表1　進行肝細胞癌に対するインターフェロン治療

報告者	薬剤と投与法	1クール(期間)	奏効率(%)
Nair[5] (1985)	IFN-α 3 MU(daily)	2 months	0/5(0)
Forbes[6] (1985)	IFN-γ 3 MU(daily)	4 weeks	0/7(0)
Sachs[7] (1985)	IFN-α 12, 50 MU/m²(3 times/week)	12 weeks	0/30(0)
GTSG[9] (1990)	IFN-α 5−15 MU/m²(3 times/week)	1−3 weeks	2/30(7)
Lai[8] (1993)	IFN-α 5 MU/m²(3 times/week)	1 week	11/35(31)
de Braud[10] (1994)	IFN-β 3 MU(3 times/week, day 1−14) IL-2 4.5 MU(5 days/week, day 7−21)	4 weeks	0/10(0)
Llovet[11] (2000)	IFN-α 3 MU(3 times/week)	1 week	2/30(7)
Reinisch[12] (2002)	IFN-γ 100 ug qd,(twice/week) rhGM-CSF 5 ug qd,(twice/week)	9 weeks	1/15(7)

注化学療法の関与が大きいことを示唆している．

3．門脈腫瘍栓(Vp 3以上)合併肝細胞癌に対する肝切除とIFNα併用5-FU動注化学療法の臨床成績

第14回原発性肝癌調査報告によればVp 3以上の門脈腫瘍栓合併肝癌の術後1年生存率は約49%である[3]．一方，IFNα併用5-FU動注化学療法の奏効(CR/PR)例のそれは42〜100%で，非奏効(NC/PD)例のそれは0%である(表4)．これらの結果は本併用療法により肝切除術(通常は肝葉切除)と同等，あるいはそれ以上の生存率が期待できることを示唆している．Vp 3肝細胞癌無治療例の予後は3カ月である[2]．当施設における奏効例の50%生存期間は18カ月であり，非奏功例及び肝切除例よりそれぞれ12カ月及び6カ月間長くなっている．つまり，門脈腫瘍栓(Vp 3, 4)合併肝細胞癌では肝切除だけでは予後を期待することは困難であり，化学療法の奏効が不可欠である．

4．IFNα併用肝動注化学療法の副作用と適応条件

門脈腫瘍栓(Vp 3以上)合併肝細胞癌に対して，最初の3例では卜部らの報告[25]にならい，5-FUを含む4剤の化学療法を行い良好な抗腫瘍効果を認めた[4]．しかし，骨髄抑制や鬱症状などの副作用が強く，継続性のある治療は難しいとの印象をもった．事実，最近のKanekoらの報告では重度の骨髄障害とともに8例に腎障害を認め，そのうち4例に透析が必要であったとしている[26]．そこで，IFNαの全身投与と5-FU単剤の肝動注の併用に変更した．副作用も少なく，奏効率も変わらないというpreliminaryな結果を得ている[4]．その後の報告(23例)でも鬱病をのぞき，特に大きな副作用を認めていない．小尾らも23例に施行し，大きな副作用を認めなかったとしている[29]．しかし，全身状態や肝機能が不良な症例では治療が完遂できない．そこで，現在の当施設における適応基準は原則として①年齢70歳未満，②GOT，GPT(100未満)，③黄疸無く(但し，閉塞性黄疸はこの限りではない)，④血小板数8万以上，⑤血清クレアチニン1.5 mg/dl以下，⑥PS(0，1)としている．

5．補助療法としてのIFNα併用肝動注化学療法

Vp 3以上の門脈腫瘍栓合併肝細胞癌患者では門脈圧の上昇に伴う腹水や食指不振，さらには食道静脈瘤破裂の危険性が常に存在する．また，本療法では動注用カテーテルのトラブルも経験する．従って，耐術可能で有効な補助療法があれば，少々肝内転移巣が遺残したとしても，早急に門脈腫瘍栓を主腫瘍とともに摘出する減量肝切除も一つの選択肢と考えられる．そこで，当施設ではVp 3以上の症例に対して耐術可能と判断されれば，IM 3であってもまず減量肝切除を行い，その後術後補助療法としてIFNα併用5-FU動注療法[4]を施行している．現在までに治療効果が判定できた症例は片葉に巨大腫瘍を認め，肉眼的に癌の遺残なく切除可能であった症例(切除可能群)9例と残肝に肉眼的な遺残病巣を認めたIM 3症例(減量切除群)

表2　進行肝細胞癌に対するインターフェロン併用化学療法(全身療法)

報告者	薬剤と投与法	期間	奏効率(%)
Creagan[13] (1989)	IFN-α 12 MU(daily, 5 days) Doxorubicin 25 mg/m², iv(day 1)	4 weeks	1/7(14)
Kardinal[14] (1993)	IFN-α 12 MU(daily, day 1−5/week) Doxorubicin 25−40 mg/m², iv(day 1)	4 weeks	1/30(3)
Collenoni[15] (1993)	IFN-β 3 MU(day 1,2,3), 6 MU(day 4−60), 6 MU(3 times/week for 10 months) Mitoxantrone 12 mg/m², iv(every 3 weeks)	8 weeks	9/38(23)
Patt[16] (1993)	IFN-α 5 MU(3 times/week) 5-FU 750 mg/m², continuous iv(5 days, 1 st week)	2 weeks	6/28(21)
Lotz[17] (1994)	IFN-α 6 MU/m²(daily, 5 days/week) Doxorubicin 35 mg/m², iv(day 1)	3 weeks	3/21(14)
Feun[18] (1994)	IFN-α 20 MU,(weekly, 1 st 3 weeks) Doxorubicin 20 mg/m², iv(weekly, 1 st 3 weeks)	5 weeks	2/21(10)
Kountouras[19] (1995)	IFN-α 6 MU,(daily, day 1−7, every 3 weeks) Doxorubicin 60 mg/m², iv(once every 3 weeks) Tamoxifen 10 mg po(twice daily) Desferrioxamine 500 mg,(day 1−7, every 3 weeks) Ascorbic acid 300 mg,(day 1−7, every 3 weeks)	3 weeks	2/7(29)
Bokemeyer[20] (1995)	IFN-α 3 MU/m²,(daily, day 1−5/week, 4 weeks) Doxorubicin 25 mg/m², iv(weekly, 4 weeks)	5 weeks	1/30(3)
Stuart[21] (1996)	IFN-α 9 MU(3 times/week) 5-FU 750 mg/m², iv(every week)		0/10(0)
Leung[22] (2002)	IFN-α 5 MU/m²(day 1−4) Doxorubicin 40 mg/m², iv(day 1) 5-FU 400 mg/m², iv(day 1−4) CDDP 20 mg/m², iv(day 1−4, every week)	3 weeks	25/149(17)
Patt[23] (2003)	IFN-α 4 MU/m²(3 times/week) 5-FU 200 mg/m², continuous iv(day 1−21)	4 weeks	4/28(14)
Feun[24] (2003)	Leukocyte IFN 6 MU/m²(day 1) Doxorubicin 20 mg/m², iv(day 1) 5 FUDR 80 mg/kg, continous iv(escalated to 3 times a week)	1 week	2/30(7)

15例である．両群とも術後少なくとも2剤併用("basic vegimen")を3クール施行することを基本とした．減量切除群の観察期間は6−18カ月であるが，1年生存率は全症例で約60%と切除可能症例の全国成績(49%)[3]より良好であった．また，鬱症状や腫瘍の進展により本療法が3クール以上施行できなかった5例は1例を除き，全例5カ月以内に死亡したが，施行可能であった10例では1年生存率が80%であった．遺残病巣(−)の切除可能群ではさらに良好な生存率(1年：100%，3年：80%)となっている．しかし，肺や骨などの肝外転移病変は制御困難であり，今後の課題である．

6．IFNα併用による抗腫瘍効果の増強機序

Chungら[27]はCDDP単独群とCDDP・IFNα併用群の無作為比較試験で後者の成績が良好であったとしている．本療法においてもIFNαの併用が不可欠かどうかの確認には5-FU動注療法とIFNα併用の5-FU動注療法との無作為比較試験が不可欠である．しかし，現実的にそれは極めて困難である．それはVp3以上の肝細胞癌患者では予後が極めて不良なことから，今回の治療がラストチャンスであることを自覚しており，IFNαによるプラスαの効果を期待して併用療法を選択するからである．従って，in vito及びin vivoの基礎的検討から相乗・相加作用を類推せざるをえない(図1)．

おわりに

IFNα併用による5-FU動注療法は肝機能が比較的良好であるが，局所療法が不可能となった症例がよい適応と考えられ，その約半数に抗腫瘍効果が期待できる．一方，Vp3，4合併例の割合が異なるものの，5-

表3　進行肝細胞癌に対するインターフェロン併用動注化学療法

報告者	薬剤と投与法	期間	奏効率(%)
Kaneko[26] (2002)	IFN-α 3 MU(3 times/week) 5-FU 750 mg/m², ia(weekly) CDDP 75 mg/m², ia(every 2 weeks) MTX 30 mg/m², ia(every 4 weeks) Leucovorin 30 mg/m², iv(every 4 weeks)	4 weeks	13/29(45)
Chung[27] (2000)	IFN-α 5 MU/m²(3 times/week) CDDP 2 mg/kg, continuous ia(every 8 weeks)	8 weeks	6/19(33)
Sakon[4] (2002)	"full regimen" IFN-α 5 MU(3 times/week) 5-FU 450−500 mg/m², continuous ia(day 1−14) CDDP 10 mg/day, continuous ia(day 1−14) MTX 90 mg/day, ia(day 1,7) Leucovorin 30 mg, iv(day 2,3,9,10)	4 weeks	3/3(100)
	"basic regimen" IFN-α 5 MU(3 times/week) 5-FU 450−500 mg/m², continuous ia(day 1−14)	4 weeks	5/8(63)

表4　門脈腫瘍栓(Vp 3, 4)合併肝細胞癌に対するIFNα/5-FU併用療法の効果

報告者	効果(例数)	奏効率(%)	生存率(%) 1年	2年	50%生存期間(月)
日本肝癌研究会[3] (2002)	肝切除(679)		49	30	12
Kaneko[26] (2002)	CR+PR(13)	45	51	33	11
	NC+PD(16)		14	7	3.5
小尾[29]	CR+PR(11)	48	42		
	NC+PD(12)		0		
当科[28]	CR+PR(11)	48	100	40	18
	NC+PD(12)		0	0	5.5

FUと他の抗癌剤との多剤肝動注療法によっても良好な成績(奏効率：20−48%)が報告されている[30〜32]．今後，個々の症例においてどの肝動注化学療法が適応となるのかを判別する必要がある．さらにIFNα併用5-FU全身療法の奏効率は依然低く，動注療法との併用でも肝外病変に対する効果は期待できない．これら無効例に対する問題解決が重要で，そのためには多方面からのアプローチが不可欠である．

