resections for primary ductal carcinomas showed high expression of HDGF for the nucleus and the cytoplasm, respectively (44). There was no significant relationship between HDGF expression and any clinicopathologic variables including lymph node metastasis or venous and neural invasion. Patients with higher nuclear HDGF-LI showed a poorer 5-year survival rate, although no significant difference was observed by the cytoplasmic HDGF expression (44). Multivariate analysis also revealed nuclear HDGF-LI to be an independent prognosticator for overall survival in patients with pancreatic ductal carcinomas.

Lung cancer

HDGF was found to be a mitogen for lung epithelial cells *in vitro* and *in vivo*. In non-small cell lung cancer (NSCLC) cells, HDGF expression was strongly-detected in the nucleus as well as other cancer cells, and HDGF labeling index (LI) was 20-95% by immunohistochemical analysis (45). In patients with early stage NSCLC who underwent curative surgery, the disease-free and disease-specific survival and overall survival were lower in those with higher HDGF expression indexes than in those with lower HDGF indexes (46). The high expression of HDGF showed distant metastasis and shortened survival time in patients with NSCLC. Iwasaki *et al.* also reported similar results in Japanese patients with completely resected NSCLC that patients with a high HDGF-LI (>/= 65%) had significantly poorer overall and disease-free survival than those with a low HDGF-LI (45). HDGF-expression in NSCLC correlated with DNA synthesis and intratumoral microvessel density analyzed by CD31 staining, which coincided with the characteristics of HDGF revealed by *in vitro* experiments. In this study, there was no significant association between HDGF-expression and clinicopathological variables. In patients with NSCLC, HDGF is a significant independent prognostic factor, also being more powerful than the pathological stage by multivariate analysis. Conversely, the relationship between HDGF expression and disease-free and overall survival remains to be clarified in patients with small cell lung cancers.

HDGF is a unique nuclear targeted growth factor, which is expressed abundantly in cancer cells and stimulates their proliferation. HDGF generated tumors and promoted their growth *in vivo* via its mitogenic activity and angiogenic activity deriving from both its own direct angiogenic activity and the induction of VEGF. Multivariate analysis of the relationship of HDGF expression and recurrence-free and overall survival in patients with HCC, NSCLC, gastric cancer, esophageal cancer and pancreatic cancer confirmed that HDGF has the potential to become a significantly efficacious prognostic marker for cancer patients. It will be expected in the future that any tool regulating HDGF expression or HDGF signal pathways may be a useful candidate for the suppression of carcinogenesis and cancer progression.

References

1. Nakamura, H., Kambe, H., Egawa, T., Kimura, Y., Ito, H., Hayashi, E., Yamamoto, H., Sato, J., and Kishimoto, S. Clin. Chim. Acta, 183, 273-84, 1989.
2. Nakamura, H., Izumoto, Y., Kambe, H., Kuroda, T., Mori, T., Kawamura, K., Yamamoto, H., and Kishimoto, T. J. Biol. Chem., 269, 25143-9, 1994.
3. Nakamura, H., Yoshida, K., Ikegame, K., Kishima, Y., Uyama, H., and Enomoto, H. J. Gastroenterol., 37 [Suppl 14], 8-14, 2002.
4. Mori, M., Morishita, H., Nakamura, H., Matsuoka, H., Yoshida, K., Kishima, Y., Zhou, Z., Kida, H., Funakoshi, T., Goya, S., Yoshida, M., Kumagai, T., Tachibana, I., Yamamoto, Y., Kawase, I., and Hayashi, S. Am. J. Respir. Cell Mol.Biol., 30, 459-69, 2004.
5. Lepourcelet M., Tou L., Cai L., Sawada J., Lazar A.J.F., Glickman J.N., Williamson J.A., Everett A.D., Rdeston M., Fox E.A., Nakatani Y., Shivdasani R.A. Development 132, 415-27, 2005.
6. Izumoto, Y., Kuroda, T., Harada, H., Kishimoto,

T., and Nakamura, H. Biochem. Biophys. Res. Commun., 238, 26-32, 1997.
7. Oliver, J.A., and Al-Awqati, Q. J. Clin. Invest., 102, 1208-19, 1998.
8. Everett, A.D. Dev. Dyn., 222, 450-8, 2001.
9. Enomoto, H., Yoshida, K., Kishima, Y., Kinoshita, T., Yamamoto, M., Everett, A.D., Miyajima, A., and Nakamura, H. Hepatology, 36, 1519-27, 2002.
10. Everett, A.D., Lobe, D.R., Matsumura, M.E., Nakamura, H., and McNamara, C.A. J. Clin. Invest., 105, 567-75, 2000.
11. Dietz, F., Franken, S., Yoshida, K., Nakamura, H., Kappler, J., and Gieselmann, V. Biochem. J., 366, 491-500, 2002.
12. Kishima, Y., Yamamoto, H., Izumoto, Y., Yoshida, K., Enomoto, H., Yamamoto, M., Kuroda, T., Ito, H., Yoshizaki, K., and Nakamura, H. J. Biol. Chem., 277, 10315-22, 2002.
13. Everett, A.D., Stoops, T., and McNamara, C.A. J. Biol. Chem., 276, 37564-8, 2001.
14. Okuda, Y., Nakamura, H., Yoshida, K., Enomoto, H., Uyama, H., Hirotani, T., Funamoto, M., Ito, H., Everett, A.D., Hada, T., and Kawase, I. Cancer Sci., 94, 1034-1041, 2003.
15. Everett, A.D., Narron, J.V., Stoops, T., Nakamura, H., and Tucker, A. Am. J. Physiol., Lung Cell. Mol. Physiol., 286, L1194-201, 2004.
16. Abouzied M.M., El-Tahir H.M., Prenner L., Haberlein H., Gieselmann V., Franken S. J. Biol. Chem., 280, 10945-54, 2005.
17. Nakamura H., Hada T. Recent Res. Devel. Biophys. Biochem., 4, 17-27, 2004.
18. Ikegame, K., Yamamoto, M.,. Kishima, Y., Enomoto,. H., Yoshida, K., Suemura, M., Kishimoto, T., and Nakamura, H. Biochem. Biophys. Res. Commun., 266, 81-7, 1999.
19. Singh, D.P., Ohguro, N., Kikuchi, T., Sueno, T., Reddy, V.N., Yuge, K., Chylack Jr, L.T., and Shinohara, T. Biochem. Biophys. Res. Commun., 267, 373-81, 2000.
20. Ge, H., Si, Y., and Roeder, R.G. EMBO J., 17, 6723-9, 1998.
21. Stec, I., Nagl, S.B., van Ommen, G-J., and den Dunnen, J.T. FEBS Lett., 473, 1-5, 2000.
22. Qiu, C., Sawada, K., Zhang, X., and Cheng, X. Nat. Struct. Biol., 9, 217-24, 2002.
23. Lukasik S.M., Cierpicki T., Borloz M., Grembecka J., Everett A.D., Bushweller J.H. Protein Sci., 15, 314-23, 2006.
24. Nameki N., Tochio N., Koshiba S., Inoue M, Yabuki T., Aoki M., Seki E., Matsuda T., Fujikura Y., Saito M., Ikari M., Watanabe M., Terada T., Shirouzu M, Yoshida M., Hirota H., Tanaka A., Hayashizaki Y., Guntert P., Kigawa T., Yokoyama S. Protein Sci., 14, 756-64, 2005.
25. Sue S.C., Chen J.Y., Lee S.C., Wu W.G., Huang T.H. J. Mol. Biol., 343, 1365-77, 2004.
26. Kamiya, A., Kinoshita, T., Ito, Y., Matsui, T., Morikawa, Y., Senba, E., Nakashima, K., Taga, T., Yoshida, K., Kishimoto, T., and Miyajima, A. EMBO J., 18, 2127-36, 1999.
27. Shiojiri, N., Lemire, J.M., and Fausto, N. Cancer Res., 51, 2611-20, 1991.
28. Yasui, O., Miura, N., Terada, K., Kawarada, Y., Koyama, K., and Sugiyama, T. Hepatology, 25, 329-34, 1997.
29. Cilley, R.E., Zgleszewski, S.E., and Chinoy, M.R. J. Ped. Surg., 35, 113-8, 2000.
30. Soga, M., Kishimoto, Y., Kawaguchi, J., Nakai, Y., Kawamura, Y., Inagaki, S., Katoh, K., Oohara, T., Makino, S., and Oshima, I. Lab. Anima. Sci., 49, 269- 75, 1999.
31. Soga, M., Kishimoto, Y., Kawamura, Y., Inagaki, S., Makino, S., and Saibara, T. Cancer Lett., 196, 43-8, 2003.
32. Yoshida, K., Nakamura, H., Okuda, Y., Enomoto, H., Kishima, Y., Uyama, H., Ito, H., Hirasawa, T., Inagaki, S., and Kawase, I. J. Gastroenterol. Hepatol., 18, 1293-1301, 2003.
33. Huang J.S., Chao C.C., Su T.L., Yeh S.H., Chen D.S., Chen C.T., Chen P.J., Jou Y.S. Biochem. Biophys. Res. Commun., 315, 950-8, 2004.
34. Zhang J., Ren H., Yuan P., Lang W., Zhang L.,

