HCC IN THE ERA OF TARGETED THERAPIES

In recent years, several molecular targets, including oncogenes, oncoproteins, and cellular receptors, have been identified in a variety of cancers as being key elements in carcinogenic pathways. Consequently, several agents have been developed that, by a variety of mechanisms, interfere with cell signaling and have demonstrated anticancer activity. In some cancers, the molecular target–targeted agent relationship is well understood—for example, the monoclonal antibody trastuzumab is only effective in tumors in which the her-2/neu oncoprotein is amplified. Conversely, there are several agents that target the transmembrane epidermal growth factor receptor (EGFR) and have demonstrated survival benefit in a broad range of tumor types, yet little is understood regarding the relationship between target expression and agent efficacy or lack thereof. Several targeted or novel biologic agents are now being tested in HCC patients. This discussion focuses on those aspects of hepatocarcinogenesis that are sufficiently well understood to provide a rational basis for developing clinical trials that use existing novel or targeted therapies in HCC.

TARGETING CARCINOGENIC PATHWAYS IN HCC

Hepatocarcinogenesis is known to be a complex multistep process that results in a large number of heterogeneous molecular abnormalities, and thus numerous potential targets for existing therapeutic agents. The pathways summarized below represent rational targets for existing therapeutic agents in HCC.

Mitogen-Activated Protein Kinase Pathway

The mitogen-activated protein kinase pathway (MAPK) pathway involves a cascade of phosphorylation of four major cellular kinases; ras, raf, MAP, and ERK (MAP, mitogen-activated protein kinase; ERK, extracellular-signal-regulated kinase), which is responsible for cellular proliferation and differentiation. These intermediates are found to be high in both HCC cell lines and human specimens.[27–31] Therapeutic agents that target this pathway include sorafenib (targets both raf and vascular endothelial growth factor receptor, VEGFR) and farnesyl transferase inhibitors (targeting ras). A phase 2 trial of sorafenib demonstrated antitumor activity in advanced HCC patients. This study did not meet its primary end point of response on the basis of WHO criteria, with limited response rate of 2.2%. However, many patients (33.6%) had stable disease for at least 4 months, with many showing central tumor necrosis.[32] On the basis of the encouraging overall survival of 9.2 months reported in the phase 2 trial, a placebo-controlled international trial was conducted in HCC patients with Childs-Pugh A cirrhosis. Preliminary data presented in abstract form from the phase 3 trial showed better survival in the sorafenib arm (10.7 months) compared with placebo (7.9 months).[33] These results indicate that this agent offers a survival advantage compared with placebo and with several cytotoxic agents (based on historical controls), but this may be comparable to survival observed with other biologic agents (Table 1).

PI3K/AKT/mTOR Pathway (Phosphoinositide-3 Kinase/Protein Kinase B/Mammalian Target of Rapamycin)

This kinase cascade is responsible for cellular proliferation and apoptosis, and is closely linked to cell cycle. PI3K is associated with cell surface growth factor receptors, and on ligand binding can trigger formation of PIP3, which in turn activates Akt and leads to a number of downstream events (mTOR being one of the targets). This pathway is known to be upregulated in a subset of HCC patients.[34–36] Molecular target therapy such as rapamycin, a naturally occurring mTOR inhibitor, showed promising results in HCC cell lines,[37,38] but no results from clinical trials of any agents that target mTOR in HCC patients are available.

Epigenetic Changes

Epigenetic modifications of the genome (mainly hypermethylation of CpG island and histone deacetylation) are accumulated during hepatocarcinogenesis in chronically injured liver. A large number of tumor suppressor genes have been shown to be inactivated by epigenetic mechanisms in HCC. Success in epigenetic therapy (such as 5-aza-2′-deoxycytidine and SAHA) had been achieved in both hematological malignancies and solid tumors. In HCC cell lines, chemosensitivity can be potentiated by epigenetic therapy.[39,40] A multicenter phase 1/2 trial on a novel histone deacetylase inhibitor, PXD-101, is currently underway in Hong Kong.

GROWTH FACTORS AS THERAPEUTIC TARGETS IN HCC

The epidermal growth factor receptor (EGFR) is frequently expressed in human hepatoma cells, and EGF may be one of the mitogens needed for the growth of hepatoma cells.[41,42] Several agents that inhibit EGF signaling are clinically available, including gefitinib, cetuximab, erlotinib, and panitumumab. Erlotinib is an orally active and selective inhibitor of the EGFR/HER1-related tyrosine kinase enzyme. EGFR/HER1 expression was detected in 88% of the patients in a phase 2 study of erlotinib.[43] In two phase 2 studies of this agent, the response rates were was < 10%, but the disease control rate was > 50%, and median survival times were 10.75 and 13 months, respectively.[43,44] Other studies of anti-EGFR agents in HCC are summarized in Table 1.

HCCs are generally hypervascular, and vascular endothelial growth factor (VEGF) promotes HCC development and metastasis.[45–49] Various agents targeting the VEGF circulating ligand or transmembrane receptor, including bevacizumab (Avastin), sorafenib (Nexavar), and TSU-68, have been studied in patients with HCC. Bevacizumab, a monoclonal antibody inhibitor of VEGF ligand, has been investigated in phase 2 studies alone or combination with other agents. These studies showed a high disease control rate of > 80% and a median progression-free survival of > 6 months.[50] Sorafenib, an oral multikinase inhibitor, blocks tumor cell proliferation mainly by targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an antiangiogenic effect by targeting VEGFR-2/-3.[51–54] TSU-68 is an oral antiangiogenesis compound that blocks VEGFR-2 (vascular endothelial growth factor receptor), PDGFR (platelet-derived growth factor receptor), and FGFR (fibroblast growth factor receptor); a phase 1/2 study has been conducted in Japan.[55]

IMMUNOTHERAPY OF HCC

Increasing evidence suggests that immune responses are important in the control of cancer and that the manipulation of the immune system to recognize and attack tumors may be a valuable form of therapy. HCC is attractive target for immunotherapy, because in addition to documented cases of spontaneous regression, lymphocytes can be seen infiltrating tumors and tumor-associated proteins such as alfa-fetoprotein (AFP) could act as targets for immune-mediated attack.[56,57] Given the limitations of current treatment modalities in the treatment of HCC, interest has been stimulated in immunotherapy of HCC, and a number of promising strategies have been developed in the laboratory, some of which have been applied in the clinical setting.

HCC are often infiltrated with lymphocytes, and patients with higher levels of tumor-infiltrating lymphocytes have a better prognosis after resection and transplantation.[56] A randomized, controlled clinical trial has shown that disease-free survival after HCC resection can be increased by infusion of lymphocytes activated by anti-CD3 and interleukin 2, suggesting a promising role for T cell adoptive immunotherapy.[58]

To generate a tumor-specific immune response, tumor-associated antigens must be presented to the immune system in an immunostimulatory context. Dendritic cells (DC) are the most efficient method of stimulating immune responses and are potent inducers of antitumor immunity when loaded with tumor-associated antigens. Animal models have shown encouraging results for DC-based vaccination strategies. DC transduced with adenovirus encoding AFP were able to prevent or delay growth of an AFP-producing tumor cell line in mice, and this was accompanied by the appearance of AFP-specific cytotoxic T lymphocytes.[59] By using fusions of DC and syngeneic hepatoma cells, Kawada and colleagues[60] were able to prevent the growth of implanted hepatoma cells and prevent local recurrence after surgical resection in rats.

The success of animal models in DC-based immunotherapy of HCC has lead to a number of clinical studies. These studies are all small and are mainly phase 1/2 studies designed primarily to assess feasibility and tolerability of this treatment modality. Currently reported DC vaccination studies have used DC loaded with autologous tumor or hepatoma cell line lysates.[61] DC have also been directly injected into tumors.[62] Clinical responses to these approaches have at best been modest, and the success of animal vaccination studies has not to date been replicated.

There are many reasons why this should be. First, the patients selected for clinical studies have been those with advanced disease and therefore may have tumor-induced immunosuppression. Additionally, questions still remain about the optimal route of administration of DC vaccines and the optimal method of loading tumor-associated antigens needs to be established. Importantly, the effect of concomitant viral infection, especially with hepatitis C virus, needs to be clarified.[63]

Currently the role for immunotherapy in HCC is limited, but from studies performed so far, we can be certain that future clinical studies should be ran-

domized and include patients with earlier disease and small tumor burden, to better identify potential benefit and truly identify the role of immunotherapy in HCC.

CLINICAL TRIAL DESIGN FOR BIOLOGIC AGENTS IN HCC

As noted previously, the availability in the clinic of several novel biologic agents and the urgent need for effective therapies for advanced HCC has led to the evaluation of many of these agents in HCC, principally in phase 2 trials. The SHARP trial[33] was the first to demonstrate a statistically significant survival benefit for any chemotherapy agent in patients with HCC. This trial was, however, conducted in patients with excellent performance status and well-preserved liver function. The efficacy and safety of sorafenib in patients with more tumor-related symptoms and advanced hepatic dysfunction remains to be established.

A key objective going forward is to assess new agents and to integrate these and sorafenib into the treatment of all stages of HCC and patients with Child-Pugh A and B cirrhosis. The classic approach is to evaluate new agents in single-arm phase 2 studies and use classic radiological response criteria such as WHO or RECIST as a measure of activity and thereby identify promising agents to take forward into phase 3 clinical trial testing against an appropriate control group. This approach, however, is being questioned because traditional radiographic tumor responses may not occur with biologic agents, although they may cause other anticancer effects that may lead to meaningful patient benefit. This is especially true in HCC, where radiological assessment is notoriously difficult because of poor delineation of tumors in the liver[64] and tumor necrosis may occur without any change in overall tumor dimensions.