文　献

1) Miyamoto A, Umeshita K, Sakon M, et al：Advanced hepatocellular carcinoma with distant metastases, successfully treated by a combination therapy of alpha-interferon and oral tegafur/uracil. J Gastroenterol Hepatol 15：1447−1451, 2000
2) Okuda K, Ohtsuki T, Obata H, et al：Natural history of hepatocellular carcinoma and prognosis in relation to treatment-study of 850 patients. Cancer 56：918−928, 1985
3) 日本肝癌研究会：第15回全国原発性肝癌追跡調査報告．進行印刷出版，京都，2002
4) Sakon M, Nagano H, Dono K, et al：Combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi

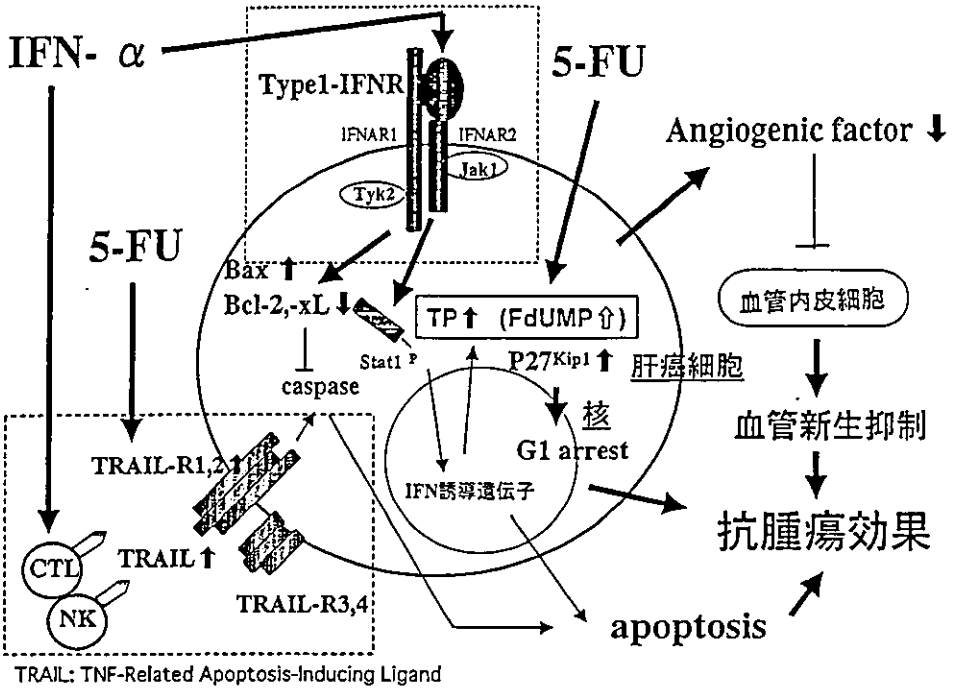

図1　インターフェロンα併用5-FU動注化学療法の作用機序(仮説)

in the major portal branches. Cancer 94：435−442, 2002

5) Nair PV, Tong MJ, Kempf R, et al：Clinical, serologic, and immunologic effects of human leukocyte interferon in HBsAg-positive primary hepatocellular carcinoma. Cancer 56：1018−1022, 1985

6) Forbes A, Johnson PJ, Williams R：Recombinant human gamma-interferon in primary hepatocellular carcinoma. JR Soc Med 78：826−829, 1985

7) Sachs E, Di Bisceglie AM, Dusheiko GM, et al：Treatment of hepatocellular carcinoma with recombinant leucocyte interferon：a pilot study. Br J Cancer 52：105−109, 1985

8) Lai CL, Lau JY, Wu PC, et al：Recombinant interferon-alpha in inoperable hepatocellular carcinoma：a randomized controlled trial. Hepatology 17：389−394, 1993

9) The Gastrointestinal Tumor Study Group：A prospective trial of recombinant human interferon alpha 2B in previously untreated patients with hepatocellular carcinoma. Cancer 66：135−139, 1990

10) de Braud F, Colleoni M, Noli F, et al：Home treatment with interleukin 2 and beta-interferon in patients with colorectal cancer and hepatocellular carcinoma. Oncology 51：472−476, 1994

11) Llovet JM, Sala M, Castells L, et al：Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. Hepatology 31：54−58, 2000

12) Reinisch W, Holub M, Katz A, et al：Prospective pilot study of recombinant granulocyte-macrophage colony-stimulating factor and interferon-gamma in patients with inoperable hepatocellular carcinoma. J Immunother 25：489−499, 2002

13) Creagan ET, Long HJ, Frytak S, et al：Recombinant leukocyte A interferon with doxorubicin-a phase I study in advanced solid neoplasms and implications for hepatocellular carcinoma. Cancer 61：19−22, 1988

14) Kardinal CG, Moertel CG, Wieand HS, et al：Combined doxorubicin and alpha-interferon therapy of advanced hepatocellular carcinoma. Cancer 71：2187−2190, 1993

15) Colleoni M, Buzzoni R, Bajetta E, et al：A phase II study of mitoxantrone combined with

beta-interferon in unresectable hepatocellular carcinoma. Cancer 72：3196−3201, 1993

16) Patt YZ, Yoffe B, Charnsangavej C, et al：Low serum alpha-fetoprotein level in patients with hepatocellular carcinoma as a predictor of response to 5-FU and interferon-alpha-2b. Cancer 72：2574−2582, 1993

17) Lotz JP, Grange JD, Hannoun L, et al：Treatment of unresectable hepatocellular carcinoma with a combination of human recombinant alpha-2b interferon and doxorubicin-results of a pilot study. Eur J Cancer 30A：1319−1325, 1994

18) Feun LG, Savaraj N, Hung S, et al：A phase II trial of recombinant leukocyte interferon plus doxorubicin in patients with hepatocellular carcinoma. Am J Clin Oncol 17：393−395, 1994

19) Kountouras J, Boura P, Karolides A, et al：Recombinant a2 interferon (a-IFN) with chemo-hormonal therapy in patients with hepatocellular carcinoma (HCC). Hepatogastroenterology 42：31−36, 1995

20) Bokemeyer C, Kynast B, Harstrick A, et al：No synergistic activity of epirubicin and interferon-α2b in the treatment of hepatocellular carcinoma. Cancer Chemother Pharmacol 35：334−338, 1995

21) Stuart K, Tessitore J, Huberman M：5-Fluorouracil and alpha-interferon in hepatocellular carcinoma. Am J Clin Oncol 19：136−139, 1996

22) Leung TW, Tang AM, Zee B, et al：Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer 94：421−427, 2002

23) Patt YZ, Hassan MM, Lozano RD, et al：Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon alfa-2b for treatment of hepatocellular carcinoma. J Clin Oncol 21：421−427, 2003

24) Feun LG, O'Brien C, Molina E, et al：Recombinant leukocyte interferon, doxorubicin, and 5 FUDR in patients with hepatocellular carcinoma-A phase II trial. J Cancer Res Clin Oncol 129：17−20, 2003

25) 卜部　健，金子周一，小林健一：門脈腫瘍栓合併肝細胞癌に対するインターフェロン併用化学療法を中心とした集学的治療による治療成績．肝臓 38 suppl(3)：44，1997

26) Kaneko S, Urabe T, Kobayashi K：Combination chemotherapy for advanced hepatocellular carcinoma complicated by major portal vein thrombosis. Oncology 62(Suppl 1)：69−73, 2002

27) Chung YH, Song IH, Song BC, et al：Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-alpha for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. Cancer 88：1986−1991, 2000

28) 永野浩昭，左近賢人，門田守人：肝細胞癌(Hepatocellular Carcinoma)の集学的治療．癌の臨床　47：1115−1120，2001

29) 小尾俊太郎，椎名秀一郎，寺谷卓為，他：進行肝細胞癌(VP 3，4)に対するIFN＋5 FU併用化学療法の有用性．第38回日本肝癌研究会抄録集 p 205，2002

30) Ando E, Tanaka M, Yamashita F, et al：Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Analysis of 48 cases. Cancer 95：588−595, 2002

31) Itamoto T, Nakahara H, Tashiro H, et al：Hepatic arterial infusion of 5-fluorouracil and cisplatin for unresectable or recurrent hepatocellular carcinoma with tumor thrombus of the portal vein. J Surg Oncol 80：143−148, 2002

32) Yamasaki T, Kurokawa F, Shirahashi H, et al：Novel arterial infusion chemotherapy using cisplatin, 5-fluorouracil, and leukovorin for patients with advanced hepatocellular carcinoma. Hepatol Res 23：7−17, 2002

TAE抵抗性の多発肝細胞癌に対して肝右葉切除術後長期予後を得た1例

中村 将人[*1] 永野 浩昭[*1] 左近 賢人[*1] 山本 為義[*1]
太田 英夫[*1] 丸橋 繁[*1] 宮本 敦史[*1] 堂野 恵三[*1]
梅下 浩司[*1] 中森 正二[*1] 平松 直樹[*2] 林 紀夫[*2]
門田 守人[*1]

(*Jpn J Cancer Chemother* 30(11): 1717-1721, *October*, 2003)

要旨 症例は55歳，女性。HCV陽性。S8のHCCに対して2回のTAE施行歴あり。1997年，CTにてS8に径1cmの再発巣を2か所認め，入院後，SMANCSとLipiodolを用いた3回目のTAEを施行した。1か月後のCTにて治療効果不十分と診断し，手術目的にて外科紹介となった。術前肝機能は良好で，左葉には肝内転移巣を認めなかったため，肝右葉切除術を施行した。術後5年2か月目に左葉に再発したが，RFA，PEITで治療可能であり，5年10か月を経過する現在生存中である。以上よりTAE抵抗性の多発病変に対して，肝機能が良好，病変が片葉に限局している場合には，肝切除により長期生存を得られる症例も存在すると考えられた。

A Case of Long-term Survival with TAE Resistant Multiple Recurrence HCC Successfully Treated by Hepatic Resection: Masato Nakamura[*1], Hiroaki Nagano[*1], Masato Sakon[*1], Tameyoshi Yamamoto[*1], Hideo Ota[*1], Shigeru Marubashi[*1], Atsushi Miyamoto[*1], Keizo Dono[*1], Koji Umeshita[*1], Shoji Nakamori[*1], Naoki Hiramatsu[*2], Norio Hayashi[*2] and Morito Monden[*1] ([*1]*Dept. of Surgery and Clinical Oncology*, [*2]*Dept. of Medicine and Therapeutics, Graduate School of Medicine, Osaka University*)