Mao L. Cancer Re., 66, 18-23, 2006.
35. Yoshida, K., Tomita, T., Nakamura, H., Okuda, Y., Yamamoto, S., Enomoto, H., Uyama, H., Hirotani, T., Ito, H., Nagano, H., Sakon, M., Aozasa, S., Kawase, I., and Monden, M. Ann. Surg. Oncol., 13, 159-167, 2006.
36. Kishima, Y., Yoshida, K., Enomoto, H., Yamamoto, M., Kuroda, T., Okuda, Y., Uyama, H., and Nakamura, H. Hepatogastroenterology, 49, 1639-44, 2002.
37. Bernard, K., Litman, E., Fitzpatrick, J.L., Shellman, Y.G, Argast, G., Polvinen, I., Everett, A.D., Fukasawa, K., Norris, D.A., Ahn, N.G, and Resing, K.A. Cancer Res., 63, 6716-25, 2003.
38. Hayashi E., Kuramatsu Y., Okada F., Fujimoto M., Zhang X., Kobayashi M., Iizuka N., Ueyama Y., Nakamura K. Proteomics, 5, 1024-32, 2005.
39. Narron J.V., Stoops T.D., Barringhaus K., Matsumura M., Everett A.D. Pediatr. Res., 59, 778-83, 2006.
40. Hu, T.H., Huang, C.C., Liu, L.F., Lin, S.Y., Chang, H.W., Changchien, C.S., Lee, C.M., Chuang, J.H., and Tai, M.H. Cancer, 98, 1444-56, 2003.
41. Yamamoto S., Yasuhiko T., Hoshida Y., Takiguchi S., Fujiwara Y., Yasuda T., Doki Y., Yoshida K., Aozasa K., Nakamura H., Monden M. Clin. Cancer Res., 12, 117-22, 2006.
42. Yamamoto S., Tomita Y., Hoshida Y., Morii E., Yasuda T., Doki Y., Aozasa K., Uyama H., Nakamura H., Monden M. Ann. Surg. Oncol., 2007 (in press).
43. Matsuyama, A., Inoue, H., Shibuta, K., Tanaka, Y., Barnard, G.F., Sugimachi, K., and Mori, M. Cancer Res., 61, 5714-7, 2001.
44. Uyama H., Tomita Y., Nakamura H., Nakamori S., Zhang B., Hoshida Y., Enomoto H., Okuda Y., Sakon M., Aozasa K., Kawase I., Hayashi N., Monden M. Clin. Cancer Res., 12, 6043-8, 2006.
45. Iwasaki T., Nakagawa K., Nakamura H., Takada T., Matsui K., Kawahara K. Oncol. Rep., 13, 1075-80, 2005.
46. Ren H., Tang X., Lee J.J., Feng L., Everett A.D., Hong W.K., Khuri F.R., Mao L. J. Clin. Oncol., 22, 3230-7, 2004.

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[15]。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。

<文　献>

1) 左近賢人，永野浩昭，門田守人．進行肝細胞癌に対する化学療法の最前線．日本内科学会雑誌 2004；93：1660-1665.
2) 科学的根拠に基づく肝癌診療ガイドライン作成に関する研究班編．肝癌診療ガイドライン2005年版，東京：金原出版：2005.
3) Yamashita T. Chemotherapy for advanced hepatocellu-

lar carcinoma : systemic chemotherapy or hepatic arterial infusion chemotherapy ? J Gastroenterol 2004 ; 39 : 404-406.
4) Kaneko S, Urabe T, Kobayashi K, et al. Combination chemotherapy for advanced hepatocellular carcinoma complicated by major portal vein thrombosis. Oncology 2002 ; 62 : 69-73.
5) Sakon M, Nagano H, Dono K, et al. Combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. Cancer 2002 ; 94 : 435-442.
6) Ota H, Nagano H, Sakon M, et al. Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil ; role of type 1 interferon receptor expression. Br J Cancer 2005 ; 93 : 557-564.
7) Nagano H, Miyamoto A, Wada H, et al. Interferon-α and 5-fluorouracil combination therapy after palliative hepatic resection in patients with advanced hepatocellular carcinoma, portal venous tumor thrombus in the major trunk, and multiple nodules. Cancer 2007 ; 110 : 2493-2501.
8) Obi S, Yoshida H, Toune R, et al. Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. Cancer 2006 ; 106 : 1990-1997.
9) Nowak AK, Chow PKH, Findlay M. Systemic therapy for advanced hepatocellular carcinoma : a review. Eur J Cancer 2004 ; 40 : 1474-1484.
10) Ikeda M, Okusaka T, Ueno H, et al. A phase II trial of continuous infusion of 5-fluorouracil, mitoxantrone, and cisplatin for metastatic hepatocellular carcinoma. Cancer 2005 ; 103 : 756-762.
11) Nakamura M, Nagano H, Marubashi S, et al. A pilot study of combination chemotherapy of S-1, a novel oral DPD inhibitor, and interferon-alpha for advanced hepatocellular carcinoma with extrahepatic metastasis. Cancer (in press).
12) Zhu AX, Blaszkowsky LS, Ryan DP, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006 ; 24 : 1898-1903.
13) Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006 ; 24 : 4293-300.
14) Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib improves survival in advanced Hepatocellular Carcinoma(HCC) : Results of a Phase III randomized placebo-controlled trial(SHARP trial) JCO. 2007 ASCO Annual Meeting Proceedings Part I 2007 ; 25 : No. 18S.
15) Sun HC, Tang ZY. Preventive treatments for recurrence after curative resection of hepatocellular carcinoma- A literature review of randomized control trials. World J Gastroenterol 2003 ; 9 : 635-640.
16) Sakon M, Umeshita K, Nagano H, et al. Clinical significance of hepatic resection in hepatocellular carcinoma : analysis by disease-free survival curves. Arch Surg 2000 ; 135 : 1456-1459.
17) Lai EC, Lo CM, Fan ST, et al. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma : a randomized controlled trial. Arch Surg 1998 ; 133 : 183-188.
18) Hasegawa K, Takayama T, Ijichi M, et al. Uracil-tegafur as an adjuvant for hepatocellular carcinoma : a randomized trial. Hepatology 2006 ; 44 : 891-895.
19) Izumi R, Shimizu K, Iyobe T, et al. Postoperative adjuvant hepatic arterial infusion of Lipiodol containing anticancer drugs in patients with hepatocellular carcinoma. Hepatology 1994 ; 20 : 295-301.
20) Tanaka S, Shimada M, Shirabe K, et al. A novel intrahepatic arterial chemotherapy after radical resection for advanced hepatocellular carcinoma. Hepatogastroenterology 2005 ; 52 : 862-865.
21) Nagano H, Sakon M, Eguchi H, et al. Hepatic resection followed by IFN-α and 5-FU for advanced hepatocellular carcinoma with tumor thrombus in the major portal branch. Hepatogastroenterology 2007 ; 54 : 172-179.

Original Paper

Hepatic Resection followed by IFN-α and 5-FU for Advanced Hepatocellular Carcinoma with Tumor Thrombus in the Major Portal Branch

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KEY WORDS:
HCC; IFN-α; 5-FU; Surgery; PVTT

ABBREVIATIONS:
Hepatocellular Carcinoma (HCC); Interferon (IFN); Alpha-Fetoprotein (AFP); Protein Induced by Vitamin K Antagonist or Absence (PIVKA-II); Portal Vein Tumor Thrombosis (PVTT); 5-Fluorouracil (5-FU); Transcatheter Arterial Embolization (TAE)

ABSTRACT

Background/Aims: The prognosis of hepatocellular carcinoma (HCC) invading the major branches of the portal vein (Vp3) is extremely poor. Recently, we reported the efficacy of combination therapy with subcutaneous interferon (IFN)-alpha and intra-arterial 5-FU for intractable HCC with Vp3. In this study, this therapy was applied for resectable advanced HCC (Vp3) as a postoperative adjuvant.

Methodology: Patients with HCC and tumor thrombi either in the major or first branch of portal vein were included (n=30). Fifteen consecutive patients with HCC and Vp3 were treated with at least 3 cycles of a combination therapy consisting of continuous arterial infusion of 5-FU (300mg/mm^3/ day, 5 days/week, for the initial 2 weeks) and subcutaneous injection of IFN (5 MIU, 3 times/week, 4 weeks) as a postoperative adjuvant therapy following hepatic resection. Another 15 patients who underwent hepatic resection with no IFN/5-FU chemotherapy acted as controls.