These observations have led some investigators to develop phase 2 studies with a major focus on correlative studies that may help delineate a mechanism of action for a particular drug (e.g., a kinase inhibitor along one of the different cell cycle pathways) such as downregulation of a downstream kinase which may predict response,[32] or by the use of novel radiological techniques that use changes in blood flow as criteria by which to assess biologic activity of antiangiogenic therapies.[32] Another option is to use the randomized phase 2 trial design that, by providing a contemporary control group, may permit a more confident assessment of the likelihood that a particular agent is worthy to progress to phase 3 trials.[65]

CONCLUSIONS

Conducting controlled clinical trials of systemic chemotherapy regimens in HCC patients is challenging. Obstacles include the multiple comorbidities of patients with cirrhosis, the intrinsic chemoresistance of HCC, the advanced nature of HCC at the time of presentation in most patients, the pharmacotherapeutic challenges of treating a cancer that arises in an already damaged liver, and the distribution of patients primarily in developing nations where multidisciplinary treatment of HCC may not be available. HCC is a heterogeneous disease in terms of its cause, underlying associations, and biologic and clinical behavior, which further complicates clinical trial design. The need for effective systemic therapies for HCC patients is clearly evident, and making progress in this area requires the talent and expertise of all of the medical disciplines involved in the care of HCC patients.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55:74–108.
2. Parkin DM. The global burden of cancer. *Semin Cancer Biol* 1998; 8:219–35.
3. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. *CA Cancer J Clin* 1999; 49:33–64.
4. Deuffic S, Poynard T, Buffat L, et al. Trends in primary liver cancer. *Lancet* 1998; 351:214–5.
5. Nagasue N, Kohno H, Chang YC, et al. Liver resection for hepatocellular carcinoma. Results of 229 consecutive patients during 11 years. *Ann Surg* 1993; 217:375–84.
6. Yamamoto S, Sato Y, Takeishi T, et al. Successful surgical treatment for hepatocellular carcinoma and concomitant risky esophageal varices. *Hepatogastroenterology* 2005; 52:1083–6.
7. Tanaka H, Kubo S, Tsukamoto T, et al. Recurrence rate and transplantability after liver resection in patients with hepatocellular carcinoma who initially met transplantation criteria. *Transplant Proc* 2005; 37:1254–6.
8. Simonetti RG, Camma C, Fiorello F, et al. Hepatocellular carcinoma. A worldwide problem and the major risk factors. *Dig Dis Sci* 1991; 36:962–72.
9. Johnson PJ. Hepatocellular carcinoma: is current therapy really altering outcome?. *Gut* 2002; 51:459–62.
10. Johnson PJ. Are there indications for chemotherapy in hepatocellular carcinoma?. *Surg Oncol Clin N Am* 2003; 12:127–34.
11. Palmer DH, Hussain SA, Johnson PJ. Systemic therapies for hepatocellular carcinoma. *Expert Opin Investig Drugs* 2004; 13:1555–68.
12. Hong RL, Tseng YL. A phase II and pharmacokinetic study of pegylated liposomal doxorubicin in patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2003; 51:433–8.
13. Lee J, Park JO, Kim WS, et al. Phase II study of doxorubicin and cisplatin in patients with metastatic hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2004; 54:385–90.
14. Okusaka T, Ueno H, Ikeda M: [Chemotherapy for hepatocellular carcinoma.] Gan To Kagaku Ryoho 2004;31:2122–8.

15. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005; 97:1532–8.
16. Gish RG, Porta C, Lazar L, et al. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007; 25:3069–75.
17. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; 24:2505–12.
18. Okada Y, Tosaka A, Nimura Y, et al. Atypical multidrug resistance may be associated with catalytically active mutants of human DNA topoisomerase II alpha. *Gene* 2001; 272:141–8.
19. Watanuki A, Ohwada S, Fukusato T, et al. Prognostic significance of DNA topoisomerase IIalpha expression in human hepatocellular carcinoma. *Anticancer Res* 2002; 22:1113–9.
20. Endicott JA, Ling V. The biochemistry of P-glycoprotein–mediated multidrug resistance. *Annu Rev Biochem* 1989; 58:137–71.
21. Ng IO, Liu CL, Fan ST, et al. Expression of P-glycoprotein in hepatocellular carcinoma. A determinant of chemotherapy response. *Am J Clin Pathol* 2000; 113:355–63.
22. Park JG, Lee SK, Hong IG, et al. MDR1 gene expression: its effect on drug resistance to doxorubicin in human hepatocellular carcinoma cell lines. *J Natl Cancer Inst* 1994; 86:700–5.
23. Tsang WP, Kwok TT. Riboregulator H19 induction of MDR1-associated drug resistance in human hepatocellular carcinoma cells. *Oncogene* 2007; 26:4877–81.
24. Chan KT, Lung ML. Mutant p53 expression enhances drug resistance in a hepatocellular carcinoma cell line. *Cancer Chemother Pharmacol* 2004; 53:519–26.
25. Zhu H, Chen XP, Luo SF, et al. Involvement of hypoxia-inducible factor-1-alpha in multidrug resistance induced by hypoxia in HepG2 cells. *J Exp Clin Cancer Res* 2005; 24:565–74.
26. Lasagna N, Fantappie O, Solazzo M, et al. Hepatocyte growth factor and inducible nitric oxide synthase are involved in multidrug resistance-induced angiogenesis in hepatocellular carcinoma cell lines. *Cancer Res* 2006; 66:2673–82.
27. Feng DY, Zheng H, Tan Y, et al. Effect of phosphorylation of MAPK and Stat3 and expression of c-fos and c-jun proteins on hepatocarcinogenesis and their clinical significance. *World J Gastroenterol* 2001; 7:33–6.
28. Ito Y, Sasaki Y, Horimoto M, et al. Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. *Hepatology* 1998; 27:951–8.
29. McKillop IH, Schmidt CM, Cahill PA, et al. Altered expression of mitogen-activated protein kinases in a rat model of experimental hepatocellular carcinoma. *Hepatology* 1997; 26:1484–91.
30. Schmidt CM, McKillop IH, Cahill PA, et al. The role of cAMP-MAPK signalling in the regulation of human hepatocellular carcinoma growth in vitro. *Eur J Gastroenterol Hepatol* 1999; 11:1393–9.
31. Toyoda M, Hashimoto N, Tokita K, et al. Increased activity and expression of MAP kinase in HCC model rats induced by 3'-methyl-4-dimethylamino-azobenzene. *J Hepatol* 1999; 31:725–33.
32. 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.
33. Llovet J, 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). *J Clin Oncol* 2007; 25(Suppl):LBA1.
34. Alexia C, Bras M, Fallot G, et al. Pleiotropic effects of PI-3' kinase/Akt signaling in human hepatoma cell proliferation and drug-induced apoptosis. *Ann N Y Acad Sci* 2006; 1090:1–17.
35. Kannangai R, Vivekanandan P, Martinez-Murillo F, et al. Fibrolamellar carcinomas show overexpression of genes in the RAS, MAPK, PIK3, and xenobiotic degradation pathways. *Hum Pathol* 2007; 38:639–44.
36. Saxena NK, Sharma D, Ding X, et al. Concomitant activation of the JAK/STAT, PI3K/AKT, and ERK signaling is involved in leptin-mediated promotion of invasion and migration of hepatocellular carcinoma cells. *Cancer Res* 2007; 67:2497–507.
37. Sieghart W, Fuereder T, Schmid K, et al. Mammalian target of rapamycin pathway activity in hepatocellular carcinomas of patients undergoing liver transplantation. *Transplantation* 2007; 83:425–32.
38. Sahin F, Kannangai R, Adegbola O, et al. mTOR and P70 S6 kinase expression in primary liver neoplasms. *Clin Cancer Res* 2004; 10:8421–5.
39. Ocker M, Alajati A, Ganslmayer M, et al. The histone-deacetylase inhibitor SAHA potentiates proapoptotic effects of 5-fluorouracil and irinotecan in hepatoma cells. *J Cancer Res Clin Oncol* 2005; 131:385–94.
40. Kanda T, Tada M, Imazeki F, et al. 5-aza-2'-deoxycytidine sensitizes hepatoma and pancreatic cancer cell lines. *Oncol Rep* 2005; 14:975–9.
41. Hisaka T, Yano H, Haramaki M, et al. Expressions of epidermal growth factor family and its receptor in hepatocellular carcinoma cell lines: relationship to cell proliferation. *Int J Oncol* 1999; 14:453–60.
42. Fausto N. Growth factors in liver development, regeneration and carcinogenesis. *Prog Growth Factor Res* 1991; 3:219–34.
43. Thomas MB, Chadha R, Glover K, et al. Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer* 2007l110:1059–67.
44. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005; 23:6657–63.
45. Yamaguchi R, Yano H, Iemura A, et al. Expression of vascular endothelial growth factor in human hepatocellular carcinoma. *Hepatology* 1998; 28:68–77.
46. Yamaguchi R, Yano H, Nakashima O, et al. Expression of vascular endothelial growth factor-C in human hepatocellular carcinoma. *J Gastroenterol Hepatol* 2006; 21:152–60.
47. Yamaguchi R, Yano H, Nakashima Y, et al. Expression and localization of vascular endothelial growth factor receptors in human hepatocellular carcinoma and non-HCC tissues. *Oncol Rep* 2000; 7:725–9.
48. El-Assal ON, Yamanoi A, Soda Y, et al. Clinical significance of microvessel density and vascular endothelial growth factor expression in hepatocellular carcinoma and surrounding liver: possible involvement of vascular endothelial growth factor in the angiogenesis of cirrhotic liver. *Hepatology* 1998; 27:1554–62.
49. Li Q, Xu B, Fu L, et al. Correlation of four vascular specific growth factors with carcinogenesis and portal vein tumor thrombus formation in human hepatocellular carcinoma. *J Exp Clin Cancer Res* 2006; 25:403–9.
50. Thomas MB, Chadha R, Iwasaki M, et al. The combination of bevacizumab (B) and erlotinib (E) shows significant biological activity in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2007; 25(Suppl):4567.
51. Gollob JA. Sorafenib: scientific rationales for single-agent and combination therapy in clear-cell renal cell carcinoma. *Clin Genitourin Cancer* 2005; 4:167–74.
52. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer* 2007; 96:1788–95.
53. Karashima T, Inoue K, Fukata S, et al. Blockade of the vascular endothelial growth factor-receptor 2 pathway inhibits the growth of human renal cell carcinoma, RBM1-IT4, in the