Summary

A 55-year-old female was admitted to our hospital for a third recurrence of hepatoma. She was treated with transcatheter arterial embolization (TAE) in April and November 1996. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed multiple tumors of S4/S8 and S7 in the liver. After the third TAE using SMANCS, Lipiodol and Spongel, abdominal CT revealed insufficient Lipiodol retention and the in efficacy of this treatment. A right lobectomy of the liver was performed for the TAE resistant multiple recurrence of HCC. After the surgery, the patient survived for over 5 years with no recurrence. It appears that this surgery may be a useful modality for TAE resistant multiple recurrence hepatoma in cases of good liver function and lesions limited to the hemi lobe. Key words: Hepatoma, TAE, TAE resistant lesion, Hepatic resection

[*2] 大阪大学大学院医学系研究科・病態情報内科

連絡先: 〒565-0871 吹田市山田丘2-2 [*1] 大阪大学大学院医学系研究科・病態制御外科
中村 将人

0385-0684/03/¥500/論文/JCLS

はじめに

多発肝細胞癌は，肝動脈塞栓術（transcatheter arterial embolization: TAE）などの治療法に抵抗性となると予後は極めて不良である。今回われわれは繰り返すTAEに対して無効病巣となった多発肝細胞癌に対して肝右葉切除術を施行し，術後5年以上の長期予後を得た1例を経験したので報告する。

I. 症　例

患者: 55歳，女性。

既往歴，家族歴: 特記すべきことなし。

現病歴: 1996年4月，HCVの経過観察中に，肝S8の径3 cmのHCCに対してTAEを施行した。同年11月，S8の再発病変に対して再度TAEを施行した。1997年6月，CTにてS8に1 cmのSOLを認め，3回目のTAE目的にて入院となった。

入院時画像所見: 肝動脈造影下CT（CTA）にて，前回治療部位の頭側のS4/S8，S7に，径1 cmの造影される腫瘍を2か所認めた。経動脈性門脈造影下CT（CTAP）において腫瘍はperfusion defectを示し，HCCの再発であると考えられた。また，右葉は反復施行したSMANCSを用いたTAEのために高度に萎縮していた（図1）。

入院後治療経過: 肝動脈造影検査施行時に中肝動脈よりSponzel，右肝動脈よりSMANCSとLipiodolを用いたTAEを併せて施行した。1か月後のCTにおいて，両腫瘍にはLipiodolの貯留をほとんど認めず治療効果不十分と診断し，手術目的にて外科紹介となった（図2）。肝機能が良好で耐術可能であること，左葉には病変が存在しないことが確認されたため，肝右葉切除術を施行した（表1）。

手術所見: 開腹時，術前の画像診断どおり，肝右葉は高度に萎縮し周囲臓器との炎症性の癒着を認め，SMANCSの動注を含む反復したTAEによるものと考えられた。術中に超音波検査を施行し，左葉には病変を認めないことを再度確認し，肝右葉切除術を施行した。

切除標本，肉眼および病理学的所見: 術前に認められた2か所の腫瘍と前回治療痕以外にさらに1か所の病変をS7に認めた。前回治療痕の他1か所の病変で細胞は脂肪変性しcomplete necrosisと診断されたが，残る2か所では壊死細胞をまったく

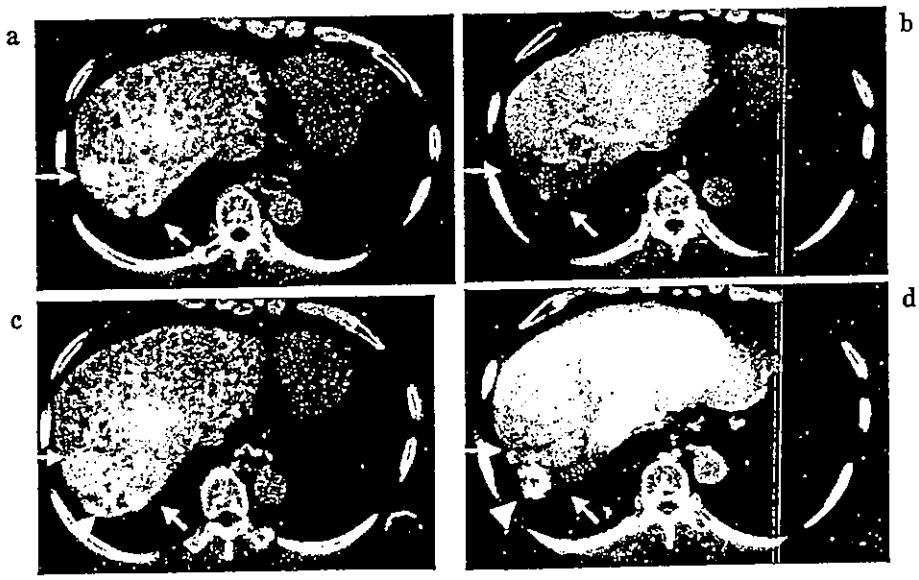

図1　TAE前画像所見

a,c: 肝動脈造影下CT（CTA）にて，前回治療部位（矢頭）の頭側のS4/S8，S7に，径1 cmの造影される腫瘍を2か所認めた（矢印）。

b,d: 経動脈性門脈造影下CT（CTAP）において腫瘍はperfusion defectを示した。

認めず，viableと診断された(図3)。TAEの治療効果は不十分であったことが，組織学的にも確認された。

術後経過は問題なく，術後28日目に退院した。退院時のAFPは8 ng/mlと低下していた(図4)。術後5年2か月目に肝左葉に再発を認めたがTAE，RFAなどの局所療法を施行し，術後5年10か月を経過する現在生存中である。

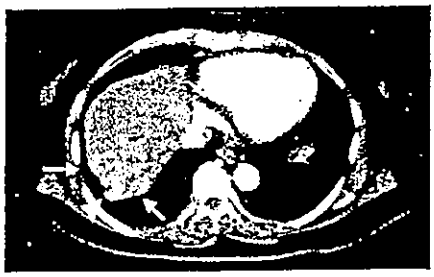

図2
3回目のTAE 1か月後のCTにおいて，両腫瘍にはLipiodolの貯留をほとんど認めず，治療効果不十分と診断した（矢印）。

II. 考　察

TAEは「進行した肝細胞癌は肝動脈のみに栄養される」という特性を用い，肝動脈末梢部を塞栓物質で塞栓することにより壊死に陥らせる方法で，切除不能な多発肝細胞癌症例や大型の肝細胞癌の術前療法などに広く施行されている[1-5]。TAEは病変が両葉多発であったり，肝機能が不良である場合でも施行可能であり，肝切除やPEIなどと比較しその適応範囲は広い。さらに，肝動脈造影検査施行時に診断と併せて治療を行い得ることが可能であり，再発を繰り返す肝細胞癌のほぼ全例において施行され，そのような意味においては肝細胞癌治療における意義と貢献度は高いといっても過言ではない。しかしながらその一方で，TAEには

表1 TAE前後および術前血液検査
(治療経過をとおして肝機能は保たれていた)

		pre TAE	post TAE	pre ope
WBC	(/μl)	2,530	3,140	2,280
RBC	(×10⁴/μ)	438	432	395
Hb	(g/dl)	12.4	13.4	12.2
Ht	(%)	38.8	39.7	36.5
Plt	(×10⁴/μ)	11.1	10.4	8.6
TP	(g/dl)	7	7.7	7.5
Alb	(g/dl)	3.5	3.9	3.5
T-Bil	(mg/dl)	0.9	0.6	0.7
D-Bil	(mg/dl)	0.2	0.2	0.2
AST	(IU/l)	16	16	21
ALT	(IU/l)	11	13	17
ALP	(IU/l)	134	106	101
LDH	(IU/l)	184	207	192
Ch-E	(IU/l)	3,356	3,213	2,821
Na	(mEq/l)	145	140	142
K	(mEq/l)	3.7	3.8	3.8
Cl	(mEq/l)	100	105	107
PT	(%)	76	63	60
APTT	(%)	29	30	29
HPT	(%)	70	76	75
AT-III	(%)	84	85	89
AFP	(ng/ml)	47	50	62
PIVKA-II	(mAU/ml)	65>	65>	65>

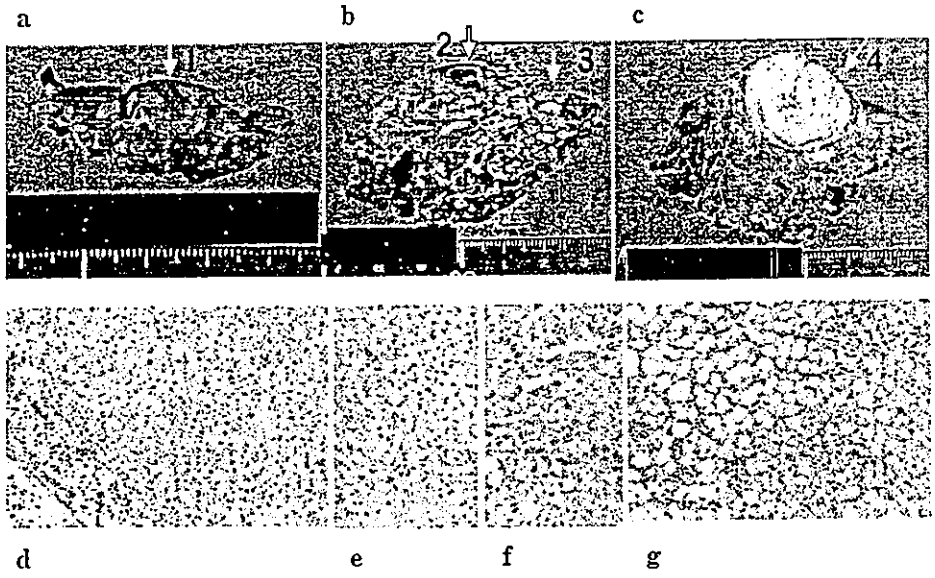

図 3

前回治療痕の他1か所の病変で細胞は脂肪変性し complete necrosis と診断されたが，残る2か所では壊死細胞をまったく認めず viable と診断された。

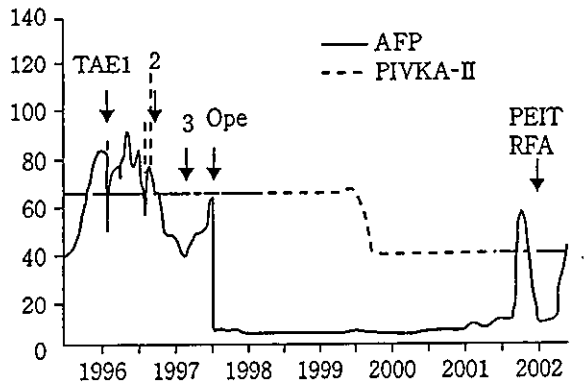

図 4 症例経過

術後5年10か月を経過，現在生存中である。

以下のような「限界」が存在するとされる。つまり，① 単回の治療では不十分であること，② 100% の壊死率が必ずしも得られないこと，③ 治療効果不良の肝癌結節が存在すること，④ 側副血行路の新生，⑤ 治療抵抗性の出現，⑥ 血管造影上非濃染の小肝癌に効果のないこと，⑦ TAE も行えない非適応症例の存在などである[6]。本症例では側副血行路の新生は明らかではなかったが，1，2回目の TAE では反応がよかったのに対し，3回目の TAE では十分な効果が得られず，治療抵抗性の出現をみた。