Results: The results were as follows in the IFN/5-FU adjuvant treatment group; disease-free survival (n=11, 5-55 months), survival with recurrence (n=2, 9, 48 months), cancer death (n=1, 18 months), death from other causes but no recurrence (n=1, 22 months). The 1-year survival rate was 100% in patients treated with IFN/5-FU, and 41% in those without IFN/5-FU historical controls (n=15). There was a significant difference in disease-free and overall survival rates between the two groups (p=0.0033 and 0.0031).

Conclusions: Combination therapy with subcutaneous IFN and intra-arterial perfusion of 5-FU seems to be a promising postoperative adjuvant treatment modality for resectable HCC with Vp3.

INTRODUCTION

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)] (2-10). Even in resectable cases, the prognosis is extremely poor despite aggressive surgery, because of the very high incidence of recurrence in the residual liver (6,8,10-12). Therefore, a new strategy is required for these patients with advanced HCC and portal tumor thrombi.

We reported previously one patient with recurrent HCC and multiple lung, bone and liver metastases (13). The malignancy was uncontrollable by conventional therapies, but showed almost complete regression following administration of tegafur/uracil (UFT) and interferon (IFN)-α (13). The patient is still alive without relapse 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. We also reported recently the efficacy of combination therapy of subcutaneously administered IFN-α and arterially infused 5-fluorouracil (5-FU) in 11 consecutive patients with unresectable HCC associated with Vp3 (14). Our results showed that this treatment regimen markedly decreased tumor size and levels of tumor markers with an encouraging response rate. It might therefore represent a promising regimen for advanced HCC with tumor thrombi in the portal vein. In the present study, we applied IFN/5-FU therapy for resectable advanced HCC (Vp3) as a postoperative adjuvant and examined its feasibility and efficacy.

METHODOLOGY

Patients

From 1986 to 2003, 538 patients with HCC were admitted and underwent curative hepatic resection

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in the Department of Surgery, Osaka University Hospital. Of these patients, 30 were included in this study based on the identification of a tumor thrombus either in the major or first branch of the portal vein (Vp3). Liver function tests and imaging techniques, including computed tomography (CT) with hepatic angiography and arterial portography, revealed that these cases were resectable and subsequently they underwent hepatectomy. Of the 30 patients, 15 recent consecutive patients, from 1998 to 2003, had an intra-arterial catheter inserted through the gastro-duodenal artery with an implanted drug delivery system (15) during the operation to facilitate postoperative adjuvant IFN/5-FU combined chemotherapy (*see below*) (14). They were treated with at least 3 cycles as a postoperative adjuvant. The demographics of these patients are shown in **Table 1**. The postoperative adjuvant was commenced as soon as possible postoperatively when the criteria for inclusion were satisfied. Fifteen previous patients, from 1987 to 2001, with the same tumor stage of advanced HCC and Vp3, underwent surgery with no combined IFN/5-FU postoperative adjuvant therapy. They were treated with appropriate local HCC therapy, and if there was recurrence postoperatively in the residual liver or other organ, no IFN/5-FU combined therapy was administered. The demographics of these patients are shown in **Table 2**. They were compared to 15 patients with postoperative adjuvant IFN/5-FU combined therapy after hepatic resection, in terms of features of HCC, hepatic function, surgery, clinical effects, disease-free and overall survival.

The TNM stage and grade of portal vein thrombus were classified according to the 3rd edition of the general rules for the clinical and pathological study of primary liver cancer by the Liver Cancer Study Group of Japan (1). The criteria for selection for intra-arterial combination treatment included; *1)* absence of extra-hepatic metastases, *2)* AST and ALT levels below 100 IU/L, *3)* a platelet count exceeding 80,000 /mm^3, *4)* successful implantation of intra-arterial catheter and drug delivery system, and *5)* a performance status (Eastern Cooperative Oncology Group, ECOG) (16) of level 0-1.

Treatment Regimen of IFN/5-FU Combined Chemotherapy and Follow-up after Surgery

After obtaining informed written consent, each patient was treated with subcutaneous administration of IFN-α (OIF, Otsuka Pharmaceutical Co., Tokyo) and an intra-arterial infusion of 5-FU (Kyowa Hakko Co., Tokyo). IFN-α (5x10^6 U, [5 MU]) was administered on days 1, 3, and 5 of every week (14). Continuous infusion chemotherapy (5-FU, 300mg/mm^3/day) through the proper hepatic artery was applied 5 days/week for 2 weeks via a catheter connected to a subcutaneously-implanted drug delivery system. All anti-cancer therapies were discontinued when adverse effects reached level 2 on the ECOG classification (16) (with the exception of platelet and leukocyte counts of less than 40,000 /mm^3 and 2,000 /mm^3, respectively, as these parameters were often low prior to treatment due to liver cirrhosis). In addition to serum chemistry, tumor markers such as alpha-fetoprotein (AFP) and PIVKA-II (Protein Induced by Vitamin K Antagonist or Absence) were measured at least once

TABLE 1. The Demographics of the IFN/5-FU Adjuvant Group (n=15)

	Age	Sex	T	M	N	Vp	Stage	Operation	Alb	PT/HPT	ICGR-15	AFP	PIVKA-II	Virus
case 1	47	M	4	0	0	3	4A	left lobectomy	4.5	81/91	4	11400	7900	B
case 2	69	M	4	0	0	3	4A	extended anterior segmentectomy	3.7	86/85	21	768	14784	C
case 3	54	M	4	0	1	3	4A	right lobectomy	3.5	64/105	16	28	1847	B+C
case 4	47	M	4	0	0	3	4A	extended right lobectomy	3.4	74/67	26	27	2067	B+C
case 5	60	M	4	0	0	3	4A	extended posterior segmentectomy	3.9	71/69	16	<5	<40	B
case 6	80	M	4	0	0	3	4A	left lobectomy	4	74/66	26	19	1568	B+C
case 7	34	M	4	0	0	3	4A	extended left lobectomy	3.9	90/89	4	456	1153	B
case 8	66	M	4	0	0	3	4A	extended medial segmentectomy	3.3	75/87	15	5	298	C
case 9	54	M	4	0	0	3	4A	right lobectomy	4.5	77/62	14	8700	353617	B
case 10	54	M	4	0	0	3	4A	right lobectomy	3.7	65/85	21	32930	<40	B+C
case 11	69	M	4	0	0	3	4A	right lobectomy and pancreatoduodenectomy	4.1	90/93	17	7473	205	B+C
case 12	54	M	4	0	0	3	4A	left lobectomy	3.8	82/78	17	680	<40	C
case 13	56	F	4	0	0	3	4A	left lobectomy	3.6	71/63	19	13260	1039	C
case 14	62	M	4	0	0	3	4A	right lobectomy	3.6	63/73	18	23500	476	B+C
case 15	58	M	4	0	0	3	4A	right lobectomy	3.8	85/87	16	6500	1200	C

TNM stage and the grade of portal vein thrombus were classified according to the 3rd edition of the general rules of the clinical and pathological study of primary liver cancer by liver cancer study group of Japan.
Alb: serum albumin (g/dL); PT: Prothrombin time (%); HPT: Hepaplastin test (%);
ICGR-15: indocyanine green retention rate at 15 minutes (%);
AFP: alpha-fetoprotein (ng/mL) and PIVKA-II: Protein Induced by Vitamin K Absence (mAU/mL).