kidney but not in the bone of nude mice. *Int J Oncol* 2007; 30:937–45.
54. Rodriguez-Viciana P, Tetsu O, Oda K, et al. Cancer targets in the Ras pathway. *Cold Spring Harb Symp Quant Biol* 2005; 70:461–7.
55. Yorozuya K, Kubota T, Watanabe M, et al. TSU-68 (SU6668) inhibits local tumor growth and liver metastasis of human colon cancer xenografts via anti-angiogenesis. *Oncol Rep* 2005; 14:677–82.
56. Unitt E, Marshall A, Gelson W, et al. Tumour lymphocytic infiltrate and recurrence of hepatocellular carcinoma following liver transplantation. *J Hepatol* 2006; 45:246–53.
57. Blondon H, Fritsch L, Cherqui D. Two cases of spontaneous regression of multicentric hepatocellular carcinoma after intraperitoneal rupture: possible role of immune mechanisms. *Eur J Gastroenterol Hepatol* 2004; 16:1355–9.
58. Takayama T, Sekine T, Makuuchi M, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. *Lancet* 2000; 356:802–7.
59. Vollmer CM Jr., Eilber FC, Butterfield LH, et al. Alpha-fetoprotein-specific genetic immunotherapy for hepatocellular carcinoma. *Cancer Res* 1999; 59:3064–7.
60. Kawada M, Ikeda H, Takahashi T, et al. Vaccination of fusion cells of rat dendritic and carcinoma cells prevents tumor growth in vivo. *Int J Cancer* 2003; 105:520–6.
61. Lee WC, Wang HC, Hung CF, et al. Vaccination of advanced hepatocellular carcinoma patients with tumor lysate-pulsed dendritic cells: a clinical trial. *J Immunother* 2005; 28:496–504.
62. Kumagi T, Akbar SM, Horiike N, et al. Administration of dendritic cells in cancer nodules in hepatocellular carcinoma. *Oncol Rep* 2005; 14:969–73.
63. Sarobe P, Lasarte JJ, Zabaleta A, et al. Hepatitis C virus structural proteins impair dendritic cell maturation and inhibit in vivo induction of cellular immune responses. *J Virol* 2003; 77:10862–71.
64. Hylton N. Dynamic contrast-enhanced magnetic resonance imaging as an imaging biomarker. *J Clin Oncol* 2006; 24:3293–8.
65. Abratt RP, Reece WH, Enas NH, et al. Randomized phase II studies and their ethics. *J Clin Oncol* 2005; 23:9443.
66. Mok TS, Leung TW, Lee SD, et al. A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1999; 44:307–11.
67. Posey J, Johnson P, Mok T, et al. Results of a phase 2/3 open-label, randomized trial of T138067 versus doxorubicin (DOX) in chemotherapy-naïve, unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2005; 23(Suppl):4035.
68. Patt YZ, Hassan MM, Lozano RD, et al. Thalidomide in the treatment of patients with hepatocellular carcinoma: a phase II trial. *Cancer* 2005; 103:749–55.
69. Pastorelli D, Cartei G, Zustovich F, et al. A phase II study of pegylated liposomial doxorubicin (PLD) and gemcitabine (G) in the treatment of hepatocellular carcinoma (HCC) not suitable for loco-regional therapy. *J Clin Oncol* 2007; 25(Suppl):4585.
70. Barbare JC, Bouche O, Bonnetain F, et al. Randomized controlled trial of tamoxifen in advanced hepatocellular carcinoma. *J Clin Oncol* 2005; 23:4338–46.
71. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol* 2007; 25:3644–8.
72. Zhu AX, Blaszkowsky L, Enzinger PC, et al. Phase II study of cetuximab in patients with unresectable or metastatic hepatocellular carcinoma. *J Clin Oncol* 2006; 24(Suppl):14096.
73. O'Dwyer PJ, Giantonio BJ, Levy DE, et al. Gefitinib in advanced unresectable hepatocellular carcinoma: results from the Eastern Cooperative Oncology Group's Study E1203. *J Clin Oncol* 2006; 24:(Suppl):4143.
74. Sun W, Haller DG, Mykulowycz K, et al. Combination of capecitabine, oxaliplatin with bevacizumab in treatment of advanced hepatocellular carcinoma (HCC): a phase II study. *J Clin Oncol* 2007; 25(Suppl):4574.
75. 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; 24:1898–903.

Original Paper

Hepatectomy for Hepatocellular Carcinoma Patients Who Meet the Milan Criteria

Hiroshi Ishii[1], Junji Furuse[1], Taira Kinoshita[2], Masaru Konishi[2], Toshio Nakagohri[2], Shinichiro Takahashi[2], Naoto Gotohda[2], Kohei Nakachi[1], Ei-ichiro Suzuki[1], Masahiro Yoshino[1]

Division of [1]Hepatobiliary and Pancreatic Medical Oncology, and [2]Upper Abdominal Surgical Oncology National Cancer Center Hospital East, Kashiwa, Japan

Corresponding Author: Hiroshi Ishii, MD, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

Tel: +81 4 7133 1111, Fax: +81 4 7131 4724, E-mail: hirishii@east.ncc.go.jp

ABSTRACT

Background/Aims: Although hepatocellular carcinoma patients who meet the Milan criteria are optimal candidates for liver transplantation, most such patients in Japan have been treated without liver transplantation.

Methodology: In this retrospective analysis, the patient selection criteria were (1) admission between 1992 and 2005, (2) fulfillment of the Milan criteria, (3) classification within the Barcelona Clinic Liver Cancer stages A1-A4, and (4) no previous anticancer treatment.

Results: Of 451 patients who met the selection criteria, 162 underwent hepatectomy. The proportion of patients who underwent hepatectomy was 58% of 106 with stage A1 and 29% of 345 with stages A2-A4. For patients with stages A2-A4, the survival probability after hepatectomy at 3, 5, and 7 years was 89%, 70%, and 61%, respectively. There were no significant differences in survival time between stages A1 and stages A2-A4 after hepatectomy. Among patients with Child-Pugh scores of 5 and 6 in stages A2-A4, 51% and 29% underwent hepatectomy, respectively.

Conclusions: Hepatectomy may be an appropriate first-line treatment option for patients with stages A2-A4 who meet the Milan criteria, when they have a good hepatic reserve and a long waiting time for liver transplantation.

KEY WORDS: Liver neoplasm; Prognosis; Liver transplantation

ABBREVIATIONS: Hepatocellular Carcinoma (HCC); Barcelona Clinic Liver Cancer (BCLC);

INTRODUCTION

Clinical cancer staging defines the prognosis and provides an outline for appropriate treatment decisions. Although there have been many staging or scoring systems proposed for hepatocellular carcinoma (HCC) (1-6), the Barcelona Clinic Liver Cancer (BCLC) staging **(Table 1)** (7) is notable for linking staging with treatment modalities (8-10). Patients classified as stage A under the BCLC system are those with early HCC who may benefit from curative therapies, such as hepatectomy, liver transplantation, or percutaneous ablation. According to the BCLC proposal (10), the treatment assignment for stage A1 is hepatectomy and for stages A2-A4 is liver transplantation. Among the 3 curative modalities, liver transplantation is the best curative option for patients who meet the Milan criteria (11), i.e., a solitary tumor up to 5cm in diameter, or no more than 3 nodules, each 3cm or less in diameter. When the criteria were instituted, 5-year survival rates of 70% and low recurrence rates were expected (12). In Japan, however, only 24 deceased donor liver transplantations have been performed for noncancer recipients in the past 6 years because the supply of liver from deceased donors is extremely limited (13). Accordingly, few Japanese HCC patients who meet the Milan criteria have received liver transplants.

The aim of this study was to evaluate the outcomes for liver transplantation candidates who did not receive transplants, in a Japanese high-volume center. The study was performed with special reference to the BCLC staging, and with a focus on the effects of hepatectomy on survival.

TABLE 1 Definition of the Barcelona Clinic Liver Cancer (BCLC) Staging

Stage	PST[a]	Tumor stage	Okuda stage	Liver function status
A1	0	Single	I	No portal hypertension and normal bilirubin
A2	0	Single	I	Portal hypertension and normal bilirubin
A3	0	Single	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumors <3 cm	I-II	Child-Pugh A-B
B	0	Large multinodular	I-II	Child-Pugh A-B
C	1-2[b]	Vascular invasion or extrahepatic spread	I-II	Child-Pugh A-B
D	3-4[b]	Any		Child-Pugh C

[a]: Performance status test; Stage A and B: all criteria should be met; Stage C: at least one of the criteria should be met, [b]: PST 1-2 or vascular invasion/extrahepatic spread; Stage D: at least one of the criteria should be met, [b]: PST 3-4 or Okuda stage III/Child-Pugh C

Hepato-Gastroenterology 2008; 55:621-626

METHODOLOGY

Patients

The patient selection criteria were: admission between July 1992 and May 2005; fulfillment of the Milan criteria (11); diagnosis of stages A1-A4 according to the BCLC staging (7); and no previous anticancer treatment. A list of all the patients who met the above criteria was compiled from a database that was approved by the Hospital Information Committee.

In the National Cancer Center Hospital East, diagnosis and staging of HCC were usually based on a characteristic arterial vascularization observed on dynamic computed tomography and/or magnetic resonance imaging. For the tumors that did not show arterial vascularization, fine-needle biopsy was mandatory before percutaneous ablation. For BCLC staging in this study **(Table 1)**, the normal bilirubin level was set at 1.2mg/dL or less, which was our institutional upper normal limit. The status of portal hypertension was clinically estimated by the presence of splenomegaly, esophageal varices, or a platelet count of less than 100,000/mm³.

TABLE 2 Clinical Data for the 451 Patients

Sex	Male/female	339 (75%)/112
Age	Median (range)	66 (30-86)
Modality of diagnosis	Histology	376 (83%)
	Imaging with AFP2>400	14 (3%)
	Imaging without AFP>400	61 (14%)
HBsAg/HCVAb†	Negative/negative	55 (12%)
	Positive/negative	38 (8%)
	Negative/positive	349 (77%)
	Positive/positive	9 (2%)
Total bilirubin (mg/dL)	Median (range)	1.0 (0.3-2.9)
Albumin (g/dL)	Median (range)	3.5 (2.2-4.6)
ICG test (%)‡	Median (range)	21.6 (1.5-98)
Platelet (10^4/mm³)	Median (range)	9.9 (2.4-39.8)
Prothrombin time (%)	Median (range)	76 (38-155)
Portal hypertension	Present/absent	308 (68%)/143
Child-Pugh stage	A/B	333 (74%)/118
Tumor number	Solitary/2/3	346 (77%)/75/30
Tumor size	<2cm	130 (29%)
	2-3cm	188 (42%)
	3-5cm	133 (29%)
AFP (ng/ml) §	Median (range)	27.3 (1.3-25046)
Barcelona Clinic Liver Cancer staging	A1	106 (24%)
	A2	153 (34%)
	A3	87 (19%)
	A4	105 (23%)
Treatment	Hepatectomy	162 (36%)
	Percutaneous ethanol injection	107 (24%)
	Percutaneous microwave coagulation	20 (4%)
	Percutaneous radiofrequency	59 (13%)
	Transcatheter arterial chemoembolization	77 (17%)
	Radiotherapy	11 (2%)
	Others	15 (3%)

†: Hepatitis B virus surface antigen/hepatitis C virus antibody; ‡: Indocyanine green retention test at 15 minutes; The ICG test was not available in 21 patients. §: Alpha-fetoprotein: AFP level was not available in 2 patients.