そこで，本症例においては TAE 無効の多発病巣に対して肝機能が保たれていること，病巣が片葉にのみ限局していることより肝切除を選択した。本来，TAE は切除，RFA，PEIT など他の modality で対処不能な場合に選択される治療法でもあるため，TAE に抵抗性を示した症例に対する治療法の選択肢は非常に少ない。しかし本症例のように TAE 無効病巣に対して，一定の条件であれば，肝切除を選択することにより長期予後を得られる可能性があることが明らかとなった。

最後に，本症例では SMANCS を複数回使用した。SMANCS は油性の Lipiodol との安定な懸濁液を作製することができ，肝腫瘍内に長く停滞することが可能である[7]。一部には，抗腫瘍効果に優れることが，臨床第 I，II 相試験や epilbicin 併用の TAE と比較試験において報告されている[8-10]。その一方で副作用も多く，動脈閉塞，A-V shunt，肝不全，肝萎縮などの重篤な合併症を誘発する可能性が高いと報告されている[11]。したがって，その適応範囲については，いわゆる一般的な TAE よりは限定される治療法であると考えるべきかもしれない。ただし，本症例において SMANCS の強力な肝動脈への副作用による肝右葉の著明な萎縮を認めたが，そのために切除量が少なくなり，より

安全に肝切除が施行し得た可能性も否定できない。

結　語

TAE反復施行後の多発肝細胞癌の再発であっても肝機能が保たれており，病変が片葉に限局しているような症例では，肝切除も考慮すべき治療法であると考えられる。

文　献

1) Breedis C and Young G: The blood supply of neoplasm in the liver. *Am J Pathol* 30: 969-985, 1954.
2) Wheeler PG, Melia W, Dubbins P, *et al*: Non-operative arterial embolization in primary liver tumors. *Br Med J* 2: 242-244, 1979.
3) Adachi E, Matsuyama T, Nishizaki T, *et al*: Effects of preoperative transcatheter hepatic arterial chemoembolization for hepatocellular carcinoma. The relationship between postoperative course and tumor necrosis. *Cancer* 72: 3598-3608, 1993.
4) Nagasue N, Kohno H and Uchida M: Evaluation of preoperative transcatheter arterial embolization in the treatment of resectable primary liver cancer. *Semin Surg Oncol* 9: 327-331, 1993.
5) Zhijian Z, Qi L, Jia H, *et al*: The effect of preoperative transcatheter hepatic arterial chemoembolization on disease-free survival after hepatectomy for hepatocellular carcinoma. *Cancer* 89: 2606-2612, 2000.
6) 池田健次・編: 肝細胞癌の予知・診断・治療—Evidence Based Hepatology—. メディカルレビュー社, 1999, 大阪, pp175-176.
7) Maeda H, Takeshita J and Kanamaru R: A lipophylic derivative of neocarzinostatin; A polymer conjugation of an antitumor protein antibiotic. *Int J Pept Protein Re* 14: 81-87, 1979.
8) 田口鐵男, 斉藤達雄, 太田　潤・他: YM881(ジノスタチン スチマラマー)懸濁液の肝動注における第I相試験. 癌と化学療法 18(10): 1657-1663, 1991.
9) 田口鐵男, 斉藤達雄, 太田　潤・他: YM881(ジノスタチン スチマラマー)油性懸濁液の肝動注における第II相試験. 癌と化学療法 18(10): 1665-1675, 1991.
10) Abe S, Okubo Y, Ejiri Y, *et al*: Focal therapeutic efficacy of transcatheter arterial infusion of styrene maleic acid neocarzinostain for hepatocellular carcinoma. *J Gastroenterol* 35: 28-33, 2000.
11) Ikeda K, Saitoh S, Kobayashi M, *et al*: Hepatic vascular side effects of styrene maleic acid neocarzinostatin in the treatment of hepatocellular carcinoma. *J Gastroenterol* 35: 353-360, 2000.

Combined Intraarterial 5-Fluorouracil and Subcutaneous Interferon-α Therapy for Advanced Hepatocellular Carcinoma with Tumor Thrombi in the Major Portal Branches

Masato Sakon, M.D.[1]
Hiroaki Nagano, M.D.[1]
Keizo Dono, M.D.[1]
Shoji Nakamori, M.D.[1]
Koji Umeshita, M.D.[1]
Akira Yamada, M.D.[2]
Sumio Kawata, M.D.[2]
Yasuharu Imai, M.D.[3]
Shohei Iijima, M.D.[4]
Morito Monden, M.D.[1]

[1] Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, Osaka, Japan.

[2] Department of Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Osaka, Japan.

[3] Department of Medicine, Ikeda Municipal Hospital, Ikeda, Osaka, Japan.

[4] Department of Surgery, Shitennoji Hospital, Osaka, Japan.

The authors thank Atsushi Miyamoto, M.D., Eguchi Hidetoshi, M.D., Motoi Kondoh, M.D., Isao Arai, M.D., Shinji Tamura, M.D., Michiki Danno, M.D., Toshihiro Hatanaka, M.D., and Masahiro Nishikawa, M.D. for providing follow-up data.

Address for reprints: Masato Sakon, M.D., Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan; Fax: 81-6-6879-3259; E-mail: msakon@surg2.med.osaka-u.ac.jp

Received July 13, 2001; revision received July 13, 2001; accepted September 7, 2001.

BACKGROUND. The prognosis of hepatocellular carcinoma (HCC) invading into the major branches of the portal vein (Vp3) is extremely poor.

METHODS. Eleven consecutive patients with HCC and Vp3 were treated with 2–6 cycles of a "basic" combination therapy consisting of continuous arterial infusion of 5-fluorouracil (450–500 mg/day, for the initial 2 weeks) and subcutaneous injection of interferon-α (5 million international units, 3 times/week, 4 weeks). In the first 3 patients, methotrexate (90 mg/day 1 of every week), cisplatin (10 mg/day), and leucovorin (30 mg/days 2 and 3 of every week) also were administered for the initial 2 weeks ("full" regimen).

RESULTS. In 8 (73%) of 11 patients, an objective response (complete response [CR] or partial response [PR]) was observed with marked regression of tumor and decrease in tumor markers. The use of the full regimen was associated with objective response in all patients; instead, they developed thrombocytopenia or leukopenia. In the subsequent 8 patients with basic regimen, 5 patients showed CR (2 cases) or PR (3 cases; objective response rate, 63%), and leukopenia was observed only in 1 patient.

CONCLUSIONS. Simple combination therapy with subcutaneous interferon-α and intraarterial 5-fluorouracil therefore is a promising treatment modality for intractable HCC with Vp3. *Cancer* 2002;94:435–42. © *2002 American Cancer Society.*

KEYWORDS: hepatocellular carcinoma, interferon-α, 5-fluorouracil, chemotherapy, portal vein, tumor thrombus.

The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, particularly in patients with tumor thrombi in the major branches of the portal vein (Vp3).[1–10] Almost all patients with unresectable tumors die within several months with poor quality of life (QOL) due to intractable ascites or esophageal bleeding. Even in resectable cases, the prognosis is extremely poor despite aggressive surgery.[6,8,10–12] Furthermore, conventional therapies such as percutaneous ethanol injection, microwave coagulation therapy, and transcatheter arterial embolization generally are not indicated for HCC with portal tumor thrombi due to lack of efficacy and possible complications.[5,7,9,13] Arterial infusion chemotherapy also has been attempted, but its effectiveness is still unsatisfactory.[4,14,15] Therefore, a new strategy is required for these patients with intractable HCC and portal tumor thrombi.

We have had experience with one patient with recurrent HCC and multiple lung, bone, and liver metastases. The malignant condition

DOI 10.1002/cncr.10246

TABLE 1
Liver Function of Patients with Tumor Thrombi in Major Branches of the Portal Vein, Treated with a Combination of 5-FU Arterial Chemotherapy and Subcutaneous Administration of IFN-α

Case	Age (yrs)	Gender	Hepatitis	Platelet ($\times 10^5/\mu L$)	Leukocyte/μL	Albumin (g/dL)	Hepaplastin test (%)	Child-Pugh classification
1	42	M	HCV	2.0	9780	3.0	80	B
2	46	M	HBV	1.5	5450	4.0	88	A
3	74	M	HCV	1.2	4420	3.0	63	B
4	70	M	HCV	1.8	4100	3.5	79	A
5	70	M	HCV	1.8	5640	3.4	78	B
6	67	F	HCV	1.3	4590	3.7	76	C
7	64	M	HCV	1.0	4730	3.7	100	A
8	60	M	HBV	2.3	4690	3.0	89	A
9	70	M	HBV	1.9	8990	3.2	80	A
10	63	M	HCV	0.9	3710	3.0	60	B
11	31	M	HBV	1.2	7460	2.6	69	C

5-FU: 5-fluorouracil; IFN: interferon; M: male; HCV: hepatitis C virus; HBV: hepatitis B virus; F: female.

was uncontrollable by conventional therapies but almost completely regressed after administration of tegafur/uracil (UFT) and interferon (IFN)-α.[16] The patient is still alive without recurrence 2.5 years after the initiation of this treatment. This remarkable outcome prompted us to systematically investigate the beneficial effect of combination therapy using an anticancer drug and IFN-α in advanced HCCs.

In this study, we used a combination therapy of subcutaneous administration of IFN-α and arterial infusion chemotherapy with 5-fluorouracil (5-FU) in 11 consecutive patients with unresectable HCC associated with Vp3. Our results showed that this treatment markedly decreased tumor size and levels of tumor markers with an encouraging response rate.

MATERIALS AND METHODS

Patients

Between April 1998 and June 1999, 17 consecutive patients with tumor thrombi in the major branches of the portal vein (Vp3) were referred to the Department of Surgery II, Osaka University Hospital. Liver function tests and imaging techniques including computed tomography (CT) scan under hepatic angiography and arterial portography revealed that tumors in three patients were resectable, and they subsequently underwent hepatectomy. Among unresectable tumors in 14 patients, extrahepatic metastases were found in 3 patients, and these patients were excluded from the study. For the remaining 11 patients, the tumors were diagnosed as unresectable because of multiple intrahepatic metastases (7 patients) and marked portal tumor thrombi extending into all 3 major branches (4 patients). All of these patients met the criteria described below and received an intraarterial catheter inserted from the subclavian or femoral artery with a subcutaneously implanted reservoir[17] and were treated with a combination therapy comprised of IFN-α and 5-FU. The demographics of these patients are shown in Table 1.