TABLE 2. The Demographics of the Non-IFN/5-FU Adjuvant Group (n=15)

	Age	Sex	T	M	N	Vp	Stage	Operation	Alb	PT/HPT	ICGR-15	AFP	PIVKA-II	Virus
case 16	72	M	4	0	1	3	4A	right lobectomy	4.3	ND/89	15	10876	ND	nonAnonB
case 17	56	M	4	0	0	3	4A	right lobectomy	3.2	ND/74	23	377	ND	nonAnonB
case 18	42	M	4	0	0	3	4A	right lobectomy	4.1	ND/82	14	67	ND	B
case 19	65	M	4	0	0	3	4A	extended left lobectomy	4.0	ND/133	6	5	ND	B
case 20	58	M	4	0	0	3	4A	right lobectomy	3.7	ND/72	16	227	ND	nonAnonB
case 21	61	M	4	0	0	3	4A	right lobectomy	3.7	ND/75	-	10256	ND	nonAnonB
case 22	62	M	4	0	0	3	4A	lateral segmentectomy	3.8	ND/73	19	105360	ND	ND
case 23	34	M	4	0	0	3	4A	right lobectomy	2.9	61/59	6	10332	10240	B
case 24	56	M	4	0	0	3	4A	left lobectomy	3.1	76/52	11	75	1450	B
case 25	48	M	4	0	0	3	4A	right lobectomy	2.8	58/57	14	9	62.5	B
case 26	54	M	4	0	1	3	4A	extended right lobectomy	3.0	85/93	-	1500	21300	-
case 27	58	M	4	0	0	3	4A	right lobectomy	4.2	84/72	19	2208	62.5	B
case 28	63	M	4	0	0	3	4A	extended posterior segmentectomy	3.4	72/84	15	21	62.5	-
case 29	69	F	4	0	0	3	4A	right lobectomy	3.7	97/97	7	2900	571	C
case 30	67	M	4	0	0	3	4A	extended posterior segmentectomy	2.9	67/60	35	4733	18625	C

TNM stage and the grade of portal vein thrombus were classified according to the 3rd edition of the general rules of the clinical and pathological study of primary liver cancer by liver cancer study group of Japan.
Alb: serum Albumin (g/dL); PT: Prothrombin time (%); HPT: Hepaplastin test (%);
ICGR-15: indocyanine green retention rate at 15 minutes (%);
AFP: alpha-fetoprotein (ng/mL) and PIVKA-II: Protein Induced by Vitamin K Absence (mAU/mL). ND: not done.

every month. An abdominal CT scan or dynamic magnetic resonance imaging (MRI) was also performed before and after treatment, at least once every 3 months. The objective response was classified according to the ECOG criteria (16).

Statistical Analysis

Survival curves were constructed using the Kaplan-Meier method (17). Survival curves were compared using the log-rank test. The features of HCC, biochemistry, ICGR-15, and virus status were compared using the Mann-Whitney test. The level of tumor markers (AFP, and PIVKA-II) was compared by the Wilcoxon matched-pair test. Significance was interpreted as $p<0.05$.

RESULTS

Features of Preoperative Hepatic Function, Hepatocellular Carcinoma, and Surgery

The features of preoperative hepatic function are shown in **Table 3**. There was no significant difference between the IFN/5-FU adjuvant and non-IFN/5-FU adjuvant groups in the preoperative hepatic function; serum albumin (g/dL), prothrombin time (PT, %), hepaplastin test (HPT, %), indocyanine green retention rate at 15 minutes (ICGR-15, %). No difference was also demonstrated in terms of tumor stage, surgical procedure, including AFP (ng/mL) and PIVKA-II (mAU/mL) **(Tables 1 and 2)**.

Clinical Effects, Disease-free and Overall Survival

All 30 patients in this study were discharged without major complications. The results of the IFN/5-FU adjuvant treatment group were as follows; disease-free survival (n=11) (5-55 months), survival with recurrence (n=2) (13, 48 months), cancer death (n=1) (18 months), death from other causes with no recurrent cancer lesion in the residual liver (n=1) (22 months). The summary of these results in each case is shown in **Table 4**. With respect to Cases 2 and 8, IFN/5-FU combined therapy could not be continued over 4 cycles, due to technical difficulties with the catheter. After stopping the treatment, recurrent lesions appeared in the residual liver in these two patients, at 18 and 8 months after surgery, respectively. They were treated again after insertion of the arterial catheter with intervention (IVR). The lesion was well-controlled over 30 months in Case 2. In Case 8, the recurrent lesion completely disappeared after re-treatment with IFN/5-FU combined chemotherapy (complete response, CR), however, the patient died suddenly due to cardiac failure secondary to ischemic heart disease.

In the other group that received no adjuvant IFN/5-FU therapy, almost all patients (11 of 15) died of recurrent cancer within 2 years. All patients developed recurrences in the residual liver, 2 also had lung metastasis, and one had lung and lymph node metastasis. Recurrence was identified within 1 year of hepatic resection in 12 of the 15 patients, and 11 died within 2 years. These clinical results for the control group are summarized in **Table 5**.

With respect to survival, the overall survival rates at 1 and 3 years were 100% and 74%, respectively, in patients on IFN/5-FU combination therapy (n=10), and 41% and 22%, respectively, in the historical controls with no IFN adjuvant (n=15). In addition, the

TABLE 3 Feature of Hepatic Function

	IFN/5-FU postoperative adjuvant (n=15)	Non-IFN/5-FU postoperative adjuvant (n=15)	
	mean ± SD (range)	mean ± SD (range)	*p* value
Albumin (g/dL)	3.8±0.4 (3.4-4.5)	3.5±0.5 (2.8-4.3)	NS
Prothrombin time (%)	75.7±8.3 (65-90)	75.0±13.2 (61-97)	NS
Hepaplastin test (%)	80.6±13.9 (62-105)	78.1±20.2 (52-133)	NS
ICGR-15 (%)	16.3±7.8 (4-26)	15.4±7.8 (6-35)	NS

TABLE 4 The Prognosis and Pathological Findings of the IFN/5-FU Adjuvant Group (n=15)

	Recurrence		Period		Prognosis		Histology	
	Recurrence	Recurrent site	Disease-free period	Survival period	prognosis	Cause of death	Cancer	Non-cancer
case 1	-	-	55	55	alive	-	EdIII(por)	B'-
case 2	+	liver	18	48	alive	-	EdII(mod)	CAH+
case 3	-	-	30	30	alive	-	EdII(mod)	B-
case 4	-	-	24	24	alive	-	EdIII(por)	CAH+
case 5	-	-	24	24	alive	-	EdIII(por)	B'-
case 6	-	-	22	22	alive	-	EdIII(por)	B'-
case 7	+	liver, lung	7	18	died	cancer	EdIII(por)	B'-
case 8	+	liver	8	22	died	cardiac failure*	EdII(mod)	B'-
case 9	-	-	13	13	alive	-	EdIII(por)	B'-
case 10	+	lymph node	6	13	alive	-	EdIII(por)	B-
case 11	-	-	12	12	alive	-	EdIII(por)	B'-
case 12	-	-	12	12	alive	-	EdIII(por)	B'-
case 13	-	-	10	10	alive	-	EdII(mod)	B-
case 14	-	-	6	6	alive	-	EdIII(por)	B'-
case 15	-	-	5	5	alive	-	EdII(mod)	CAH+

* Although the recurrent lesion had completely disappeared after the re-treatment with IFN/5-FU combined chemotherapy (CR), he died suddenly due to cardiac failure of ischemic disease.

1- and 3-year disease-free survival rates were 72% and 60%, respectively, in patients on IFN/5-FU combination therapy (n=10), and 39% and 20%, respectively, in historical controls with no IFN adjuvant (n=15). There was a significant difference in disease-free and overall survival between these two groups (overall; $p=0.0031$, disease-free; $p=0.0033$). The overall survival curves are shown in **Figure 1**.

A Representative Case Successfully Treated with IFN/5 FU Adjuvant Therapy and Hepatic Resection

A representative patient who was successfully treated is described below.

Case 1

A 47-year-old man with hepatitis B virus infection, advanced HCC (massive type in left lobe) and portal thrombus in the left branch of the major trunk **(Figure 2)** underwent left lobectomy in October 1998. Tumor markers were highly elevated before surgery (AFP: 11,400ng/mL, PIVKA-II: 7,900mAU/ mL). Histopathological examination of the resected tissue showed poorly-differentiated HCC with Vp3 and metastasis to the gallbladder **(Figure 2)**. For the prevention of recurrent tumor development, a combination of IFN/5-FU therapy (4 cycles) was administered over 7 months. No recurrence of the tumor occurred after cessation of treatment and no tumor progression has been observed for 55 months after surgery.

Adverse Effects

No leukopenia, thrombocytopenia, or myelosuppression was observed in the 15 patients of the IFN/5-FU group. Other adverse effects were, in general, clinically manageable. Fever was commonly observed but was easily controlled by non-steroidal anti-inflammatory drugs prior to IFN injection. No depression due to IFN administration was observed in any of the 15 patients.

