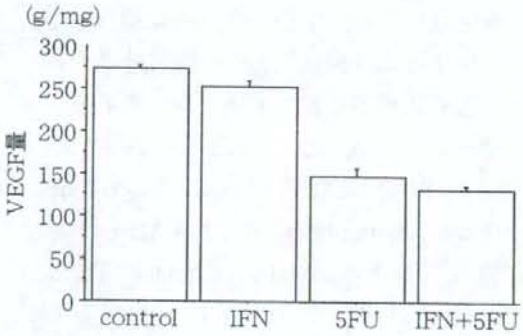

図3　IFN/5-FU併用による肝細胞癌培養液中の血管新生因子(VEGF)の発現の増強（文献No.33より引用，改変）

また，最近では，これら*in vitro*の検討に加えて，PCR-array法による網羅的遺伝子解析の施行[35]による，FAITの治療前効果予測の可能性についての報告もある．この抗腫瘍効果の治療前予測については，今後の基礎的検討課題の一つである．

3　IFN/5FU併用化学療法―適応・方法・治療成績・副作用―

IFN/5FU併用化学療法の治療成績につい

表1　IFN 5-FU併用化学療法に関する報告

報告者	奏効例/症例数	奏効率(%)	備　考
【全身化学療法】			
Patt YZ et al (2003)[36]	4/28	14.3%	FLHCCを除くHCC症例の成績
【動注化学療法】			
Sakon M et al (2002)[37]	5/ 8	62.5%	門脈内腫瘍栓症例
Ota H et al (2005)[28]	24/ 55	43.6%	
Obi S et al (2006)[38]	61/116	52.5%	
Uka K et al (2007)[39]	9/ 31	29.0%	
Uka K et al (2007)[40]	16/ 55	29.0%	門脈内腫瘍栓(−)症例を含む
【肝切除併用動注化学療法】			
Nagano H et al (2007)[41]	(−)/15	(−)	術後補助療法1年生存率：100%
Nagano H et al (2007)[30]	10/30	33.0%	減量肝切除術後療法

ての報告を表1にまとめた．5-FUの投与方法については，全身投与ではPattらの，肝細胞癌28症例(FLHCCを除く)に対するIFN-αと5-FU持続静脈内投与の14.3％の奏効率についての報告のみであった[36]．本邦からは，教室からの報告もあわせすべて動脈内投与であった[28,30,37-41]．したがって，以後は，IFNを併用した5-FUの肝動注化学療法について述べる．

表2　IFN 5-FU併用化学療法の適応基準

肝細胞癌	門脈内腫瘍栓	Vp3以上
	肝外転移	なし
肝機能	AST	< 100 IU/l
	ALT	< 100 IU/l
	T-Bil	正常(閉塞性黄疸は除く)
血液検査	血小板	80,000/ml以上
腎機能	血清Cr	< 1.5 mg/dl
PS		0, 1

1．適応と投与方法

本療法の対象は，一部の症例を除き既存の治療法が効を奏さない，門脈一次分枝または本幹侵襲(Vp3以上)を伴う高度進行肝細胞癌症例となる．切除不能症例のみならず肝機能良好で肝切除可能症例においては，肉眼的治癒切除後もしくは減量肝切除後の集学的治療の基軸として本療法を施行している．適応は，副作用や抗癌剤投与による肝障害を考慮して，総ビリルビン値が正常範囲内で，AST，ALTがともに100 IU/l未満，血小板80,000/mm³以上，血清クレアチニン値が1.5 mg/dl以下で，外来通院が可能なPerformance Statusが0，1を，教室では原則としている(表2)．全肝多発病変を伴う症例や耐術が不可能と考えられる切除不能症例では，Seldinger法にて肝動注カテーテルを挿入する．肝切除可能例では，術中にカテーテルを留置し，肝切除後の補助療法として本療法を施行している．教室での治療スケジュールは，皮下埋め込み式動注リザーバーより5-FUを300 mg/m²/dayで2週間持続投与を行い，2週間休薬を1クールとする．同時に天然型IFN-αを500万単位/回，週3回投与，4週間を1クールとして皮下投与する(図4)．ただ，このIFNの種類については，recombinantでも天然型と差はなかったとの報告もある[39]．

2．治療成績

門脈内腫瘍栓を伴う進行肝癌症例に対し