Criteria for Treatment Regimen

The criteria for this regimen include 1) tumor thrombi invading to at least 1 of the main branches of the portal vein, 2) absence of extrahepatic metastases, 3) a platelet count $> 0.8 \times 10^5/\mu L$, 4) successful implantation of intraarterial catheter and drug delivery system, and 5) performance status (Eastern Cooperative Oncology Group [ECOG])[18] level 0–2 .

Treatment Regimen

After obtaining their informed consent, 11 patients were treated with subcutaneous administration of IFN-α (OIF; Otsuka Pharmaceutical Co., Tokyo) and intraarterial infusion of 5-FU (Kyowa Hakko Co., Tokyo, Japan). Interferon-α (5×10^6 U, [5 MU]) was administered on Days 1, 3, and 5 of every week. Continuous infusion chemotherapy (5-FU, 450–500 mg/day) through the proper hepatic artery was performed every 2 weeks for 2 weeks via a catheter connected to a subcutaneously implanted drug delivery system. In addition to this "basic" regimen, we administered methotrexate (90 mg/Day 1 of every week), cisplatin (10 mg/day), and leucovorin (30 mg/Days 2 and 3 of every week) in the first 3 patients. However, severe myelosuppression was observed in all of these patients and therefore we tried the basic regimen only in the subsequent eight patients. All anticancer therapies were discontinued when adverse effects reached level 2 of the ECOG classification[18] (with the exception of

TABLE 2
Clinical Outcome of Patients with Tumor Thrombi in Major Branches of the Portal Vein, Treated with a Combination of 5-FU Arterial Chemotherapy and Subcutaneous Administration of IFN-α

Case	Tumor pathology	Tumor diameter (cm)	Treatment cycles	AFP (ng/mL) (pre/post)	PIVKA-II (mAU/mL) (pre/post)	Response	Side effects*	Outcome (mos)
1	Vp3, multiple	4.5	3	9900/< 5	7140/< 40	CR	Thrombocytopenia	21, alive
2	Vp3, multiple	4.0	1	448/< 5	8988/< 65	PR	Leukopenia	17, alive, brain metastases
3	Vp3, multiple	5.5	1	32/9	7056/630	PR	Depression, thrombocytopenia	15, dead, recurrence
4	Vp3/Vv3	3.5	6	5/5	< 65/< 65	PR	Leukopenia	15, alive
5	Vp3, multiple	5.0	2	12/5	3750/14,637	SD	—	13, alive
6	Vp3/Vv2	6.0	2	191/5	448/< 40	CR	—	8, alive
7	Vp3, multiple	5.0	3	4400/< 5	4430/< 40	CR	—	6, alive
8	Vp3, multiple	Right lobe Diffuse type	2	10/12	40,110/195,300	PD	—	5, alive
9	Vp3	6.0	3	336/364	ND	PR	Depression	5, alive
10	Vp3, multiple	Right lobe Diffuse type	2	28,700/28,100	5635/11,739	PD	—	5, dead
11	Vp3, B2	5.0	2	70,000/41,200	790/< 40	PR	—	3, alive

AFP: α-Fetoprotein; PIVKA-II: protein induced by vitamin K antagonist or absence; Vp3: tumor thrombus in the first branch with or without extension to the trunk or the opposite branch of the portal vein; Vv2: tumor thrombus in the right, middle, or left hepatic vein trunk; Vv3: tumor thrombus extending to the inferior vena cava; B2: bile duct invasion to the hilar or extrahepatic portion; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ND: not determined due to warfarin administration.
* Thrombocytopenia and leukopenia represent platelet and leukocyte counts $<0.4 \times 10^5/\mu L$ and $2000/\mu L$, respectively.

platelet and leukocyte counts of $<0.4 \times 10^5/\mu L$ and $2000/\mu L$, respectively, because these parameters were often decreased before treatment because of cirrhosis). In addition to serum chemistry, tumor markers such as α-fetoprotein (AFP) and PIVKA-II (protein induced by vitamin k antagonist or absence) were measured at least once every 3 months. Abdominal CT scan or dynamic magnetic resonance imaging (MRI) also was performed before and after treatment. The objective response was classified according to the ECOG criteria.[18]

RESULTS

Clinical Effects

In 8 (73%) of 11 consecutive patients with an objective response (complete response [CR] or partial response [PR]), marked regression of tumor and decrease in tumor markers were observed after the initiation of combination therapy with IFN-α and 5-FU, as shown in Table 2. In the first three patients treated by the "full" regimen, all patients had an objective response, and portal vein tumor was markedly decreased or disappeared completely, consistent with loss of tumor vascular staining. Regrowth of hepatic tumor was observed in one patient with PR (Case 3) after cessation of therapy due to depression. With regard to the last 8 patients (Cases 4–11) receiving 2–6 cycles of the basic regimen, 5 patients (63% of response rate) demonstrated a CR (2 cases) or PR (3 cases). The remaining patient (stable disease [SD], Case 5) who demonstrated no changes survived for 13 months without tumor progression. One of the 2 patients with progressive disease (PD, Case 10) died of pontine hemorrhage 5 months after initiation of therapy. Two representative patients who were treated successfully are described.

Patient 4

A 70-year-old man with HCC (5-cm dimension in subsegment 5) underwent subsegmentectomy in 1994. Tumor markers were not elevated before surgery (AFP <5 ng/mL; PIVKA-II 65 mAU/mL), but histologic examination revealed moderately differentiated HCC. Multiple recurrent tumors developed 2 years after surgery and transcatheter arterial chemoembolization (TAE) was repeated on 3 occasions. In April 1998, tumor recurrence was detected with portal tumor thrombi extending throughout nearly the entire portal vein system (Fig. 1a). Markedly dilated collateral veins developed because of complete obstruction of the main trunk of the portal vein (Fig. 1b). A combination of IFN-α and 5-FU therapy (6 cycles) was administered for 7 months. After therapy, the abdominal CT scan showed marked reductions in the size of tumors and portal thrombi, with loss of staining of portal tumor thrombus. Tumor size gradually diminished after treatment cessation, and no tumor progression has been observed for more than 8 months (Fig. 1c).

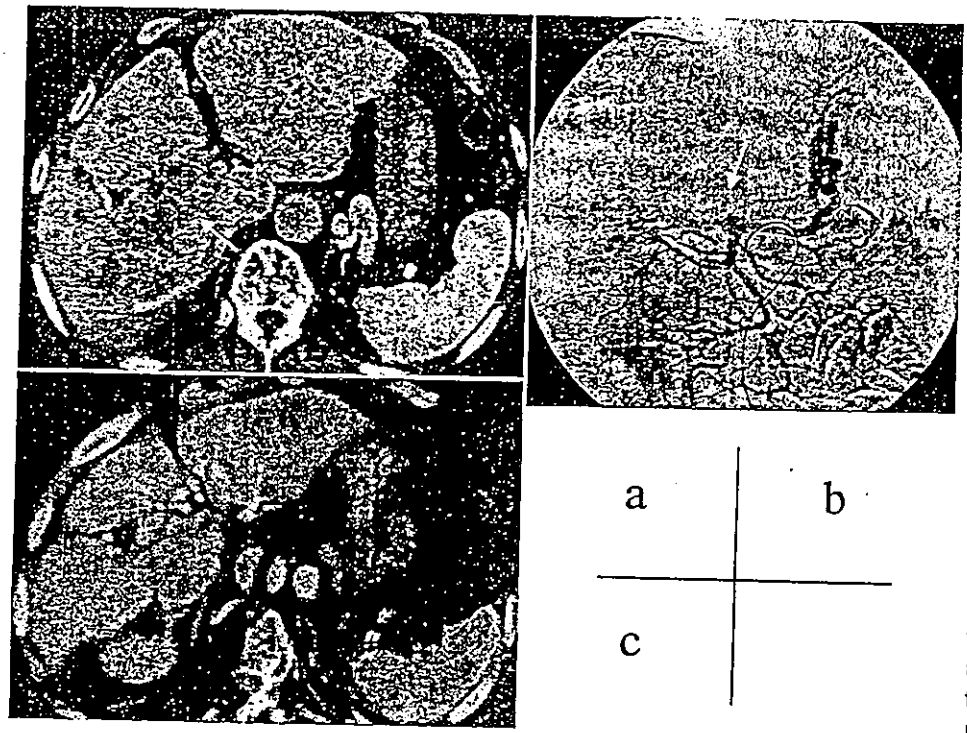

FIGURE 1. Patient 1. (a) Multiple intrahepatic recurrences detected 2 years after partial hepatectomy were treated by transcatheter arterial embolization (TAE) on three occasions. However, TAE was not effective and tumor thrombi developed subsequently, invading into nearly all branches of the portal vein. (arrow) Tumor thrombus in the major branches of the portal vein. (b) Portography demonstrated tumor thrombus extending up to the superior mesenteric vein (arrow), from which the collateral vein (the left gastric vein) originated. No portal blood flow was observed. (c) After 6 cycles of combination interferon (IFN)-α/5-fluorouracil (5-FU) therapy, portal tumor thrombi were markedly smaller, and no tumor progression was observed for another 8 months without any treatment.

Patient 6

A 67-year-old woman with multiple HCCs (6-cm primary tumor in subsegment 8) associated with tumor thrombus in the right first branch of the portal vein underwent laparotomy but was classified as unresectable because of insufficient functional liver reserve. Nearly all portal branches in the anterior segment were occupied by the tumor thrombus extending from the main tumor (Fig. 2a,b). Histologic examination revealed moderately to poorly differentiated HCC. The levels of AFP and PIVKA-II before treatment were 191 ng/mL and 448 mAU/mL, respectively. After commencement of IFN-α/5-FU combination therapy (basic regimen), both tumor markers rapidly decreased and returned to normal levels within one cycle of treatment. Consistent with these changes in tumor markers, tumors and portal tumor thrombus regressed in association with loss of vascularity (Fig. 2c). No side effects were observed during this period. Tumor markers remained normal and imaging modalities detected no recurrence at 8 months after the commencement of combination treatment.

Adverse Effects

There were no apparent side effects resulting from catheter insertion and subcutaneous implantation of the reservoir. Leukopenia and thrombocytopenia were observed in all three patients who were treated by the full regimen, Grade 3 level leukopenia was observed in one patient (Case 2) and was well managed by the administration of granulocyte colony-stimulating factor. In contrast, myelosuppression was observed in only one of eight patients treated with the basic regimen. Other adverse effects were, in general, manageable. Fever was commonly observed but was easily controlled by nonsteroidal antiinflammatory drugs before IFN-α injection. Depression due to IFN-α administration was observed in two patients. Pontine bleeding was observed in 1 patient with PD (Case 10) 5 months after initiation of the therapy. Because bleeding tendency, such as thrombocytopenia, was not observed in this patient, the relation between cause of death and IFN-α/5-FU combination therapy could not be confirmed.