DISCUSSION

In the present study, a combination therapy of subcutaneous administration of IFN-α and arterial infusion chemotherapy with 5-FU was applied as a postoperative adjuvant to 15 consecutive patients with resectable HCC associated with Vp3, following hepatic resection. Our results showed that this treatment regimen markedly decreased the incidence of recurrence in the residual liver and significantly prolonged the disease-free and overall survival periods compared with historical controls, as shown in **Figures 1 and 2**. Unexpectedly, the 1-year overall survival rate was 100% in the IFN/5-FU treatment group. These results showed that combination therapy with subcuta-

TABLE 5. The Prognosis and Pathological Findings of the Non-IFN/5-FU Adjuvant Group (n=15)

	Recurrence		Period		Prognosis		Histology	
	Recurrence	Recurrent site	Disease-free period	Survival period	prognosis	Cause of death	Cancer	Non-cancer
case 16	+	liver	50	58	died	cancer	EdIII(por)	CAH
case 17	+	liver, lung	1	3	died	cancer	EdIII(por)	B'-
case 18	+	liver	1	5	died	cancer	EdIII(por)	B'-
case 19	+	liver	12	18	died	cancer	EdIII(por)	unknown
case 20	+	liver	5	5	died	cancer	EdII(mod)	BA'+
case 21	+	liver	42	63	died	cancer	EdIII(por)	B+
case 22	+	liver	4	33	died	unknown	EdIII(por)	B+
case 23	+	liver	5	10	died	cancer	EdIII(por)	CIH-
case 24	+	liver	3	5	died	cancer	EdIII(por)	glissonitis,se
case 25	+	liver	2	4	died	cancer	EdIV (undifferentiated)	glissonitis
case 26	+	liver	1	3	died	cancer	EdIV (undifferentiated)	chr.glissoniti
case 27	+	liver	31	58	died	cancer	EdIII(por)	B-
case 28	+	liver, lymph node	6	6	died	cancer	EdIII(por)	chr.glissoniti
case 29	+	liver, lung	3	8	died	cancer	EdIII(por)	CIH
case 30	+	liver	4	7	died	cancer	EdIII(por)	B-

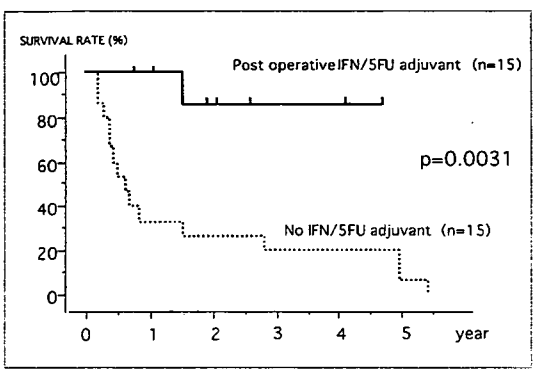

FIGURE 1 Overall survival rates of patients grouped according to whether they received IFN/5-FU combined chemotherapy or not as a postoperative adjuvant following hepatic resection. There was a statistically significant difference in survival ($p=0.0031$).

neous IFN and intra-arterial 5-FU may be therefore a promising treatment modality for resectable HCC with Vp3, as a postoperative adjuvant.

Development of tumor thrombi in a major branch or main trunk of the portal vein is a frequent terminal feature of HCC, either with primary or recurrent tumors. The prognosis of such patients is extremely poor and survival is generally limited to a few months after diagnosis (2-10). For these advanced HCCs, conventional therapies like percutaneous ethanol injection, microwave coagulation therapy, and transcatheter arterial embolization (TAE) are generally not indicated due to lack of efficacy and associated complications (6,8,18). Arterial infusion chemotherapy has also been attempted, but its effectiveness remains unsatisfactory (5,19,20). Even in resectable cases, the prognosis is extremely poor despite aggressive surgery, because of the very high incidence of recurrence in residual liver (7,9,10-12). In addition, the recurrent lesions are very severe and massive in almost all cases. Based on this point of view, in the absence of effective pre- and/or postoperative adjuvant therapy, hepatic resection should not be offered in such cases; no treatment except hepatic resection would be anticipated to improve AFP status or long-term survival. To date, several reports have mentioned the feasibility of hepatic resection for patients with portal vein tumor thrombosis (PVTT), however the outcome of this treatment is in general unsatisfactory. A recent study (21) reported very low rates of disease-free and overall survival for HCC with PVTT. In that report, disease-free survival rates at 1, 3, and 5 years were 15.0, 5.0 and 5.0%, respectively; overall survival rates at 1, 3 and 5 years were 30.0, 13.0 and 13.0%, respectively. Several other previous reports (7,9,10-12,22) were similar. Compared with these previous reports, our clinical outcome using IFN/5-FU combined therapy as a postoperative adjuvant was excellent and highly satisfactory, in terms of disease-free and overall survival rates.

The anti-tumor effects of systemic IFN-α therapy in HCC remain controversial. Several studies with IFN-α alone demonstrated only a minimal clinical effect (23-26). In a randomized controlled study, Lai *et al.* (27) demonstrated the beneficial effect of IFN-α with a 31% response rate in patients with inoperable HCC. In other studies, systemic combination therapy with IFN-α and doxorubicin was also found to be ineffective with a response rate ranging from 3 to 17% (28-30). The response rate in combination therapy with IFN-α and multiple anticancer agents including 5-FU and doxorubicin was 26% (31), and appeared better than other combination therapies with doxorubicin only.

Using intra-arterial infusion chemotherapy and systemic IFN-α administration, Urabe *et al.* (32) reported a response rate of 47% in patients with Vp3. More recently, Chung *et al.* (33) reported a partial response in 33% (6/18) of patients with major portal vein thrombosis or distant metastases, who received systemic combination therapy with IFN-α and cisplatin (CDDP). We also reported the anti-tumor effect of IFN/5-FU combined chemotherapy; complete or partial response was observed in 63% (5/8) of patients (14). It is difficult to accurately compare the effectiveness of various therapeutic regimens among different studies because of patient selection bias in liver function or extent of tumor progression and differences in the evaluation methods of the clinical effect. Although the limitations in comparing the clinical response between studies cannot be neglected, the marked effect and acceptable toxicity of our therapy in HCC patients with extremely poor prognosis suggests that combination therapy of IFN-α and 5-FU may be a promising treatment regimen.

This incredible clinical effect of IFN/5-FU combined chemotherapy after surgery could not be induced by 5-FU chemotherapy alone as a postoperative adjuvant. Cases 24 and 25 were treated with intra-arterial perfusion of 5-FU alone. Both patients refused the IFN/5-FU combined chemotherapy because of their experience of depression induced by IFN-α for treatment of HCV infection. These two patients developed tumor recurrence in residual liver at 3 and 4 months postoperatively, and died of cancer 8 and 7 months postoperatively, respectively, despite 5-FU intra-arterial perfusion chemotherapy without IFN as a postoperative adjuvant.

With respect to postoperative adjuvant therapy for HCC, a recent review mentioned systemic chemotherapy, hepatic-artery chemotherapy or TAE, as well as a combination of these therapies did not improve overall or disease-free survival after potentially curative surgery for localized HCC (34). This report referred to pre- and/or post-adjuvant therapy only for resectable low stage HCCs, and not for advanced cases, with common prevention of recurrence in the liver. To date, there are few reports about adjuvant therapy for advanced HCC with PVTT. Radiotherapy was effective for reduction of the size of tumor thrombus, especially combined with TAE in recent reports of the treatment of PVTT (35-37). However, no prolongation of survival was expected and it may be considered as a preoperative adjuvant therapy. Another report suggested that for long-term survival in advanced HCC with tumor thrombus, preoperative TAE is necessary and the ICGR-15 (%) should be better than 20% (38). The survival rates at 1 and 3 years in that study were 82% and 42%, respectively. Their results compared favorably with the previous reports, and our data were better than their results in terms of overall survival at 1 and 3 years (100% and 74%, respectively, in the present study). With respect to liver function, a low ICGR-15 was the one of the conditions

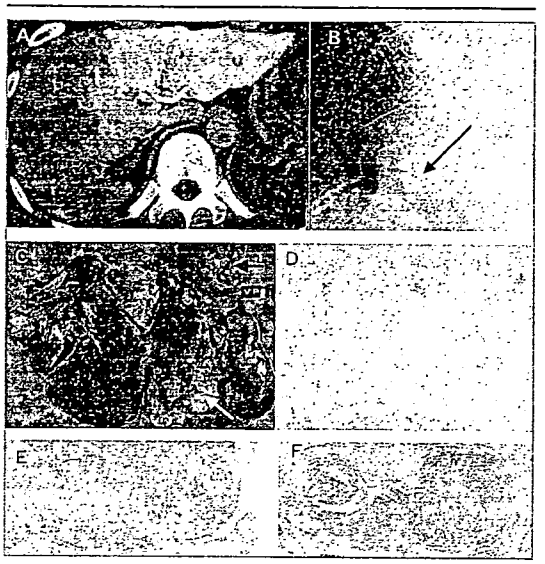

FIGURE 2 Case 1. **(A)** CT arteriography (CT-A) showing the main tumor of the left lobe of the liver. The tumor is massive with tumor thrombus of the left branch. **(B)** Arterial portography demonstrates tumor thrombus extending up to the main trunk of the portal vein (arrow), from the main tumor occupying the whole left lobe. Arrow; tumor thrombus in the major branches of the portal vein. **(C)** Morphological findings of the resected left lobe of the liver. Black arrow; portal venous thrombus of the main trunk. White arrow; metastatic lesion of the gallbladder. **(D)** Pathological findings of the main tumor of the resected liver. The postoperative histological examination revealed poorly-differentiated HCC with Vp3 **(E)** and metastasis to gallbladder **(F)**.

for long-term survival after surgery. In our report, the ICGR-15 in 40% of patients (4 of 10) in the post-adjuvant IFN/5-FU group was worse than 20%. Therefore, our present study is the first to describe a promising strategy for advanced HCC with PVTT, with 1-year survival rate of 100%.