Treatment choice for each patient was determined at a conference held every Tuesday evening that was attended by surgeons, medical oncologists, and radiologists. The strategy for treatment assignment was as follows. All patients were first assessed for hepatectomy. Patients who met the Milan criteria and wanted to receive living donor liver transplantation were referred to other university hospitals where transplantation was available. Patients for whom hepatectomy was not feasible received percutaneous ablation if they had 3 or fewer HCC nodules without vascular invasion, of which the largest diameter was 3cm or smaller. This treatment included ethanol injection, microwave coagulation, and radiofrequency ablation therapy. Microwave coagulation was used between April 1998 and December 1999, and radiofrequency ablation has been used since June 1999. Even in technically resectable cases, percutaneous ablation was selected as the treatment modality for some elderly patients and for those with cardiopulmonary complications or deeply located small tumors that did not show the arterial vascularization, based on the consensus at the conference. External beam radiotherapy, including proton beam radiotherapy (14), was also an option for those unresectable cases with a solitary tumor. Transcatheter arterial chemoembolization was indicated for patients who were not candidates for hepatectomy, percutaneous ablation, or definitive radiotherapy.

Follow-up examination was performed 1 month after the treatment and then every 3-4 months using dynamic computed tomography or magnetic resonance imaging, and diagnosis of recurrence was made by typical arterial vascularization. The treatment modality for recurrence was assigned the same way as for the initial treatment.

Analysis and Statistics

Overall survival was measured from the first day of the initial treatment to the time of the final follow-up evaluation or death by any cause. Progression-free survival was measured from the first day of the initial treatment to the first day when recurrence was diagnosed by follow-up imaging or hepatic failure (development of clinical jaundice or irreversible ascites). All the patients were censored on November 30, 2005; 5 months after treatment of the last patient. Survival curves were calculated using the Kaplan-Meier method (15). Differences in survival among subgroups were evaluated with log-rank tests. Continuous variables were grouped by the median value. The Cox proportional hazards model (16) was used to determine the most significant variables related to survival. Forward and backward stepwise regression procedures based on the partial likelihood ratio were used to determine which factors were the major independent predictors of survival. The variables entered into the Cox regression included those found to be associated with survival based on the log-rank tests. For comparison of patients' clinical data, differences in continuous variables between the sub-

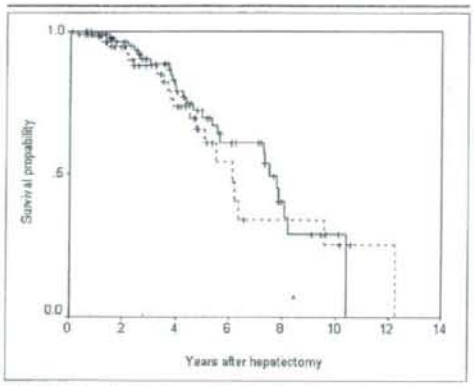

FIGURE 1 Overall survival curves after hepatectomy according to the BCLC staging. The dotted line indicates stage A1 (N=62) and the solid line indicates stages A2-A4 (N=100). There are no significant differences between them ($p=0.50$).

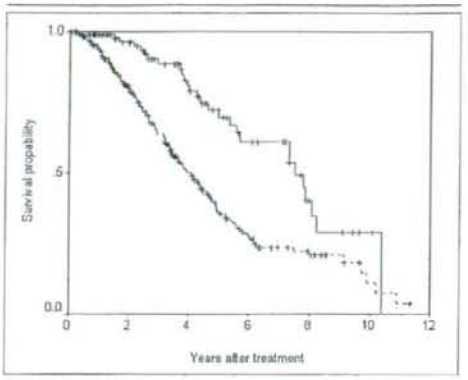

FIGURE 2 Overall survival curves in patients with BCLC stages A2-A4. The solid line indicates the hepatectomy group (N=100) and the dotted line indicates the nonhepatectomy group (N=245). The data for the 2 groups are significantly different ($p<0.001$).

groups were compared using the Mann-Whitney test. Frequency analysis was performed using the Fisher exact test for 2 x 2 tables. All the analyses were performed using the statistical software package SPSS 11.0J for Windows (SPSS Inc, Chicago, IL). Statistical significance was defined as a 2-sided p value of .05 or less.

RESULTS

Four hundred fifty-one patients met the selection criteria. The patients' clinical data are shown in **Table 2**. Of the 451 patients, it was established at the time of analysis that 192 (43%) had died and 195 (43%) were still alive, while 64 (14%) were not available for follow-up evaluation. The proportion of patients who were lost to follow-up was 22 (14%) of 162 hepatectomy patients, 42 (15%) of 289 nonhepatectomy patients, 15 (14%) of 106 patients with stage A1 and 49 (14%) of 345 patients with stages A2-A4. The median observation period (25%-75%) was 34 (18-56) months. Of the 192 patients who died, 179 (93%) died from cancer-related or hepatic failure deaths and 13 died from other causes.

Stage A1 *vs.* Stages A2-A4

The survival probability at 3, 5, 7, and 10 years was 84%, 65%, 40%, and 32%, respectively, for patients in stage A1 (N=106), and 71%, 45%, 33%, and 15%, respectively, for those in stages A2-A4 (N=345). Survival for stage A1 was significantly better than for stages A2-A4 ($p=0.005$). The proportion of patients who underwent hepatectomy with stages A1, A2, A3 and A4 was 58% (62/106), 39% (60/153), 16% (14/87) and 25% (26/105), respectively. Of 345 patients with stages A2-A4, 100 (29%) underwent hepatectomy.

TABLE 3 Comparison of Clinical Data between the Hepatectomy and Nonhepatectomy Groups for the 345 Patients with BCLC Stages A2-A4

		Hepatectomy (N=100)	Nonhepatectomy (N=245)	*p*-value
Sex	Male/female	76/24	175/70	0.426
Age	Median (range)	64 (38-78)	65 (33-86)	0.237
HBsAg†	Positive/negative	19/81	22/223	0.016
HCVAb‡	Positive/negative	69/31	212/33	<0.001
Total bilirubin (mg/dL)	Median (range)	0.9 (0.4-2.1)	1.1 (0.4-2.9)	< 0.001
Albumin (g/dL)	Median (range)	3.7 (2.9-4.4)	3.4 (2.2-4.5)	< 0.001
ICG test (%)§	Median (range)	16.6 (1.5-93.7)	31.2 (2.9-98.0)	< 0.001
Platelet (10^4/mm^3)	Median (range)	9.6 (4.5-30.8)	7.9 (2.4-32.4)	< 0.001
Prothrombin time (%)	Median (range)	77 (54-155)	72 (40-134)	0.001
Portal hypertension	Present/absent	63/37	174/71	0.160
Tumor number	Solitary/2/3	74/22/4	166/53/26	0.137
Tumor size (mm)	Median (range)	27 (11-50)	22 (7-50)	< 0.001
AFP (ng/ml) ¶	Median (range)	43 (1.3-25046)	40 (2.4-8466)	0.467

†: Hepatitis B virus surface antigen ; ‡: Hepatitis C virus antibody; §: Indocyanine green retention test at 15 minutes. The ICG test was not available for 20 patients in the nonhepatectomy group. ¶: Alpha-fetoprotein. The AFP was not available for 2 patients in the hepatectomy group.

TABLE 4 The Relationship between Clinical Data and Survival Times in Patients with BCLC Stages A2-A4

		Median survival years (95% confidence interval)	*p*-value
Sex	Male	4.94 (4.30-5.57)	0.038
	Female	3.94 (3.42-4.45)	
Age	Younger than 66	4.93 (3.75-6.11)	0.131
	66 or older	4.45 (3.70-5.21)	
HBsAg†	Negative	4.63 (4.10-5.17)	0.119
	Positive	7.47 (1.21-13.7)	
HCVAb‡	Negative	5.58 (3.20-7.96)	0.088
	Positive	4.59 (3.95-5.24)	
Total bilirubin (mg/dL)	≤1.2	5.34 (4.74-5.94)	<0.001
	>1.2	3.22 (2.29-4.16)	
Albumin (g/dL)	≤3.5	4.05 (3.54-4.56)	<0.001
	>3.5	7.47 (5.48-9.46)	
ICG test (%)§	≤22	5.74 (3.54-7.93)	<0.001
	>22	4.27 (3.55-4.99)	
Platelet (10^4/mm^3)	≤10	4.40 (3.70-5.10)	0.044
	>10	5.35 (4.08-6.63)	
Prothrombin time (%)	≤70	3.75 (2.79-4.71)	0.038
	>70	4.96 (4.29-5.64)	
Portal hypertension	Absent	6.14 (3.36-8.92)	0.264
	Present	4.63 (4.10-5.16)	
Tumor number	Solitary	4.76 (3.83-5.68)	0.138
	2 or 3	4.36 (3.35-5.37)	
Tumor size (mm)	≤30	4.63 (4.11-5.14)	0.783
	>30	5.35 (3.19-7.51)	
AFP (ng/mL) ¶	≤27	5.55 (5.12-5.97)	0.001
	>27	3.99 (3.41-4.56)	
Treatment	Hepatectomy	7.51 (6.86-8.16)	<0.001
	Nonhepatectomy	4.05 (3.51-4.59)	

†: Hepatitis B virus surface antigen ; ‡: Hepatitis C virus antibody;
§: Indocyanine green retention test at 15 minutes. The ICG test was not available for 20 patients in the nonhepatectomy group. ¶: Alpha-fetoprotein. The AFP was not available for 2 patients in the hepatectomy group.

Stage A1 *vs.* Stages A2-A4 in Hepatectomy Cases

The survival probability at 3, 5, 7, and 10 years was 88%, 66%, 34%, and 25%, respectively, for hepatectomy patients with stage A1 (N=62), and 89%, 70%, 61%, and 29%, respectively, for those with stages A2-A4 (N=100). There were no significant differences between these groups (**Figure 1**, p=0.50).

Hepatectomy *vs.* Nonhepatectomy in Stages A2-A4

Of 345 patients with stages A2-A4, 245 (71%) received nonsurgical treatments, including percutaneous ablation (N=152) and transcatheter arterial chemoembolization (N=78). The survival probability at 3, 5, 7 and 10 years was 64%, 37%, 24% and 11%, respectively, for the 245 patients. Survival for the hepatectomy group was significantly better than for the nonhepatectomy group in stages A2-A4 (**Figure 2**, p<0.001). **Table 3** shows the patients' clinical data for the hepatectomy and nonhepatectomy groups. In the hepatectomy group, patients negative for hepatitis C virus antibody, with good hepatic reserve, and with larger tumors were seen significantly more frequently than in the nonhepatectomy group.