DISCUSSION

Development of tumor thrombi in major branches of the portal vein is a frequent terminal feature of HCC, with either primary or recurrent tumors. The prognosis of such patients is extremely poor and survival generally is limited to a few months after diagnosis.[1-10] In the first three HCC patients with Vp3, we used the full regimen, i.e., administration of IFN-α with multiple anticancer drugs such as 5-FU, cisplatin, methotrexate, and leucovorin and found that it was markedly effective in all these patients. However, because this regimen was complex, it is difficult to determine whether all the anticancer agents that were used were

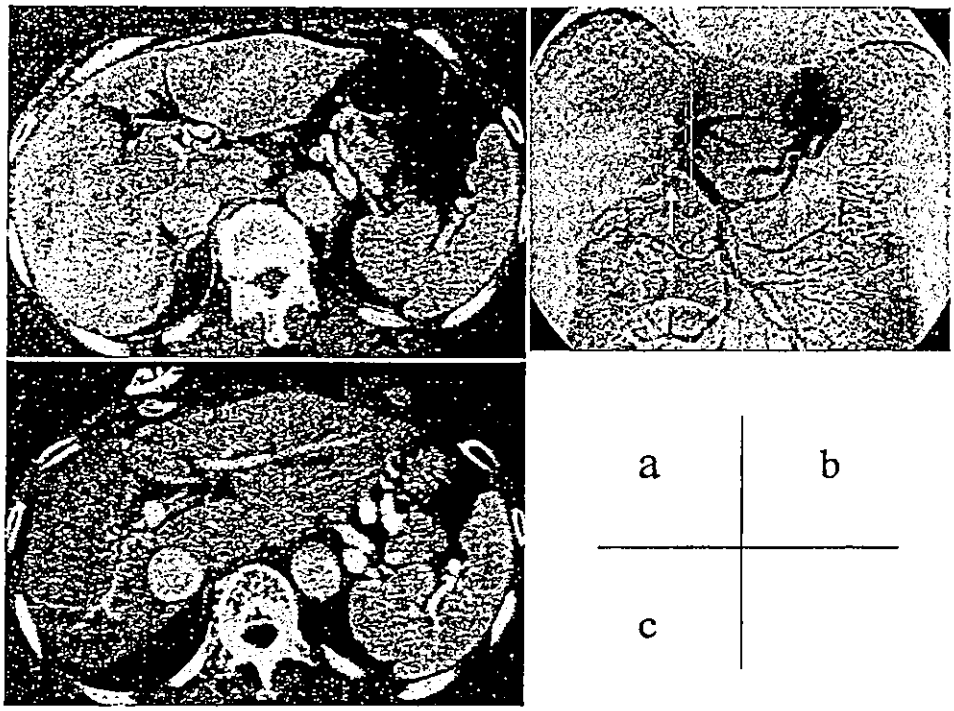

FIGURE 2. Patient 6. (a) Abdominal computed tomography (CT) scan showing multiple hepatocellular carcinomas with tumor thrombus extending into the first right branch of the portal vein. Nearly all branches of the anterior segment were occupied by tumor thrombi. (b) Arterial portography demonstrated portal tumor thrombi (arrow) that completely interrupted the portal blood flow into the right lobe. (c) After one cycle of combination interferon (IFN)-α/5-fluorouracil (5-FU) therapy, the main tumor and portal tumor thrombi markedly regressed with recannulation of the right branches of the portal vein. The portal tumor thrombus was not detectable by CT scan 8 months later.

therapeutically essential. In addition, severe leukopenia or thrombocytopenia occurred in all three patients, indicating that this regimen is not practical despite the excellent antitumor effect. These myelosuppressive adverse effects are particularly important in patients with HCC. It is not only because thrombocytopenia and/or leukopenia are frequently present before the initiation of anticancer therapy but also because treatment often has to be discontinued because of these side effects. To design a simple combination therapy from the above regimen, with less adverse effect, we next examined the effects of the basic regimen, i.e., subcutaneous IFN-α and intraarterial 5-FU administration in the subsequent eight patients. The response rate in this series of patients was as high as 63% and was comparable to the response rate (47%) reported by Urabe et al,[19] who tried the full regimen. Another advantage of this combination therapy is the markedly low incidence of myelosuppressive side effects; only one of eight patients developed leukopenia in the current study (Table 2). Thus, a combination of intraarterial chemotherapy with 5-FU and systemic IFN-α administration appears to be highly effective and promising in advanced HCC invading major branches of the portal vein.

Individual treatments with arterial 5-FU infusion only or systemic IFN-α only need to be performed to analyze the synergistic effect of this combination therapy. However, this was not practical in this study because the efficacy of these treatments remained unsatisfactory and informed consent for randomized controlled trials therefore would be problematic in these patients with advanced HCC with Vp3. Most investigators in fact have reported that the response rate to intraarterial chemotherapy with 5-FU in unresectable HCC was low, ranging from 13% to 22% with a median survival of 3.5–13.8 months[14,15,20,21] although 1 study by Ando et al.[4] reported a relatively high response rate (44%) in similar patients. The antitumor effect of systemic IFN-α therapy on HCC also is still controversial, as shown in Table 3. Several studies with IFN-α alone demonstrated only a minimal clinical effect.[22–25] In a randomized controlled study, Lai et al.[26] demonstrated a beneficial effect of IFN-α with a 31% response rate in patients with inoperable HCC. However, most of their patients were hepatitis B surface antigen positive whereas 7 of 11 patients were hepatitis C virus (HCV) antibody positive in this study (Table 1). Because viral serostatus correlate significantly with the biologic behavior of HCC,[27] it may be difficult to expect similar ant-tumor effect for IFN-α on HCV antibody positive HCC. Systemic combination therapy with IFN-α and doxorubicin also was found to be ineffective with response rate ranging from 3% to 17%.[28–30] The response rate for combination therapy with IFN-α and multiple anticancer agents including 5-FU and doxorubicin was 26%[31] and appears to be better than that for other combination therapies with doxorubicin only.

Using intraarterial infusion chemotherapy and

TABLE 3
Studies of Immunochemotherapy with Interferon-α for Hepatocellular Carcinoma

Author	Drugs	One term	Response CR + PR/total (%)
Nair et al.[22]	IFN-α 3 MU, i.m. (daily)	2 mos	0/2 (0)
Sachs et al.[23]	IFN-α 12 and 50 MU/m^2, i.m. (3 times/week)	12 wks	0/30 (0)
Creagan et al.[28]	IFN-α 12 MU, i.m. (daily, 5 days) doxorubicin 25 mg/m^2, i.v. (day 1)	4 wks	1/7 (17)
GTSG[24]	IFN-α 5–15 MU/m^2, i.m. (3 times/week)	1–3 wks	2/30 (7)
Kardinal et al.[29]	IFN-α 12 MU, i.m. (daily, Day 1–5/week) doxorubicin 25–40 mg/m^2, i.v. (Day 1)	4 wks	1/30 (3)
Feun et al.[30]	IFN-α 20 MU, i.m. (weekly, 1st 3 weeks) doxorubicin 20 mg/m^2, i.v. (weekly, 1st 3 weeks)	5 wks	2/21 (10)
Patt et al.[45]	IFN-α 5 MU, i.m. (3 times/week) 5-FU 750 mg/m^2, continuous i.v. (5 days, 1st week)	2 wks	6/28 (21)
Lai et al.[26]	IFN-α 5 MU/m^2, i.m. (3 times/week)	1 wk	11/35 (31)
Leung et al.[31]	CDDP (20 mg/m^2 i.v. Days 1–4, every week) doxorubicin (40 mg/m^2 i.v., Day 1), 5-fluorouracil (400 mg/m^2 i.v., Days 1–4) IFN-α (5 MU/m^2 s.c., Days 1–4)	3 wk	13/50 (26)
Urabe et al.[19]	IFN-α 3 MU, i.m. (3 times/week), 5-FU 750 mg/m^2, i.a. (weekly), CDDP 75 mg/m^2, i.a. (every 2 weeks), MTX 30 mg/m^2, i.a. (every 4 weeks) leucovorin 30 mg/m^2, i.v. (every 4 weeks)	4 wks	7/15 (47)
Llovet et al.[25]	IFN-α 3 MU, i.m. (3 times/week)	1 yr	2/30 (7)
Chung et al.[32]	5 MU/m^2, i.m. (3 times/week), CDDP 2 mg/kg, continuous i.a. (every 8 weeks)	8 wks	6/18 (33)
Current study			total: 8/11 (73)
	full regimen	4 wks	3/3 (100)
	IFN-α 5 MU, i.m. (3 times/week), 5-FU 450–500 mg/day continuous i.a. (first 2 weeks), CDDP 10 mg/day, continuous i.a. (first 2 weeks), MTX 90 mg/day, i.a. (Days 1 and 7), Leucovorin 30 mg, i.v. (Days 2, 3, 9, 10)		
	"basic" regimen	4 wks	5/8 (63)
	IFN-α 5 MU, i.m. (3 times/week), 5-FU 450–500 mg/day, continuous i.a. (first 2 weeks)		

IFN: interferon; GTSG: Gastrointestinal Tumor Study Group; 5-FU: 5-fluorouracil; CDDP: cisplatin; MTX: methotrexate.

systemic IFN-α administration (nearly identical to our full regimen), Urabe et al.[19] reported 47% of response rate in patients with Vp3. More recently, Chung reported 33% (6 of 18) of partial response rate in patients with major portal vein thrombosis or distant metastases, who received systemic combination therapy with IFN-α and cisplatin.[32] In our study, CR or PR was observed in 73% (8 of 11) of all patients and in 63% (5 of 8) of patients with simple basic regimen. It is usually difficult to compare exactly the effectiveness of regimen among the studies because of patient selection bias in liver function or extent of tumor progression and evaluation method of clinical effect. With liver function, it was nearly comparable among these studies. For example, 5 of 11 patients were Child–Pugh Class 1, 4 patients were Class 2, and 2 patients were Class C in the current study (Table 1). This patient distribution by Child–Pugh classification was nearly similar to previous studies by Urabe et al.[19] or Chung et al.[32] The mean platelet count in this study ($1.5 \times 10^5/\mu L$) was equivalent to that reported in Urabe et al.'s study ($1.4 \times 10^5/\mu L$). With extent of tumor progression, locally advanced HCC complicating Vp3 cases were enrolled in Urabe et al.'s study and ours. Although HCC patients not only with Vp3 (74%) but also with extrahepatic metastasis (42%) were examined in the study by Chung et al., the effectiveness of treatment was evaluated basically by the same method in these studies, using the response criteria defined by the Eastern Cooperative Oncology Group[18] or its modified criteria. Thus, patient characteristics and evaluation of clinical response appear to be almost comparable between these three studies. Although the limitations in comparing the clinical response between studies cannot be neglected, the marked effect and acceptable toxicity of this therapy in HCC patients with extremely poor prognosis suggest that combination therapy with IFN-α and 5-FU may be a promising treatment regimen of choice currently.