Myelosuppressive adverse effects are particularly important in patients with HCC. This is not only because thrombocytopenia and/or leukopenia are often present before the initiation of anticancer therapy, but also because treatment often has to be discontinued due to these side-effects. Another advantage of this combination therapy is the markedly low incidence of myelosuppressive side-effects; no patient developed leukopenia in this study (data not shown).

Other side-effects were also well controlled by conventional treatment. These relatively mild side-effects allowed continuation of treatment, and may enhance the marked clinical effect because treatment was never interrupted due to adverse effects. In addition, the QOL of patients in this study was excellent, because IFN/5-FU adjuvant therapy was performed at outpatient clinics. No hospital admission was necessary to receive IFN injection combined with intra-arterial perfusion chemotherapy. The patients could maintain their social life while on IFN/5-FU adjuvant

therapy. Moreover, they had no symptoms related to liver dysfunction.

In conclusion, our present study indicated that combination chemotherapy with subcutaneous IFN-α and intra-arterial 5-FU is a promising strategy for resectable HCC with tumor thrombus in major branches of the portal vein, as a postoperative adjuvant therapy following surgery. To obtain conclusive evidence of the effect of this treatment, a large phase II trial and further investigation are essential.

REFERENCES

1 The general rules for the clinical and pathological study of primary liver cancer. The 3rd Edition. Liver Cancer Study Group of Japan. February 1992.

2 **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; 79:2087-2094.

3 **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; 30:660-668.

4 **The Cancer of the Liver Italian Program (CLIP) investigators:** A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 1998; 28:751-755.

5 **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; 79:1890-1896.

6 **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; 204:787-790.

7 **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; 46:1862-1869.

8 **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 chemoembolization. J Gastroenterol Hepatol 1994; 9:1-6.

9 **Tanaka A, Morimoto T, Yamaoka Y:** Implications of surgical treatment for advanced hepatocellular carcinoma with tumor thrombi in the portal vein. Hepatogastroenterology 1996; 43:637-643.

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; 23:105-109.

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; 43:1172-1181.

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; 16:1172-1176.

13 **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 tegaful and uracil. J Gastroenterol Hepatol 2000; 15:1447-1451.

14 **Sakon M, Nagano H, Dono K, Nakamori S, Umeshita K, Yamada A, Kawata S, Imai Y, Iijima S, Monden M:** Combined intraarterial 5-fuluorouracil and subcutaneus interferon-a therapy for advanced hepatocellular carcioma with tumor thrombi in the major portal branches. Cancer 2002; 94:435-442.

15 **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; 52:295-299.

16 **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; 5:649-655.

17 **Kaplan EL, Meier P:** Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

18 **Lin DY, Lin SM, Liaw YF:** Non-surgical treatment of hepatocellular carcinoma. J Gastroenterol Hepatol 1997; 12:S319-328.

19 **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; 208:23-25.

20 **Doci R, Bignami P, Bozzetti F, Bonfanti G, Audisio R, Colombo M, et al:** Intrahepatic chemotherapy for unresectable hepatocellular carcinoma. Cancer 1988; 61:1983-1987.

21 **Poon R T-P, Fan ST, Ng I O-L, Wong J:** Prognosis after hepatic resection for stage IVA hepatocellular carcinoma: A need for reclassification. Ann Surg 2003; 237:376-383.

22 **Ikai I, Yamaoka Y, Yamamoto Y, Ozaki N, Sakai Y, Satoh S, Shinkura N, Yamamoto M:** Surgical intervention for patients with stage IV-A hepatocellular carcinoma without lymph node metastasis proposal as a standard therapy. Ann Surg 1998; 227:433-439.

23 **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; 56:1018-1022.

24 **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; 52:105-109.

25 **The Gastrointestinal Tumor Study Group:** A prospective trial of recombinant human interferon alpha 2B in previously untreated patients with hepatocellular carcinoma. Cancer 1990; 66:135-139.

26 **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; 31:54-58.

27 **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; 17:389-394.

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; 71:2187-2190.

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; 17:393-395.

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; 5:1676-1681.

32 **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.

33 **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; 88:1986-1991.

34 **Schwartz JD, Schwartz M, Mandeli J, Sung M:** Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials. The Lancet Oncology 2002; 3:593-603.

35 **Ishikura S, Ogino T, Furuse J, Satake M, Baba S, Kawashima M, Nihei K, Ito Y, Maru Y, Ikeda H:** Radiotherapy after transcatheter arterial chemoembolization for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Clin Oncol 2002; 25:189-193.

36 **Yamada K, Soejima T, Sugimoto K, Mayahara H, Izaki K, Sasaki R, Maruta T, Matsumoto S, Hirota S, Sugimura K:** Pilot study of local radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. Jpn J Clin Oncol 2001; 31:147-152.

37 **Tazawa J, Maeda M, Sakai Y, Yamane M, Ohbayashi H, Kakinuma S, Miyasaka Y, Nagayama K, Enomoto N, Sato C:** Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. J Gastroenterol Hepatol 2001; 16:660-665.

38 **Minagawa M, Makuuchi M, Takayama T, Ohtomo K:** Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. Ann Surg 2001; 233:379-384.

FOOTNOTE

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CASE REPORT

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Successful treatment of multiple hepatocellular carcinoma with tumor thrombi in the major portal branches by intraarterial 5-fluorouracil perfusion chemotherapy combined with subcutaneous interferon-alpha and hepatectomy

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Abstract We experienced a patient who received successful treatment for multiple hepatocellular carcinoma (HCC) nodules, with tumor thrombi in the major portal branches, with intraarterial 5-fluorouracil perfusion chemotherapy combined with subcutaneous interferon-alpha administration. The patient was a 50-year-old man with hepatitis C virus and HCC. The tumors consisted of a 5-cm main nodule in the right lobe (segment 8) and multiple intrahepatic metastases. The tumor also involved portal vein thrombosis throughout the right portal branch. After two cycles of interferon-alpha/5-fluorouracil combination chemotherapy, tumor markers demonstrated a decreasing tendency. Nine months after the initiation of this therapy, the tumors were limited to the right lobe and were surgically removed by S8 subsegmentectomy, S5 partial hepatectomy, and portal thrombectomy. The serum levels of both alpha-fetoprotein and protein induced by vitamin K absence II fell to normal levels after hepatic resection. Fifty-eight months after the first treatment, he is alive with several recurrent nodules in the liver. In conclusion, the interferon-alpha/5-fluorouracil combination therapy is a useful treatment for HCC in patients who have multiple intrahepatic metastases and portal vein thrombosis. In addition to this therapy, combined modality therapy including, for example, surgical resection, can sometimes have a dramatic therapeutic effect, shown by tumor markers reverting to normal levels.

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Key words Hepatocellular carcinoma · Portal vein tumor thrombi · Interferon · Chemotherapy · Hepatectomy

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide.[1] The prognosis of HCC remains unsatisfactory in spite of newly developed therapeutic modalities, such as radiofrequency ablation and microwave coagulation therapy.[2,3] Especially, the prognosis of HCCs with macroscopic tumor thrombi in the major branch of the portal vein (Vp3–4) is extremely poor.[4] Most HCC patients with Vp3–4 tumors develop recurrences, and half of them die within 1 year after surgery even if curative resection is performed.[5] The prognosis of unresectable patients with Vp3–4 is much worse, and most patients die within several months.[6–8] Therefore, the development of new antitumor therapy for HCC patients is urgent and mandatory.

Recently, we reported that intraarterial 5-fluorouracil (5-FU) perfusion chemotherapy combined with subcutaneous interferon-alpha (IFN-α) administration showed an excellent clinical response in patients with advanced HCC with macroscopic tumor thrombi in the major branch of the portal vein.[9–11] However, the clinical response rate of this combination theraphy is about 50%.[10] In addition, complete remission was not always achieved, even in patients for whom the treatment was considered effective (i.e., CT showed all enhanced regions in the liver disappeared). In this report, we describe our experience of a patient with HCC associated with liver cirrhosis due to hepatitis C, who, when first admitted was assessed as unresectable because of multiple intrahepatic metastases and major portal vein thrombosis. He was given subcutaneous injections of IFN-α and intraarterial infusions of 5-FU, and subsequently hepatic resection and thrombectomy were performed. This led

to the dramatic eradication of multiple tumor nodules and portal vein thrombosis, and the reduction to normal range of serum levels of both alpha-fetoprotein (AFP) and protein induced by vitamin K absence II (PIVKA-II).