Prognostic Factors in Stages A2-A4

The univariate analysis of the 345 patients with stages A2-A4 is shown in **Table 4**. Gender, total bilirubin, albumin, indocyanine green retention test at 15 minutes, platelet count, prothrombin time, alpha-fetoprotein and treatment (hepatectomy or not) were associated with survival by log-rank tests. Among these, hepatectomy, higher albumin level, lower total bilirubin level and lower alpha-fetoprotein level were identified as favorable independent prognostic factors by Cox regression. The same result was obtained with forward and backward analysis. **Table 5** shows the relative risk of each factor calculated by backward analysis.

Progression-Free Survival for Hepatectomy in Stages A2-A4

The progression-free survival probability at 1, 2, 3, 5 and 7 years was 79%, 51%, 32%, 21% and 15%, respectively, for 100 patients with stages A2-A4 who underwent hepatectomy. Of 64 patients with documented progression, 63 had cancer recurrence in the remnant liver and the remaining individual had hepatic failure.

DISCUSSION

Hepatocellular carcinoma patients with BCLC stages A2-A4 who meet the Milan criteria are believed to be the most favorable candidates for liver

TABLE 5 Significant Prognostic Factors as Determined by Multivariate Analysis in Patients with BCLC Stages A2-A4

		Hazard ratio (95% confidence interval)	Standard error	*p*-value
Treatment	Hepatectomy	0.487 (0.318-0.745)	0.217	0.001
	Nonhepatectomy	1		
Albumin (g/dL)	>3.5	0.584 (0.405-0.843)	0.187	0.004
	≤3.5	1		
Total bilirubin (mg/dL)	≤1.2	0.613 (0.437-0.862)	0.173	0.005
	>1.2	1		
AFP (ng/mL) †	≤27	0.709 (0.503-0.997)	0.175	0.048
	>27	1		

†: Alpha-fetoprotein

transplantation (8-12). However, hepatectomy is the main practical treatment modality for such patients in Japan because of the limited donor resource (13). The current study aimed to evaluate the treatment outcome for hepatectomy in these patients.

In this series, the 5-year survival rate after hepatectomy was 70% for patients with stages A2-A4 who met the Milan criteria, which might be comparable with liver transplantation for the same population (11,12). Although favorable factors for survival time such as lower total bilirubin and higher albumin levels were more frequently seen in the hepatectomy group than in the nonhepatectomy group with stages A2-A4, multivariate analysis showed that the treatment choice of hepatectomy was one of the independent favorable prognostic factors. Accordingly, it is likely that the good outcome after hepatectomy results from both proper patient selection and the efficacy of hepatectomy as a treatment for patients with stages A2-A4.

One limitation of this study was the difficulty in defining the criteria for hepatectomy. The feasibility of hepatectomy depends mainly on the correlation between hepatic reserve and anatomical location of the tumor(s), but these factors are difficult to characterize precisely. Regarding hepatic reserve, total bilirubin and albumin are not only prognostic factors for patients with stages A2-A4 **(Table 5)** but are also factors included in the Child-Pugh score. Of 100 patients who underwent hepatectomy, 92 were classified as Child-Pugh class A **(Table 6)**. Among patients with Child-Pugh scores of 5 and 6, 51% (53/104) and 29% (39/134) underwent hepatectomy, respectively. Hepatectomy candidates had therefore been selected mainly from those with Child-Pugh class A. However, tumor location is another factor that determines the feasibility of hepatectomy. A deeply located tumor can be difficult to resect even in patients with Child-Pugh class A, whereas for a tumor located near the liver surface it is easy to perform a partial resection. In our opinion, when considering criteria for hepatectomy, terms describing tumor location such as "deeply located (central)" or "near the liver surface (peripheral)" are inadequate. Furthermore, it can be difficult to define whether a tumor is central or peripheral in an individual patient.

Since the report of Bruix *et al.* in 1996 (17), the presence of portal hypertension has been an important factor used for identifying optimal candidates for hepatectomy. In their report, portal hypertension status was defined using the hepatic venous pressure gradient obtained from a hemodynamic study. Such hemodynamic studies are not popular in Japan and have not been carried out for hepatectomy candidates at our hospital, so portal hypertension was estimated using clinical parameters and the platelet count. We cannot rule out the possibility that portal hypertension was not a strong prognostic factor in this study because the means for estimating it did not accurately reflect the real portal pressure.

TABLE 6 The Relationship between Treatment and the Child-Pugh Classification in Patients with BCLC Stages A2-A4

Child-Pugh Class	Score	Hepatectomy	Nonhepatectomy	Total
A	5	53	51	104
	6	39	95	134
B	7	8	75	83
	8	0	15	15
	9	0	9	9
Total	100	245	354	

The outcome for the nonhepatectomy group with stages A2-A4 was not as good as for the hepatectomy group with the same stages **(Figure 2)**. There may have been some patients among the hepatectomy group who would have survived even longer if they had been treated with percutaneous ablation at the time they underwent hepatectomy (18,19). However, we suggest that of all the patients with stages A2-A4, the nonhepatectomy group would receive the maximum benefit from liver transplantation.

Liver transplantation appears to give the best chance for recurrence-free survival, given that in this series the recurrence rate after hepatectomy reached 70% within 3 years. However, the supply of donated liver for the treatment of HCC is limited worldwide. Given this situation, and based on the findings of this study, we propose that patients with stages A2-A4 should not be uniformly assigned to liver transplantation as a first-line surgical intervention. Even in stages A2-A4, there are a considerable number of patients for whom hepatectomy is a reasonable first-line treatment, particularly among patients with Child-Pugh class A. In this population, salvage transplantation for recurrence after primary hepatectomy might be a reasonable strategy (20,21).

In conclusion, hepatectomy may be an appropriate treatment option for patients with stages A2-A4 who meet the Milan criteria, especially when they have a good hepatic reserve and when there is a long waiting time for liver transplantation.

REFERENCES

1 **Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al:** AJCC cancer staging manual. 6th Edition. New York: Springer-Verlag, 2002.

2 **Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al:** Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985; 56:918-928.

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; 28:751-755.

4 **Liver Cancer Study Group of Japan:** General rules for the clinical and pathological study of primary liver cancer. 2nd English Edition. Tokyo: Kanehara, 2003.

5 **Kudo M, Chung H, Osaki Y:** Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003; 38:207-215.
6 **Tateishi R, Yoshida H, Shiina S, Imamura H, Hasegawa K, Teratani T, et al:** Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. Gut 2005; 54:419-425.
7 **Llovet JM, Bru C, Bruix J:** Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19:329-338.
8 **Bruix J, Llovet JM:** Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002; 35:519-524.
9 **Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al:** Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35:421-430.
10 **Bruix J, Sherman M:** Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42:1208-1236.
11 **Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al:** Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334:693-699.
12 **Llovet JM, Schwartz M, Mazzaferro V:** Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 2005; 25:181-200.
13 **Todo S, Furukawa H, Japanese Study Group on Organ Transplantation:** Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg 2004; 240:451-461.
14 **Kawashima M, Furuse J, Nishio T, Konishi M, Ishii H, Kinoshita T, et al:** Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol 2005; 23:1839-1846.
15 **Kaplan EL, Meier P:** Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 63:457-481.
16 **Cox DR:** Regression models and life-tables [with discussion]. J R Stat Soc 1972; 34B:187-220.
17 **Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al:** Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996; 111:1018-1022.
18 **Yamamoto J, Okada S, Shimada K, Okusaka T, Yamasaki S, Ueno H, et al:** Treatment strategy for small hepatocellular carcinoma: comparison of long-term results after percutaneous ethanol injection therapy and surgical resection. Hepatology 2001; 34:707-713.
19 **Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ, Lau WY:** A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006; 243:321-328.
20 **Poon RT, Fan ST, Lo CM, Liu CL, Wong J:** Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002; 235:373-382.
21 **Margarit C, Escartin A, Castells L, Vargas V, Allende E, Bilbao I:** Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl 2005; 11:1242-1251.

Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma

Junji Furuse,[1,3] Hiroshi Ishii,[1] Kohei Nakachi,[1] Eiichiro Suzuki,[1] Satoshi Shimizu[1] and Keiko Nakajima[2]

[1]Division of Hepatobiliary and Pancreatic Medical Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, [2]Bayer Yakuhin, 3-5-36 Miyahara, Yodogawa-ku, Osaka 532-8577, Japan

(Received July 31, 2007/Revised September 13, 2007/Accepted September 20, 2007/Online publication October 22, 2007)

Sorafenib is an orally active multikinase inhibitor that targets serine and threonine, and tyrosine kinases that are involved in tumor-cell signal transduction and tumor angiogenesis. This phase I trial was conducted to evaluate the pharmacokinetics (PK), safety, and preliminary efficacy of sorafenib in Japanese patients with hepatocellular carcinoma (HCC) with underlying liver dysfunction. Patients with unresectable HCC, Child–Pugh status A or B, and adequate organ functions were treated. A single dose of sorafenib was administered, followed by a 7-day wash-out period, after which patients received either sorafenib 200 mg (cohort 1) or 400 mg (cohort 2) twice daily. The PK were investigated after a single dose and during steady state. The efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors. A total of 27 patients were evaluated for PK, safety, and efficacy. Although both area under the concentration–time curve for 0–12 h and maximal concentration at steady state were slightly lower in Child–Pugh B patients than in Child–Pugh A patients, the difference was not considered to be clinically relevant. Common adverse drug events included elevated lipase, amylase, rash or desquamation, diarrhea, and hand–foot skin reaction. A dose-limiting toxicity of hand–foot skin reaction was observed in one patient (cohort 2). Among the 24 patients evaluable for tumor response, one patient (4%) achieved a partial response, 20 (83%) had stable disease, and three (13%) had progressive disease. Sorafenib demonstrated a favorable tolerability and safety profile in Japanese HCC patients. Moreover, promising preliminary antitumor activity has been observed. Finally, there were no clinically relevant differences in PK between Child–Pugh A and B patients. (*Cancer Sci* 2008; 99: 159–165)

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Surgery and local ablation therapy, including radiofrequency, are considered curative treatment for HCC.[1–3] Transcatheter arterial chemoembolization (TACE) has been applied to patients with advanced incurable HCC.[3–5] The majority of patients, however, have recurrence or metastasis after these treatments. Although systemic therapy, including chemotherapeutic agents, is available for metastatic or TACE-refractory advanced HCC, the prognosis remains poor. No standard systemic therapy that prolongs survival has been identified.