Although the mechanism of action of this combination therapy in vivo is not yet clear, it is possible that IFN-α and 5-FU exert an additive antitumor effect. In in vitro experiments, IFN-α induces cyclin-dependent kinase inhibitors involved in G1/G0 arrest.[33] Consistent with this, IFN-α directly inhibits the proliferation of cultured hepatoma cells.[34] Interferon-α also may exert its antitumor effect indirectly via the immune system because IFN-α is known to augment T-cell cytotoxicity.[35,36] Furthermore, IFN-α induces apoptosis of various cancer cells.[37,38] It thus is possible that IFN-α directly exerts an antineoplastic effect on HCC. Another possible mechanism is via its antiangiogenesis activity; IFN-α has been shown to

inhibit tumor angiogenesis in various experimental settings.[39-41] This antiangiogenesis activity may be clinically important because we observed reduced tumor blood flow demonstrated by dynamic CT scan as an initial finding leading to clinical response. In addition, several experimental studies demonstrated that IFN-α enhanced the cytotoxic effect of 5-FU in various cultured malignant cells.[42,43] This is considered to result partly from augmented metabolism of 5-FU to fluoro-deoxy-uridylate.[44] Taken together, these in vitro findings provide supportive evidence for the beneficial effect of combination therapy with IFN-α and 5-FU on HCC.

Interferon-α is known to result in severe adverse effects (fever and myelosuppression).[23] Thrombocytopenia or leukopenia appeared to be the most clinically important adverse effect. These were observed in all three patients who were treated by the full regimen. In contrast, only 1 of the 8 patients treated with the basic regimen developed leukopenia (<2000/μL), and the leukocyte count recovered soon after cessation of treatment. Other side effects also were well controlled by conventional treatment. This relatively mild side effect enabled to continue the basic regimen and may lead to the marked clinical effect because tumor regrowth often is observed while treatment is interrupted because of adverse effects. The QOL of patients in this study was excellent, without any symptoms due to liver dysfunction. Because patients with portal vein tumor thrombi commonly develop severe complications such as liver dysfunction or intractable ascites soon after diagnosis, our results suggest that combination therapy with IFN-α and 5-FU may be the treatment of choice in patients with terminal stage aggressive HCC.

The current pilot study indicated that combination chemotherapy with subcutaneous IFN-α, and intraarterial 5-FU is a very promising strategy in unresectable HCC with tumor thrombus in major branches of the portal vein. A large Phase II trial is, however, essential to obtain conclusive evidence.

REFERENCES

1. Lee HS, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY. The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction: a prospective controlled study. *Cancer* 1997;79:2087–94.
2. Yamakado K, Tanaka N, Nakatsuka A, Matsumura K, Takase K, Takeda K. Clinical efficacy of portal vein stent placement in patients with hepatocellular carcinoma invading the main portal vein. *J Hepatol* 1999;30:660–8.
3. The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology* 1998;28: 751–5.
4. Ando E, Yamashita F, Tanaka M, Tanikawa K. A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. *Cancer* 1997;79:1890–6.
5. Furuse J, Iwasaki M, Yoshino M, Konishi M, Kawano N, Kinoshita T, et al. Hepatocellular carcinoma with portal vein tumor thrombus: embolization of arterioportal shunts. *Radiology* 1997;204:787–90.
6. Asahara T, Itamoto T, Katayama K, Nakahara H, Hino H, Yano M, et al. Hepatic resection with tumor thrombectomy for hepatocellular carcinoma with tumor thrombi in the major vasculature. *Hepatogastroenterology* 1999;46: 1862–9.
7. Chen SC, Hsieh MY, Chuang WL, Wang LY, Chang WY. Development of portal vein invasion and its outcome in hepatocellular carcinoma treated by transcatheter arterial chemo-embolization. *J Gastroenterol Hepatol* 1994;9:1–6.
8. Tanaka A, Morimoto T, Yamaoka Y. Implications of surgical treatment for advanced hepatocellular carcinoma with tumor thrombi in the portal vein. *Hepatogastroenterology* 1996;43:637–43.
9. Fujii T, Takayasu K, Muramatsu Y, Moriyama N, Wakao F, Kosuge T, et al. Transcatheter arterial embolization for hepatocellular carcinoma with portal vein thrombosis. *J Gastroenterol Hepatol* 1995;10:237–40.
10. Fujii T, Takayasu K, Muramatsu Y, Moriyama N, Wakao F, Kosuge T, et al. Hepatocellular carcinoma with portal tumor thrombus: analysis of factors determining prognosis. *Jpn J Clin Oncol* 1993;23:105–9.
11. Tanaka A, Morimoto T, Ozaki N, Ikai I, Yamamoto Y, Tsunekawa S, et al. Extension of surgical indications for advanced hepatocellular carcinoma: is it possible to prolong life span or improve quality of life? *Hepatogastroenterology* 1996;43:1172–81.
12. Yamaoka Y, Kumada K, Ino K, Takayasu T, Shimahara Y, Mori K, et al. Liver resection for hepatocellular carcinoma (HCC) with direct removal of tumor thrombi in the main portal vein. *World J Surg* 1992;16:1172–6.
13. Lin DY, Lin SM, Liaw YF. Non-surgical treatment of hepatocellular carcinoma. *J Gastroenterol Hepatol* 1997;12:S319–28.
14. Stehlin JS Jr., de Ipolyi PD, Greeff PJ, McGaff CJ Jr., Davis BR, McNary L. Treatment of cancer of the liver: twenty years experience with infusion and resection in 414 patients. *Ann Surg* 1988;208:23–5.
15. Doci R, Bignami P, Bozzetti F, Bonfanti G, Audisio R, Colombo M, et al. Intrahepatic chemotherapy for unresectable hepatocellular carcinoma. *Cancer* 1988;61:1983–7.
16. Miyamoto A, Umeshita K, Sakon M, Nagano H, Eguchi H, Kishimoto S, et al. A case of advanced hepatocellular carcinoma with lung metastasis, successfully treated by a combination therapy with interferon-α and UFT, an oral antineoplastic agent combining tegafur and uracil. *J Gastroenterol Hepatol* 2000;15:1447–51.
17. Toyoda H, Nakano S, Kumada T, Takeda I, Sugiyama K, Osada T, et al. The efficacy of continuous local arterial infusion of 5-fluorouracil and cisplatin through an implanted reservoir for severe advanced hepatocellular carcinoma. *Oncology* 1995;52:295–9.
18. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649–55.

19. Urabe T, Kaneko S, Matsushita E, Unoura M, Kobayashi K. Clinical pilot study of intrahepatic arterial chemotherapy with methotrexate, 5-fluorouracil, cisplatin and subcutaneous interferon-alpha-2b for patients with locally advanced hepatocellular carcinoma. *Oncology* 1998;55:39–47.
20. Kajanti M, Pyrhonen S, Mantyla M, Rissanen P. Intra-arterial and intravenous use of 4' epidoxorubicin combined with 5-fluorouracil in primary hepatocellular carcinoma: a randomized comparison. *Am J Clin Oncol* 1992;15:37–40.
21. Minoyama A, Yoshikawa M, Ebara M, Saisho H, Sugiura N, Ohto M. Study of repeated arterial infusion chemotherapy with a subcutaneously implanted reservoir for advanced hepatocellular carcinoma. *J Gastroenterol* 1995;30:356–66.
22. Nair PV, Tong MJ, Kempf R, Co R, Lee SD, Venturi CL. Clinical, serologic, and immunologic effects of human leukocyte interferon in HBsAg-positive primary hepatocellular carcinoma. *Cancer* 1985;56:1018–22.
23. Sachs E, Di Bisceglie AM, Dusheiko GM, Song E, Lyons SF, Schoub BD, et al. Treatment of hepatocellular carcinoma with recombinant leucocyte interferon: a pilot study. *Br J Cancer* 1985;52:105–9.
24. The Gastrointestinal Tumor Study Group. A prospective trial of recombinant human interferon alpha 2B in previously untreated patients with hepatocellular carcinoma. *Cancer* 1990;66:135–9.
25. Llovet JM, Sala M, Castells L, Suarez Y, Vilana R, Bianchi L, et al. Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. *Hepatology* 2000;31:54–8.
26. Lai CL, Lau JY, Wu PC, Ngan H, Chung HT, Mitchell SJ, et al. Recombinant interferon-alpha in inoperable hepatocellular carcinoma: a randomized controlled trial. *Hepatology* 1993; 17:389–94.
27. Yamanaka N, Takada M, Tanaka T, Yamanaka J, Yasui C, Ando T, et al. Viral serostatus and coexisting inflammatory activity affect metachronous carcinogenesis after hepatectomy for hepatocellular carcinoma. A further report. *J Gastroenterol* 2000;35:206–13.
28. Creagan ET, Long HJ, Frytak S, Moertel CG. Recombinant leukocyte A interferon with doxorubicin: a phase I study in advanced solid neoplasms and implications for hepatocellular carcinoma. *Cancer* 1988;61:19–22.
29. Kardinal CG, Moertel CG, Wieand HS, Schutt AJ, O'Connell MJ, Wright K, et al. Combined doxorubicin and alpha-interferon therapy of advanced hepatocellular carcinoma. *Cancer* 1993;71:2187–90.
30. Feun LG, Savaraj N, Hung S, Reddy R, Jeffers L, Benedetto P, et al. A phase II trial of recombinant leukocyte interferon plus doxorubicin in patients with hepatocellular carcinoma. *Am J Clin Oncol* 1994;17:393–5.
31. Leung TW, Patt YZ, Lau WY, Ho SK, Yu SC, Chan AT, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. *Clin Cancer Res* 1999;5:1676–81.
32. Chung YH, Song IH, Song BC, Lee GC, Koh MS, Yoon HK, et al. Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-α for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. *Cancer* 2000;88:1986–91.
33. Sangfelt O, Erickson S, Castro J, Heiden T, Gustafsson A, Einhorn S, et al. Molecular mechanisms underlying interferon-alpha-induced G0/G1 arrest: CKI-mediated regulation of G1 Cdk-complexes and activation of pocket proteins. *Oncogene* 1999;18:2798–810.
34. Yano H, Iemura A, Haramaki M, Ogasawara S, Takayama A, Akiba J, et al. Interferon alfa receptor expression and growth inhibition by interferon alfa in human liver cancer cell lines. *Hepatology* 1999;29:1708–17.
35. Lindahl P, Leary R, Gresser I. Enhancement by interferon of the specific cytotoxicity of sensitized lymphocytes. *Proc Natl Acad Sci USA* 1972;69:721–5.
36. Trinchieri G, Santoli D, Koprowski H. Spontaneous cell-mediated cytotoxicity in humans; role of interferon and immunoglobulins. *J Immunol* 1978;120:1849–55.
37. Horowitz RW, Heerdt BG, Hu X, Schwartz EL, Wadler S. Combination therapy with 5-fluorouracil and IFN-α2a induces a nonrandom increase in DNA fragments of less than 3 megabases in HT29 colon carcinoma cells. *Clin Cancer Res* 1997;3:1317–22.
38. Sabaawy HE, Farley T, Ahmed T, Feldman E, Abraham NG. Synergistic effects of retrovirus IFN-alpha gene transfer and 5-FU on apoptosis of colon cancer cells. *Acta Haematol* 1999;101:82–8.
39. Folkman J, Ingber D. Inhibition of angiogenesis. *Semin Cancer Biol* 1992;3:89–96.
40. Slaton JW, Perrotte P, Inoue K, Dinney CP, Fidler IJ. Interferon-alpha-mediated down-regulation of angiogenesis-related genes and therapy of bladder cancer are dependent on optimization of biological dose and schedule. *Clin Cancer Res* 1999;5:2726–34.
41. Dinney CP, Bielenberg DR, Perrotte P, Reich R, Eve BY, Bucana CD, et al. Inhibition of basic fibroblast growth factor expression, angiogenesis, and growth of human bladder carcinoma in mice by systemic interferon-alpha administration. *Cancer Res* 1998;58:808–14.
42. Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. *Cancer Res* 1990; 50:3473–86.
43. Elias L, Sandoval JM. Interferon effects upon fluorouracil metabolism by HL-60 cells. *Biochem Biophys Res Commun* 1989;163:867–74.
44. Schwartz EL, Hoffman M, O'Connor CJ, Wadler S. Stimulation of 5-fluorouracil metabolic activation by interferon-alpha in human colon carcinoma cells. *Biochem Biophys Res Commun* 1992;182:1232–9.
45. Patt YZ, Yoffe B, Charnsangavej C, Pazdur R, Fischer H, Cleary K, et al. Low serum alpha-fetoprotein level in patients with hepatocellular carcinoma as a predictor of response to 5-FU and interferon-alpha-2b. *Cancer* 1993;72:2574–82.