Case report

The patient was a 50-year-old man with a history of blood transfusion at 33 years for treatment of hemorrhage due to a traffic accident. Abnormal liver function was identified for the first time at 38 years of age, and chronic hepatitis due to infection with hepatitis C virus was diagnosed. At age 48 years, multiple liver tumors were found by ultrasound examination. The tumors were diagnosed as HCC by computed tomography (CT) and magnetic resonance imaging (MRI) and consisted of a main nodule 5 cm in diameter in the right lobe (segment 8) and multiple intrahepatic metastases around the main nodule and in segment 3. In addition, the tumor involved portal vein thrombosis throughout the right portal branch.

Clinical tests on admission indicated abnormal liver function. The levels of aspartate aminotransferase (AST; 63 IU/l), alanine aminotransferase (ALT; 97 IU/l), and total bilirubin (T-Bil; 1.8 mg/dl) were abnormally high. Prothrombin time (PT) was 63% and the indocyanine green test rate at 15 min (ICGR-15) was 27%. Elevation of the tumor markers AFP, at 43 ng/ml, and PIVKA-II, at 8127 mAU/ml, revealed advanced HCC. After hospitalization, the background liver cirrhosis was defined as B according to the Child-Pugh classification. Because there were multiple nodules in the whole liver and thrombosis in the major portal branch, hepatectomy and embolization therapy were judged to be contraindicated. After the permission of the ethics committee at Osaka University Hospital and written informed consent were obtained, the patient was treated with subcutaneous administration of IFN-α (OIF; Otsuka Pharmaceutical, Tokyo, Japan) and intraarterial infusion of 5-FU (Kyowa Hakko, Tokyo, Japan). The regimen was as follows: IFN-α (5×10^6 U) was administered on days 1, 3, and 5 of each week for 4 weeks, and continuous infusion chemotherapy (5-FU, 300 mg/m^2 per day) through the proper hepatic artery was performed every 2 weeks for 4 weeks via a catheter connected to a subcutaneously implanted drug delivery system.[9]

After two cycles of this IFN-α/5-FU combination chemotherapy, tumor markers demonstrated a decreasing tendency. The level of PIVKA-II fell to 361 mAU/ml. The AFP level demonstrated no marked elevation (Fig. 1). After three cycles of IFN-α/5-FU combination chemotherapy, the main nodule had decreased in size and the tumor thrombus in the first branch of the portal vein and some of satellite lesions were disappeared (Fig. 2a–d). Nine months after the initiation of this therapy, the tumors were limited to the right lobe and the tumor thrombus had disappeared. Therefore, we could avoid right lobectomy, which would have been an extensive resection in this patient, and we surgically removed the tumor by S8 subsegmentectomy with S5 partial hepatectomy, and portal thrombectomy. The macroscopic finding of portal vein tumor thrombus was necrotic (Fig. 3a). Histological examination revealed that there were no intrahepatic metastatic lesions in the resected specimen. Moreover, the portal vein thrombosis had become organized (Fig. 3a) and showed no evidence of malignant cells (Fig. 3c). Serum levels of both AFP and PIVKA-II fell to normal after the hepatic resection. Furthermore, one cycle of IFN-α/5-FU combination chemotherapy was performed as postoperative adjuvant therapy, and the serum levels of these markers were maintained at normal levels, and no evidence of recurrence was shown by computed tomography for 8 months after the hepatic resection.

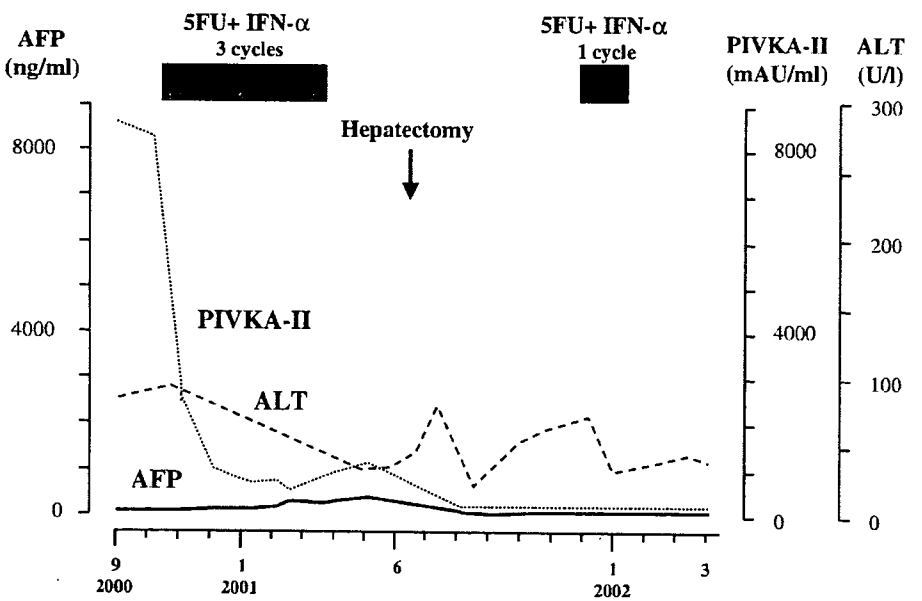

Fig. 1. Clinical course of the patient. Serum alpha-fetoprotein (*AFP*), protein induced by vitamin K absence II (*PIVKA-II*), and alanine aminotransferase (*ALT*) levels are indicated by the *solid line*, *dotted line*, and *dashed* line, respectively. *5-FU*, 5-fluorouracil; *IFN-α* interferon-alpha

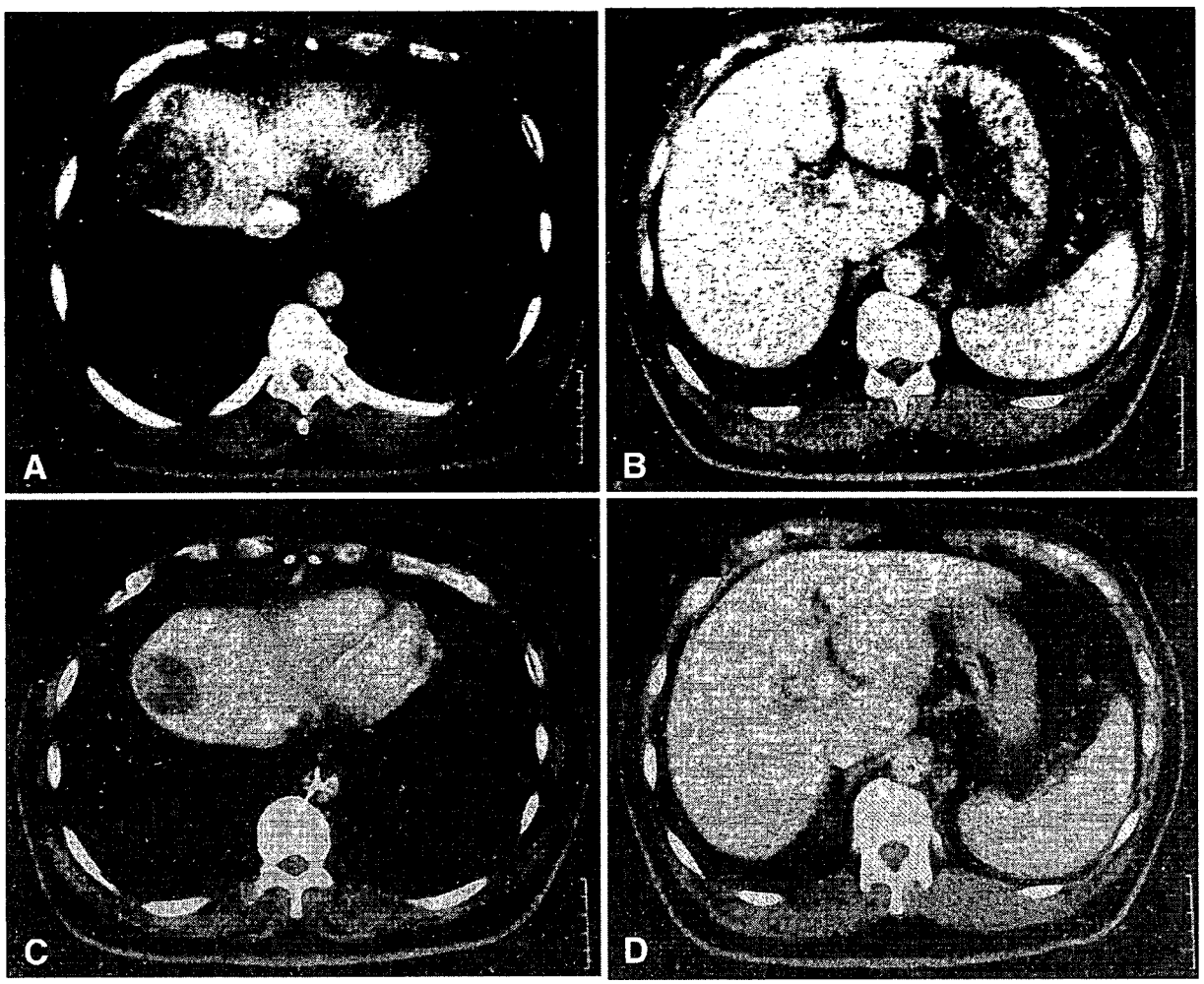

Fig. 2a–d. Computed tomography of the abdomen before the initiation of IFN-α/5FU combination therapy showed **a** hepatocellular carcinoma involved with satellite nodules around the main nodule, and **b** portal vein thrombosis. **c** After three cycles of IFN-α/5FU combination therapy, the main hepatocellular carcinoma nodule had markedly decreased in size and the number of satellite lesions had decreased, and **d** portal vein thrombosis had diminished