Sorafenib (BAY 43-9006; Bayer HealthCare Pharmaceuticals, West Haven, CT, USA) was discovered based on its potent activity against Raf kinase in a battery of biochemical, cellular, and *in vivo* assays.[6,7] Extensive mechanism of action studies have shown that sorafenib may inhibit tumor growth through multiple mechanisms: by inhibiting tumor-cell proliferation that is dependent on activation of the mitogen-activated protein kinase (MAPK) pathway, and by inhibiting tumor angiogenesis through inhibition of vascular endothelial growth factor receptor (VEGFR)-2 and platelet-derived growth factor receptor (PDGFR)-β. Some evidence points to the MAPK signal-transduction pathway as playing an important role in tumor growth and progression in HCC.[8] Published data suggest that vascular endothelial growth factor (VEGF) also plays a critical role in angiogenesis of HCC, which is important for the growth and progression of HCC.[9] Sorafenib has been investigated in various solid tumors in clinical studies[10–15] and has been approved in many countries for the treatment of renal cell carcinoma. Promising results with sorafenib were recently observed in a phase II study in HCC patients.[15]

Various factors, such as liver function or disease extension, influence treatment selection and prognosis for HCC.[2,3,16] Etiology, underlying condition, and treatment for HCC vary across countries or regions.[2,3,17] Most HCC patients in Japan have hepatitis or cirrhosis due to hepatitis B or C virus[2] and suffer from complications of liver dysfunction, with potential changes in the activity of metabolic enzymes, a reduction in blood flow in the liver, or protein-binding ability due to low serum albumin. However, the degree of influence of these factors on the pharmacokinetics (PK) and tolerability of sorafenib in Japanese patients with HCC is unknown. A phase I study in Japanese patients with advanced solid tumors was conducted before the present study,[18] and found that sorafenib at 400 mg b.i.d. was well tolerable and recommended for phase II studies based on safety and efficacy data. To investigate the effect of liver dysfunction and its complications on the PK, safety, and tolerability of sorafenib in Japanese patients with HCC, a phase I study was conducted. The primary objective of the present study was to evaluate the PK of sorafenib, and the secondary objectives were to evaluate the safety and tolerability of sorafenib, tumor response, time to progression (TTP), and overall survival in Japanese patients with HCC.

Materials and Methods

Patient eligibility. The eligibility criteria for enrolment in the study were: (1) histologically confirmed HCC; (2) unresectable and incurable with ablation therapy or TACE; (3) age ≥ 20 years; (4) Eastern Cooperative Oncology Group performance status of 0 or 1; (5) adequate bone marrow (absolute neutrophil count ≥ 1500 cells/mm^3, platelet count ≥ 75 000 cells/mm^3, and hemoglobin ≥ 8.0 g/dL), coagulation (prothrombin time ≤ 1.5 × upper limit of normal [ULN] and activated partial thromboplastin time ≤ 1.5 × ULN), renal function (serum creatinine concentration ≤ 1.5 × ULN), and hepatic function (serum total bilirubin level ≤ 3.0 mg/dL, serum aspartate and alanine transaminase levels ≤ 5.0 × ULN); (6) cirrhotic status of Child–Pugh A or B; (7) life expectancy of at least 12 weeks; and (8) written informed consent from the patient.

Exclusion criteria included clinically evident congestive heart failure, serious cardiac arrhythmias, active or symptomatic coronary artery disease or ischemia, active clinically serious infections, seizure disorder requiring medication, history of organ allograft, prior malignancy (any cancer treated curatively

[3]To whom correspondence should be addressed. E-mail: jfuruse@east.ncc.go.jp

doi: 10.1111/j.1349-7006.2007.00648.x

>3 years prior to entry was not excluded), metastatic brain or meningeal tumors, anticancer therapy within 3 months of study entry, and pregnancy or lactation for women. This protocol was approved by the National Cancer Center's institutional review board for clinical investigation with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

Treatment methods. The dose for the first cohort was 200 mg bid sorafenib, and the dose for the second cohort was escalated to 400 mg bid. To investigate the PK profile of sorafenib, including its elimination phase, a single dose was given as one-time administration followed by a 7-day wash-out period. Subsequently, the drug was given twice daily for 28 days without a resting period (cycle 1). Either 200 mg or 400 mg sorafenib was given to all patients orally twice daily, in the morning and in the evening (every 12 h as far as possible). Patients were allowed to continue on sorafenib after cycle 1 if they consented to continue, and no intolerable adverse event was experienced, as assessed by investigators. Treatment was continued until disease progression, intolerable adverse event, or consent of withdrawal.

Examination and observation for safety was conducted every 2 weeks, and administration of the drug was to be terminated immediately when the patient met the criteria for removal from the study, described in this protocol with due consideration for the patient's safety.

Study design. The present study was a non-randomized, uncontrolled, non-blinded, single-center phase I study to investigate the PK, safety, and tolerability of sorafenib in Japanese patients with HCC. The dose level investigated in this study was 200 mg bid for the first cohort and 400 mg bid for the second cohort. Twelve patients, including six with Child–Pugh A and six with Child–Pugh B, were to be enrolled in each cohort. Tolerability was evaluated at the end of cycle 1 by Child–Pugh classification. If less than two out of six patients experienced dose-limiting toxicity (DLT) in the 200-mg bid cohort, the study would proceed to the 400-mg bid cohort. DLT that needed dose modification was defined as: (1) grade 3 and grade 4 non-hematological toxicity, except for pancreatic enzyme abnormality and hand–foot skin reaction; (2) grade 4 pancreatic enzyme elevation with values that persisted on two consecutive determinations with a 3-day interval, or clinical and/or imaging findings of pancreatitis, or pancreatic adverse event considered to be life threatening, or having a high risk of serious or chronic disorders; (3) severe hand–foot skin reaction, moist desquamation, ulceration, blistering, or severe pain of the hands or feet, or severe discomfort that caused the patient to be unable to work or carry out the activities of daily living; (4) grade 4 neutropenia (absolute neutrophil count less than 500/μL) for 7 days duration; (5) grade 4 neutropenia of any duration with fever of 38.5°C and above; and (6) platelet count < 25 000 cells/mm^3. Toxicity was graded according to the National Cancer Institute common toxicity criteria version 2.0. The independent safety committee for this study gave advice on the evaluation of tolerability of the dose level and the cohort transition.

Pharmacokinetics. All patients who received at least one dose of study medication were included in the PK analysis. Blood samples for the determination of plasma concentrations of sorafenib (and its metabolites) were collected prior to drug administration, as well as 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h after single-dose administration. For the first cycle, blood was sampled prior to the first dosing on days 1, 4, 7, 10, 14, 21, and 28, along with 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h after the first dose on days 14 and 28. Urine voided up to 48 h after single administration was collected.

Concentrations of sorafenib and its metabolites in plasma and urine were determined using validated liquid chromatography and tandem mass spectrometry methods. Plasma PK parameters were calculated by non-compartment analysis by the KINCALC program (Bayer HealthCare Pharmaceuticals).[10] Primary plasma PK parameters were area under the concentration–time curve (AUC), AUC for 0–12 h (AUC_{0-12}), and maximal concentration (C_{max}). Plasma concentrations and PK parameters were analyzed by dose and Child–Pugh classification.

Clinical assessments. Physical examination, complete blood cell counts, serum chemistries, and urinalysis were carried out at baseline and at least twice monthly after initiating treatment with sorafenib. Patients underwent dynamic computed tomography (CT) to evaluate tumor response at baseline, the end of cycle 1, and every two cycles thereafter. CT was carried out by obtaining contiguous transverse sections with the helical scanning method at a section thickness of 5 mm. Tumor evaluation was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST).[19]

Statistical analysis. The data were analyzed using SAS (SAS Institute, Cary, NC, USA). The safety and efficacy were evaluated on an intention-to-treat basis. Progression-free survival was calculated from the first day of treatment until evidence of tumor progression, clinical progression, or death due to any cause. Overall survival was calculated from the first day of treatment until death due to any cause. Survival data were analyzed using the Kaplan–Meier method.

Results

Patient characteristics and treatments. From April 2004 through January 2005, a total of 27 patients were enrolled in the present study. Thirteen patients were enrolled at the treatment level of 200 mg (cohort 1) and 14 at the treatment level of 400 mg (cohort 2) twice daily (b.i.d.) for 28 days (cycle 1). One out of 13 patients in cohort 1 discontinued the study due to consent withdrawal after single-dose administration. One out of 14 patients in cohort 2 dropped out of this study due to adverse events during cycle 1. Patient characteristics are shown in Table 1. The median number of cycles administered per patient was five (range, 1–13 cycles). None of the patients from the 200-mg group reduced the dose of sorafenib, whereas two patients required dose reduction in the 400-mg group.

Evaluation of PK. Plasma drug concentrations were analyzed in 27 patients in the PK analysis. Plasma PK parameters of patients in the 200 and 400 mg bid groups are shown in Tables 2 and 3. There was a large interpatient variability in the PK of sorafenib. Geometric means of AUC, AUC_{0-12}, and C_{max} on day 1 of single-dose administration were not statistically different between 200 and 400 mg bid or between Child–Pugh A and B. Dose-dependent increases in AUC_{0-12} and C_{max} were observed at steady state (day 14) in the 200-mg bid and 400-mg bid patients; however, these increases were not dose proportional. Geometric means of AUC_{0-12} and C_{max} were slightly lower in the Child–Pugh B patients compared with the Child–Pugh A patients at steady state. The $t_{1/2}$ after single dose was similar between the Child–Pugh A and B groups for both dose levels.