02-87

■一難治性癌に対する戦略—■

門脈内腫瘍栓を伴う肝細胞癌に対する動注化学療法

山本　為義，永野　浩昭，左近　賢人，門田　守人*
大阪大学大学院医学系研究科　病態制御外科　*教授

はじめに

肝細胞癌はその特性により、仮に局所の腫瘍に対する治療が十分であっても，高率に残肝再発を来し，再度局所治療が必要となる．これら肝内再発巣に対する治療を繰り返していくと，最終的には門脈や肝静脈に腫瘍栓を伴う病態，あるいはびまん性結節や塊状の癌腫となり難治性となる．本稿では、難治性肝細胞癌の一病態である門脈内腫瘍栓(VP)を伴う肝細胞癌に対する治療戦略の現状と，我々が行っているIFN-alpha/5-FU併用療法の実際と成績について述べる．

1．門脈浸潤を伴う進行肝細胞癌に対する治療戦略の現状

門脈浸潤を伴う進行肝細胞癌に対しては，経皮的エタノール注入療法(PEI)，マイクロ波凝固療法(MCT)，ラジオ波焼却療法(RFA)などの局所療法では対処困難で，化学塞栓療法(TACE)も本幹まで腫瘍が及ぶ場合は，肝不全を誘発する危険性が高く，一般的には適応とはならない．外科的切除単独の治療成績も満足できるものではなく，猪飼らは門脈，肝静脈腫瘍栓合併肝細胞癌85例に対し肝切除を施行し，1，3年生存率が33.7%，10.4%であったと報告している[1]．このため，現時点においては，既存の治療法に放射線治療を加えた集学的治療や，後述する動注化学療法がその主たる治療法となる．

たとえば，田沢らは門脈内腫瘍栓の局所制御を放射線外照射により行い，肝内の腫瘍はTACEで治療する併用療法を行い，24例中12例で門脈内腫瘍栓に対する局所効果が認められ，有効例では予後の改善が認められたと報告している[2]．

2．門脈浸潤を伴う進行肝細胞癌に対する多剤併用動注療法

最近，予後の改善が認められる多剤併用動注化学療法が多く報告され，注目されている（表1）．5-fluorouracil(5-FU)とcisplatin(CDDP)との併用化学療法は，33%から44%の有効率が得られ，平均生存期間は8カ月から15カ月であったと報告されており，今後，切除不能進行肝細胞癌に対する治療として期待される[3,4]．一方，抗癌剤とIFN-alphaを併用する免疫化学療法もいくつか試みられている．Chungらは，門脈腫瘍栓もしくは遠隔転移を伴う肝細胞癌に対し，CDDPの肝動注に加えIFN-alphaの全身投与を組み合わせることによって，33%の奏功率，平均生存期間5カ月，1年生存率27%とCDDP単独投与群に比べ，有意に良好な結果を報告している[5]．さらに，IFN-alphaの全身投与とCDDP, 5-FUに加えてmethotrexate＋leucovolinあるいはdoxorubicinを加えた多剤併用肝動注も試みられており17%から45%の奏功率が得られている．しかし，骨髄障害からの敗血症や腎障害など重篤な副作用を呈する症例がある[6,7]．

現在，我々の施設においては，IFN-alphaと5-FUのみの肝動注を併用する治療法を1997年より行い，pilot studyでは奏功率63%と極めて良好な結果を得た[8]．骨髄抑制，発熱，鬱状態などの副作用は認められるが，治療を中断しなければならない症例は少なく，外来通院のみで繰り返し治療を継続出来ている．次に我々が行っているIFN-alpha/5-FU併用療法の実際と治療成績について述べる．

表1　門脈浸潤を伴う進行肝細胞癌に対する多剤併用動注療法（文献8を改変）

Author	Drugs	one term	Response CR+PR / total (%)
Ando et al.[3]	CDDP 10mg/m² i.a. (Days 1-5/week), 5-FU 10mg/m² i.v. (Days 1-5/week)	1 wk	4/9 (44)
Chung et al.[5]	IFN-α 3 MU,i.m. (3 times/week), CDDP 2mg/kg continuous i.a. (every 8 weeks)	8 wks	6/18 (33)
Itamoto et al.[4]	CDDP 10mg/m² i.a. (Days 1-5/week), 5-FU 10mg/m² i.v. (Days 1-5/week)	1 wk	2/6 (33)
Kaneko et al.[6]	IFN-α 3 MU,i.m. (3 times/week), 5-FU 750mg/m² i.a. (weekly), CDDP 75mg/m² i.a. (Every 2 weeks), MTX 30mg/m² i.a. (every 4 weeks) leucovolin 30mg/m² i.v. (every 4 weeks)	4 wks	13/29 (45)
Leung et al.[7]	CDDP (20mg/m² i.v. Days 1-4, every week) doxorubicin (40mg/m² i.v., Day 1), 5-fluorouracil (400mg/m² i.v., Days 1-4) IFN-α (5 MU/m² s.c., Days 1-4)	3wks	25/149* (17)
Sakon et al.[8]	IFN-α 5 MU,i.m. (3 times/week), 5-FU 450-500mg/day, continuous i.a. (first 2 weeks)	4wks	5/8 (63)

IFN：interferon；5-FU：5-Fluorouracil；CDDP：cisplatin；MTX：methotrexate. *：vascular involvement 66/149(44.3%)

表 2a　IFN-alpha/5-FU併用療法の適応症例

肝細胞癌		
	門脈内腫瘍栓	VP3以上
	肝外転移	無し
年　齢		70歳未満
肝機能	GOT	<100
	GPT	<100
	T.Bil	正常(閉塞性黄疸は除く)
血液検査	血小板	8万以上
腎機能	血清Cr	<1.5
P　S		0、1

表 2b　切除不能症例に対する治療成績

	症例数	治療効果	観察期間	1年生存率
有効	n=7	CR	6~53カ月	100%
	n=5	PR	10~12カ月	
無効	n=11	PD	5~6カ月	0%

表 2c　肉眼的に癌遺残のない肝切除例に対する治療成績
(術後補助療法)

	症例数	観察期間	1年生存率
無再発生存	n=6	6~43カ月	100%
再発生存	n=1	36カ月	
再発癌死	n=1	18カ月	
再発他因死	n=1	22カ月	

3．門脈浸潤を伴う進行肝細胞癌に対するIFN-alpha/5-FU併用療法

1) 方法と対象症例

治療方法であるが，非手術症例においてはセルディンガー法にて，肝切除例では術中に，肝動脈カテーテルを挿入し，カテーテルより5-FUを450～500mg/日，2週間投与・2週間休薬の4週間を1クールとして持続動注を行う．同時にIFN-alphaを500万単位/回，3回/週，4週を1クールとして皮下投与する[9]．

対象症例は，門脈一次分枝または門脈本幹に肉眼的門脈腫瘍栓(Vp3以上)を伴う高度進行肝細胞癌であり，切除不能症例のみならず肝機能が良好で肝切除が可能であった症例をも術後補助療法として組み入れている．肉眼的に癌遺残の無い肝切除ができた場合には，残肝内再発を抑えることを，癌遺残があり減量肝切除となった場合には，残存腫瘍の消退を目標とする．

また，副作用および5-FU肝動注による肝障害を考慮し，70歳未満，T.Bilが正常，GOT，GPTがともに100未満，血小板が8万以上，血清Crn<1.5を条件とし，外来通院加療を基本としているため，PS:0，1が保たれている症例を対象としている（表2a）．

2) 切除不能症例に対する治療成績

全肝に拡がる多発病変(IM3)と門脈内腫瘍栓を伴うため，切除不能と判断された進行肝細胞癌23例に対し本療法を施行した．治療回数は2クール以上で効果のある症例には繰り返し施行した．

治療の効果は肝内病巣に限り評価すると，CR：7例，PR：5例の計12例(53%)の症例において有効であった．その一方で，11例47%については無効であり，無効例は全例6カ月以内に癌死した（表2b）．23例の1年生存率は，52%であった．

これら成績は，既存の治療法がなくsupportive careのみの場合ほとんどの症例が6カ月以内に死亡することと比較すると，極めて有効であると考えられる．

3) 術後補助療法としての成績

9例に対し，肉眼的に癌遺残の無い肝切除術(規約第3版：相対的非治癒切除)後に，補助療法として本療法を最低3クール以上施行した．その成績は現時点で，無再発生存6例(6～50カ月)，再発生存1例（36カ月)，癌死1例(18カ月：肺転移)，再発他因死1例(22カ月)で，1年生存率は100%であった(表2c)．

当院においてこれら9例と同一進行度で，同様に癌遺残の無い手術を施行しIFN-alpha/5-FU併用療法を施行しなかった症例18例の1年生存率は41%であり，有意に術後にIFN-alpha/5-FU併用療法を施行したほうが予後がよかった．

また，VP3，4かつIM3である16症例に対し，門脈腫瘍栓摘出と減量肝切除を行い，術後に本療法を施行した．16例中3例に残肝内多発病巣の完全消失(CR)を認めた．観察期間は短いが現時点での1年生存率は65%である．