Before the initial treatment, this patient's hepatitis C virus (HCV) genotype was group 1b and HCV RNA concentration in serum was 280 kIU/ml. After three courses of the therapy, HCV RNA was not detected by reverse-transcription-polymerase chain reaction (RT-PCR). After the hepatectomy, the viral load of HCV RNA was positive. However, after one more course of the combination therapy, HCV RNA was not detected again. The serum ALT level was less than 100 U/l during the course of the treatment. During the clinical course, a gastric ulcer occurred. The catheter had fallen out of the gastroduodenal artery (GDA) and had become inserted into the common hepatic artery; the catheter was re-inserted into the GDA and fixed in an appropriate position.

The patient is alive 58 months after the first IFN-α/5-FU combination chemotherapy, with some recurrent nodules in the liver.

Discussion

In Japan, intraarterial perfusion chemotherapy is the most common treatment for advanced HCC which can not be treated by either surgery or embolization is contraindicated. This treatment is thought to deliver a higher concentration of chemotherapeutic drug to the tumor cells in the whole liver and to induce a greater antitumor effect that systemic chemotherapy. Nevertheless, the response rate of the hepatic arterial infusion chemotherapy has been still unsatisfactory.[12]

In general, HCCs are resistant to anticancer drugs.[13] However, recent studies, including those from our group, have demonstrated an excellent clinical response to the combination therapy of IFN-α and 5-FU in HCC patients complicated with Vp3–4.[9,14,15] We have previously reported

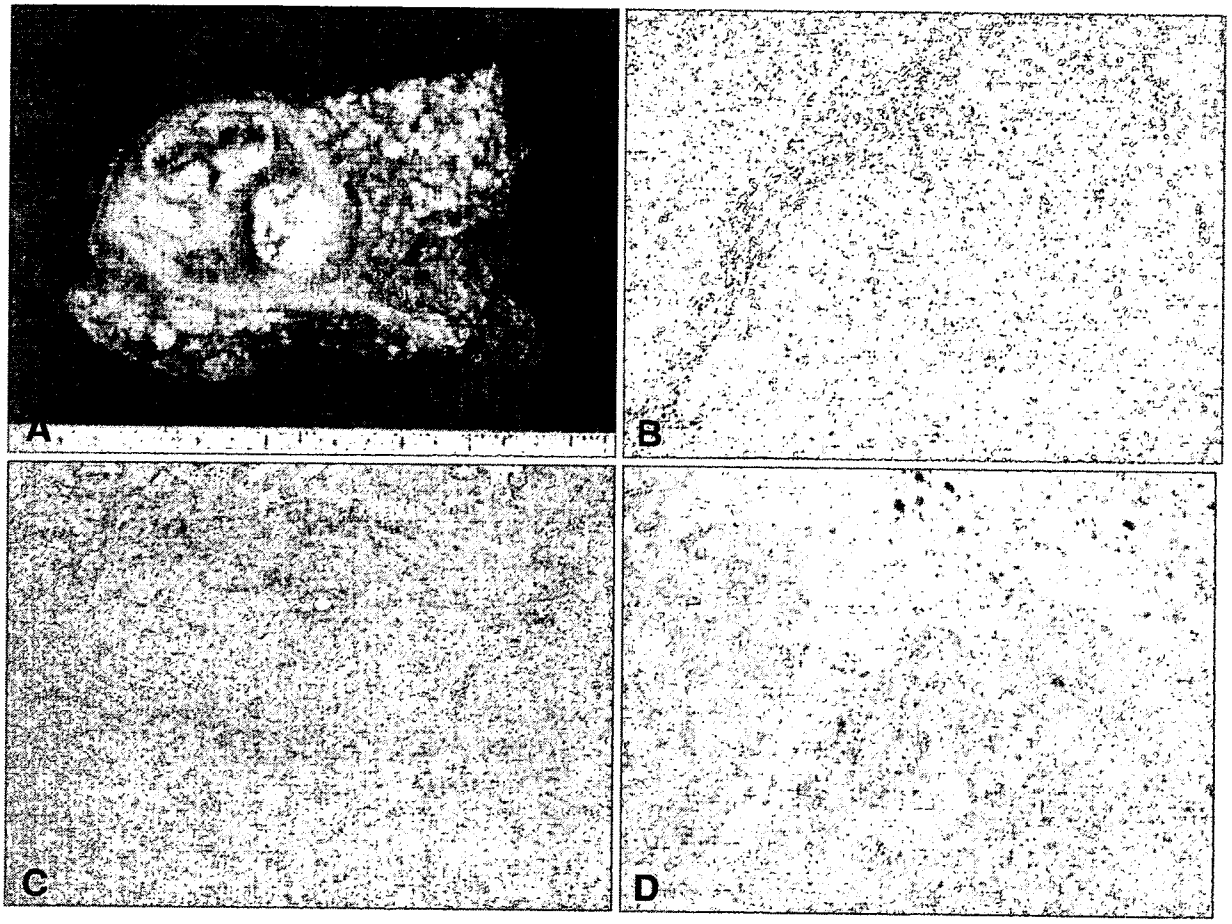

Fig. 3. a Surgical specimen of the liver shows that the portal vein thrombosis had become organized (*arrow*). **b** Histological examination shows residual viable hepatocellular carcinoma cells in the main nodule, and **c** no evidence of tumor cells in the portal vein thrombosis. **d** Immunohistochemical staining for type I IFN receptors (IFNAR) in the hepatocellular carcinoma tissues of the patient who received IFN-α/5FU combination therapy. The resected surgical specimen shows high IFNAR expression. Immunohistochemistry was performed according to our previous report.[21] **b** ×100; **c** ×40, H&E; **d** ×200

the efficacy of IFN-α and 5-FU combination therapy against advanced HCC, based on its high response rate and low incidence of side effects.[9] In our experience, in approximately half of 55 patients who were deemed unresectable because of multiple intrahepatic metastases and major portal vein thrombosis, IFN-α/5-FU combination chemotherapy was effective.[10]

Although the exact mechanism of action of this combination therapy has not yet been established, it has been reported that, in colon carcinoma cells, IFN-α enhances the expression of thymidine phosphorylase, which converts 5-FU to an active metabolite and enhances the DNA damage caused by 5-FU.[15,17] We also demonstrated previously that IFN-α and 5-FU synergistically reduced tumor cell proliferation through cell-cycle arrest[18] and that IFN-α also exerted immunomodulatory effects by stimulating natural killer (NK) cells and monocytes through the upregulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which induces apoptosis in HCC cells.[19]

IFN-α exerts its multiple functions through type I IFN receptors (IFNAR). We also demonstrated the importance of this receptor for antitumor effects.[20] We estimated the expression of IFNAR in tumor tissues by means of immunohistochemistry[21] in 13 HCC patients who received IFN-α/5-FU combination chemotherapy;[10] in the HCC patients who received IFN-α/5-FU combination therapy, the expression of IFNAR in tumor tissue was significantly higher in clinical responders than in nonresponders.[10] It should be noted that none of the responders were negative for IFNAR expression. It is conceivable that the existence of IFNAR is a minimal requirement for an effective response to IFN-α/5-FU combination therapy. In the patient described in the present report, there was high IFNAR expression in the tumor tissue (Fig. 3d).

The complete remission in this patient was thought to be due to the following factors: (1) high sensitivity of the HCC to 5-FU; (2) IFN-α exerting its multiple antitumor effects through positive IFNAR in tumor cells; (3) appropriate