Dose-dependent increases in the AUC_{0-12} and C_{max} of metabolites M-2 (*N*-oxide), M-4 (*N*-demethyl), and M-5 (*N*-oxide, desmethyl derivative) were observed. M-2 was the main metabolite in plasma. Ratios of each metabolite to the sum of all analytes were similar between the 200-mg bid and 400-mg bid patients and for baseline Child–Pugh class (Tables 2,3). M-7 (glucuronide of sorafenib) and M-8 (glucuronide of M-2) were detected in urine though no unchanged substance or M-2 was detected. There was no difference between the Child–Pugh A (1.21% for M-7 and 0.02% for M-8 at 400 mg) and B (1.18% and 0.02%, respectively, at 400 mg) groups in the urinary excretion rate of compounds at steady state. Interestingly, these PK results were similar to those obtained from the Japanese phase I study in non-HCC tumors.[18]

Adverse events. Adverse events of all 27 patients are shown in Table 4. Twenty-six out of 27 patients (96.3%) experienced an adverse event: 12 out of 13 patients (92.3%) in the 200-mg

doi: 10.1111/j.1349-7006.2007.00648.x

Table 1. Patient characteristics

Characteristic	200 mg bid (n = 13)	400 mg bid (n = 14)	Total (n = 27)
Sex (n)			
Male	12	13	25
Female	1	1	2
Median age (years)	69 (range 48–77)	70 (range 63–79)	70 (range 48–79)
Eastern Cooperative Oncology Group performance status			
0	13	14	27
Child–Pugh classification			
A	7	6	13
B	6	8	14
Viral markers			
HB antigen$^+$, HCV antibody$^-$	3	1	4
HB antigen$^-$, HCV antibody$^+$	9	11	20
HB antigen$^-$, HCV antibody$^-$	1	2	3
Previous treatment			
–	1	3	4
+	12	11	23
Tumor stage			
II	1	2	3
III	7	8	15
IVa	1	1	2
IVb	4	3	7
Portal vein tumor thrombus			
–	12	13	25
+	1	1	2
Metastasis			
–	9	11	20
+	4	3	7
Lung	3	1	4
Lung + lymph node	1	1	2
Lymph node	0	1	1

HB, hepatitis B; HCV, hepatitis C virus.

Table 2. Pharmacokinetic parameters of sorafenib and metabolites M-2, M-4, and M-5: sorafenib following single dose and multiple dose of 200 mg and 400 mg geometric mean (coefficient of variation)

Sorafenib	Parameter	Unit	200 mg bid				400 mg bid			
			Child–Pugh A		Child–Pugh B		Child–Pugh A		Child–Pugh B	
Single	n		7		6		6		8	
Dose	AUC	mg*h/L	28.29	190.29[1]	18.64	74.1	20.33	90.31	26.87	96.97
Day 1	AUC_{0-12}	mg*h/L	5.02	190.36	2.75	61.06	3.82	86.06	3.11	88.16
	C_{max}	mg/L	0.81	195.96[1]	0.49	67.85	0.55	83.75	0.53	86.68
	T_{max}	h[1]	7	3–12[1]	18	4–24	8	6–24	24	4–24
	$T_{1/2}$	H	25.14	30.13[1]	30.44	35.67	22.28	12.49	27.2	45.19
Cycle 1	N		6		6		6		6	
Day 14	AUC_{0-12}	mg*h/L	25.52	75.04	15.28	55.26	33.47	60.13	29.45	59.44[1]
	C_{max}	mg/L	3.36	87.29	1.89	62.14	4.66	66.12	3.04	94.39
Cycle 1	N		6		6		6		5	
Day 28	AUC_{0-12}	mg*h/L	31.63	101.64	20	73.4	28.91	86.79	20.71	72.06
	C_{max}	mg/L	4.22	92.32	3.32	78.65	3.32	113.47	4.01	79.12

[1]Median (range), [1]n = 6, [1]n = 5. AUC_{0-12}, area under the concentration–time curve for 0–12 h.

group and 14 out of 14 patients (100%) in the 400-mg group. The most common drug-related adverse events were elevated lipase or amylase (88.9%), dermatological events (81.5%), and gastrointestinal events (70.4%). Common dermatological events were rash or desquamation (55.6%), and hand–foot skin reaction (44.4%). The incidence of adverse events in the 400-mg dose level was higher than that in the 200-mg dose level by ≥20%. These events fell under the categories of dermatology/skin (100.0 *vs* 61.5%), general cardiovascular (35.7 *vs* 7.7%), and renal/genitourinary (21.4 *vs* 0%).

Elevation of lipase and amylase was transient in most of the cases, and decreased gradually in all patients without treatment. One patient on 400 mg bid experienced acute pancreatitis that necessitated sorafenib withdrawal. The patient experienced abdominal pain 6 months after beginning treatment (cycle 6). Moreover, high lipase and amylase, as assessed by blood test,

Table 3. Pharmacokinetic parameters of sorafenib and metabolites M-2, M-4, and M-5: metabolites following multiple dose of 200 mg and 400 mg, measured at steady state (cycle 1, day 14) geometric mean (% coefficient of variation)

Parameter	200 mg bid			400 mg bid		
	M-2	M-4	M-5	M-2	M-4	M-5
Child–Pugh A						
n	6	6	6	6	6	6
AUC_{0-12} (mg × h/L)	4.18 (126)	0.92 (158)	0.79 (167)	6.18 (127)	1.68 (159)	1.22 (193)
Ratio[1] (%)	13.08 (30)	2.89 (60)	2.48 (81)	14.16 (39)	3.85 (55)	2.79 (85)
Child–Pugh B						
n	6	5	4	5	5	5
AUC_{0-12} (mg × h/L)	1.62 (173)	0.36 (131)	0.44 (351)	5.67 (90)	2.13 (142)	1.25 (117)
Ratio[1] (%)	9.05 (67)	1.85 (42)	1.95 (157)	14.46 (36)	5.44 (56)	3.19 (47)

[1]Median ratio of each metabolite to sum of all analytes. BAY 43-9006: M-2, BAY 67-3472; M-4, BAY 43-9007; and M-5, BAY 68-7769. AUC_{0-12}, area under the concentration–time curve for 0–12 h.

Table 4. Adverse events

Child–Pugh	Grade 3/4				All grades			
	200 mg bid		400 mg bid		200 mg bid		400 mg bid	
	A (*n* = 7)	B (*n* = 6)	A (*n* = 6)	B (*n* = 8)	A (*n* = 7)	B (*n* = 6)	A (*n* = 6)	B (*n* = 8)
Hematological								
Leukocytopenia	0	0	0	0	2 (29%)	0	1 (17%)	0
Lymphopenia	2 (29%)	1 (17%)	1 (17%)	1 (13%)	2 (29%)	1 (17%)	1 (17%)	2 (25%)
Platelets	0	0	1 (17%)	1 (13%)	0	1 (17%)	2 (33%)	3 (38%)
Non-hematological								
Hypertension	0	1 (17%)	1 (17%)	3 (38%)	0	1 (17%)	1 (17%)	3 (38%)
Fatigue	0	0	0	0	0	1 (17%)	0	0
Fever	0	0	0	0	1 (14%)	2 (33%)	0	1 (13%)
Weight loss	0	0	0	0	2 (29%)	1 (17%)	1 (17%)	4 (50%)
Hand–foot skin reaction	0	0	0	2 (27%)	2 (29%)	2 (33%)	5 (83%)	3 (38%)
Rash	0	0	0	2 (27%)	2 (29%)	3 (50%)	4 (67%)	6 (75%)
Alopecia	0	0	0	0	2 (29%)	1 (17%)	2 (33%)	0
Dry skin	0	0	0	0	0	0	0	3 (38%)
Pruritus	0	0	0	0	0	1 (17%)	4 (67%)	3 (38%)
Anorexia	0	0	0	0	2 (29%)	1 (17%)	1 (17%)	2 (25%)
Diarrhea	0	0	1 (17%)	0	4 (57%)	4 (67%)	2 (33%)	5 (63%)
Stomatitis	0	0	0	0	0	0	1 (17%)	2 (25%)
Lipase	3 (43%)	4 (67%)	4 (67%)	6 (75%)	6 (86%)	6 (100%)	6 (100%)	6 (75%)
Amylase	1 (14%)	1 (17%)	1 (17%)	1 (13%)	4 (57%)	3 (50%)	4 (67%)	5 (63%)

and swelling of the pancreas were observed. The patient's abdominal pain resolved 1 day after stopping sorafenib, and lipase and amylase normalized 2 days later. Sorafenib was restarted 20 days after resolution and continued over 122 days, without recurrence of pancreatitis.

Grade 3 or worse drug-related adverse events were observed in 23 patients (85.2%), the majority of which were related to laboratory abnormalities: 10 patients in the 200-mg group and 13 in the 400-mg group. One patient with Child–Pugh B in the 400-mg bid group experienced DLT of hand–foot skin reaction at the end of cycle 1. There were no drug-related deaths in either of the groups.

There was no major difference in the incidence and grade of drug-related adverse events between the Child–Pugh A and B groups. At the dose level of 200 mg, the drug-related adverse event whose incidence was at least 20% higher in the Child–Pugh B group than in the Child–Pugh A group was rash or desquamation (50.0 *vs* 28.6%). The differences at the 400-mg dose level were diarrhea (62.5 *vs* 33.3%), weight loss (50.0 *vs* 16.7%), hypertension (37.5 *vs* 16.7%), dry skin (37.5 *vs* 0%), and fatigue (25.0 *vs* 0%).

Table 5. Tumor response

Response	200 mg bid (*n* = 13)	400 mg bid (*n* = 14)	Total (*n* = 27)
Partial response	1	0	1 (3.7%)
Stable disease	10	11	21 (77.8%)
Progressive disease	1	2	3 (11.1%)
NA	1	1	2 (7.4%)

NA, not assessed because these patients did not complete cycle 1.

Tumor response and survival. Partial response was achieved in one of the 27 patients. No complete response was observed (Table 5; Fig. 1). The overall response rate was 3.7% (95% confidence interval, 0.1–14.0%). Stable disease was noted in 21 patients (77.8%) and the disease control rate (partial response + stable disease rate) was 81.5% in 27 patients. Progressive disease was noted in three patients (11.1%).

Disease progression or death was observed in all patients. Sixteen of the 27 patients died of disease progression, and two

doi: 10.1111/j.1349-7006.2007.00648.x

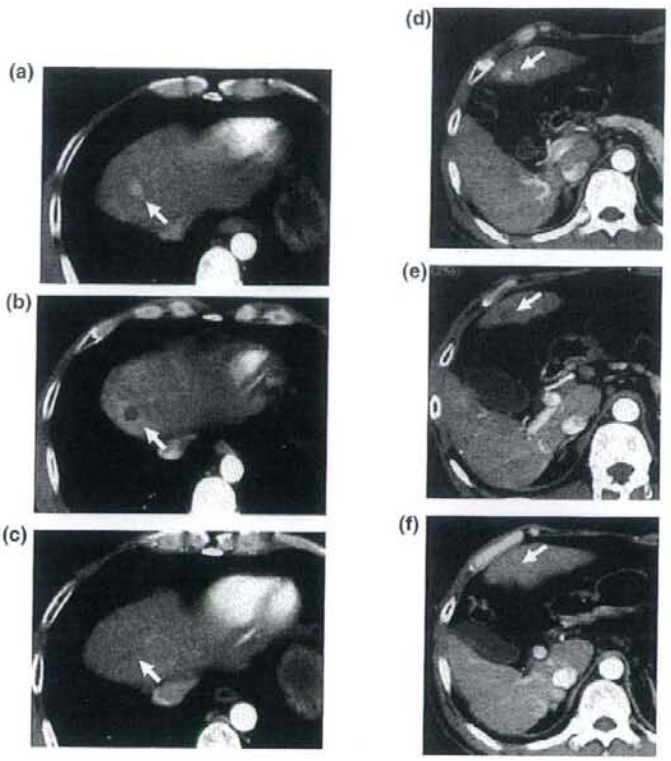

Fig. 1. A 48-year-old man with multiple tumors of hepatocellular carcinoma (HCC) after hepatectomy, percutaneous ethanol injection, and transcatheter arterial embolization. (a) Hypervascular HCC lesion, 1 cm in diameter, was revealed at the early phase of dynamic computed tomography (CT) before administration of sorafenib at the anterior superior segment of the liver (arrow). (b) The vascularity of this tumor disappeared 1 month after the administration of sorafenib. (c) The tumor was reduced 3 months after the administration of sorafenib. (d) Another hypervascular HCC lesion, 1 cm in diameter, was revealed at the early phase of dynamic CT before administration of sorafenib in the left lobe of the liver (arrow). (e) The vascularity of this tumor disappeared 8 months after the administration of sorafenib. (f) The tumor almost completely disappeared 10 months after the administration of sorafenib.

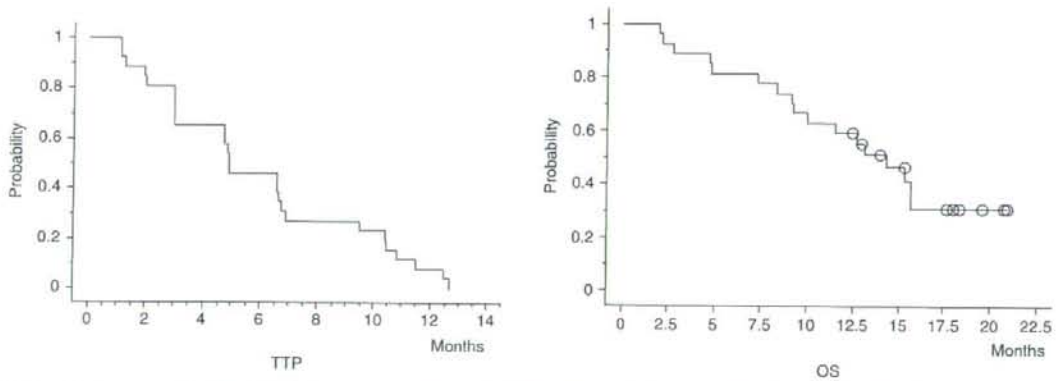

Fig. 2. Time to progression (TTP) in all 27 patients treated with sorafenib. The median TTP was 4.9 months, and the 6-month survival rate was 46.2%. Overall survival (OS) in the 27 patients treated with sorafenib. The median OS period was 15.6 months, and the 1-year survival rate was 59.3%.

died of cerebral infarction or myocardial infarction. Of the 27 patients, the median TTP was 4.9 months, and the median overall survival (OS) was 15.6 months (Fig. 2). The 6-month progression-free rate based on TTP was 46.2%, and 1- and 2-year OS were 59.3 and 30.9%, respectively.

Discussion

The PK, safety, and tolerability of sorafenib were investigated in Japanese patients with HCC treated with doses of 200 mg bid or 400 mg bid.

Most of the HCC patients had hepatitis or cirrhosis with underlying liver disorder and a reduction in hepatic blood flow to various degrees. Liver dysfunction in patients with HCC may affect the PK of sorafenib. When comparing the PK by Child–Pugh classification, geometric means of AUC_{0-12} and C_{max} at steady state were lower in the Child–Pugh B group than in the Child–Pugh A group, whereas after multiple doses of sorafenib, the mean plasma concentrations were highly variable and showed no clear dose dependency. Although the numerical differences in geometric means for PK parameters such as AUC, C_{max}, and $t_{1/2}$ were observed between Child–Pugh classifications, these differences were considered not to be clinically relevant in consideration of their large intersubject variability. No significant difference in clinical findings between these two groups was observed. There was also no major difference (i.e. over 20%) in the incidence of adverse events between Child–Pugh A and B groups. However, geometric means of AUC_{0-12} and C_{max} at steady state were slightly lower in the Child–Pugh B patients compared with the Child–Pugh A patients.

There were no remarkable differences in the overall incidence of adverse events for each dose level (92% for the 200-mg group and 100% for the 400-mg group). For a few drug-related adverse events, the incidences were at least 20% higher in the 400-mg group than in the 200-mg group, including rash or desquamation (71.4 *vs* 38.5%), hand–foot skin reaction (57.1 *vs* 30.8%), pruritus (50.0 *vs* 7.7%), decrease of platelets (35.7 *vs* 7.7%), hypertension (28.6 *vs* 7.7%), dry skin (21.4 *vs* 0%), and stomatitis or pharyngitis (21.4 *vs* 0%). DLT of hand–foot skin reaction was observed in a patient with Child–Pugh B at the end of cycle 1 with 400 mg bid, whereas no DLT was observed in the 200-mg bid group.

The most common drug-related adverse events were elevated lipase (88.9%) and amylase (59.3%). Twenty-four (88.9%) of the 27 patients showed high values of grade 3 or worse. Most of the patients were asymptomatic and only one patient had abdominal pain with findings to indicate pancreatitis on ultrasonography during cycle 6. His pancreatitis resolved shortly after discontinuation of sorafenib, and the patient restarted and continued with a reduced dose of sorafenib after recovery.

A separate phase I clinical study was carried out to evaluate the safety of sorafenib in patients with solid tumor, excluding HCC, at doses of 100, 200, 400, and 600 mg bid.[18] In that study, the most common type of adverse events included skin reaction, elevation of pancreatic enzyme, and gastrointestinal (GI) toxicity such as diarrhea. In the current study, a similar pattern of adverse events was observed. These results suggest that 'gastrointestinal' and 'dermatology/skin' are common adverse events regardless of cancer type and liver function status. One finding to note is that the incidence of elevation (grade 3/4) of lipase (63.0%) or amylase (14.8%) in the present study in HCC patients was higher than that observed in non-HCC patients (lipase 23% and amylase 10%).[18]

In summary, the present study showed no clinically significant difference in PK, safety, tolerability, or efficacy by Child–Pugh status or between HCC patients and non-HCC patients, whereas some dose dependency in adverse events was observed.

Investigations into cytotoxic agents for HCC have been conducted.[20,21] However, no standard chemotherapy has been established. Recently, a number of agents targeting growth factors were investigated in HCC. Through these investigations, it was indicated that epidermal growth factor receptor/human epidermal growth factor receptor 1 (EGFR/HER1) is actively expressed in human hepatoma cells.[22,23] Erlotinib, which is an EGFR/HER1 tyrosine kinase inhibitor, and lapatinib, which is an EGFR/HER1 and ErbB-2 (Her2/neu) dual tyrosine kinase inhibitor, have been investigated in phase II studies in HCC patients.[24–26] For erlotinib, the response rate was 4–9%, the median TTP was 2.1–3.2 months, and the OS was 5.8–13 months,[24,25] whereas for lapatinib, the response rate was 0%, and the median progression-free survival time was 1.8 months.[26]

Hepatocellular carcinoma, given its hypervascular characteristics, may be sensitive to antiangiogenic agents.[9] It is known that VEGF augments the development and metastasis of HCC. Bevacizumab, a monoclonal antibody against VEGF, has been investigated in phase II studies.[27] The response rate with bevacizumab was 10% and the disease control rate was 80%. A combination of gemox (gemcitabine plus oxaliplatin) and bevacizumab showed a better response rate of 20%.[28]

Sorafenib, an orally active multikinase inhibitor, blocks tumor-cell proliferation by targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an antiangiogenic effect by targeting VEGFR-2, VEGFR-3, and PDGFR-β tyrosine kinases. In phase II studies in non-Japanese and Japanese HCC patients, comparable median TTP of 4.2 and 4.9 months, respectively, and response rates of 2 and 4%, respectively, were shown.[15] However, OS in the two studies were different: 9.2 months in the non-Japanese study and 15.6 months in the Japanese study. Difference in backgrounds such as liver function or treatment after progression may play a role in this discrepancy in survival time.

In the current study, one patient achieved partial response (Fig. 1). The patient had several small viable HCC lesions after hepatectomy, percutaneous ethanol injection, and TACE. Following administration of sorafenib, tumor vascularity decreased dramatically preceding a gradual tumor reduction. Time to tumor shrinking varied across lesions, ranging from 1 to 8 months after initiation of treatment with sorafenib. It is likely that, with anti-VEGF agents such as sorafenib, it may take time to achieve tumor reduction to meet partial response by RECIST, whereas the duration of stable disease may persist due to its tumor stabilization activity.

With the relatively long TTP of VEGF pathway-targeting agents such as bevacizumab or sorafenib, these agents may have antitumor effects on HCC and prolong survival. With its profile of tumor stabilization and tolerability, sorafenib may be applicable not only for advanced HCC but also for the adjuvant setting after curative treatment, such as surgery or radiofrequency ablation therapy.

In conclusion, in the present phase I study, sorafenib demonstrated favorable safety and tolerability, and promising preliminary antitumor activity in Japanese HCC patients. Considering that DLT was observed in one of 14 patients treated with 400 mg bid, 400 mg bid could also be recommended for future studies in Japanese HCC patients, as well as non-HCC Japanese and Caucasian patients. However, as the number of patients was limited in this phase I study, a confirmatory study will be required with a larger number of patients.

Acknowledgments

This study was supported by Bayer Yakuhin.

References

1 Ryu M, Shimamura Y, Kinoshita T *et al*. Therapeutic results of resection, transcatheter arterial embolization and percutaneous transhepatic ethanol injection in 3225 patients with hepatocellular carcinoma: a retrospective multicenter study. *Jpn J Clin Oncol* 1997; **27**: 251–7.

2 Okuda K, Mitchell DG, Itai Y *et al*. Hepatobiliary disease. *Primary Malignant Tumors of the Liver*. London: Blackwell Science, 2001: 343–89.

3 Bruix J, Sherman M, Llovet JM *et al*. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421–30.

doi: 10.1111/j.1349-7006.2007.00648.x

4 Llovet JM, Real MI, Montana X *et al*. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **18**: 1734–9.
5 Takayasu K, Arii S, Ikai I *et al*. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology* 2006; **131**: 461–9.
6 Wilhelm S, Chien DS. BAY 43-9006: preclinical data. *Curr Pharm Des* 2002; **8**: 2255–7.
7 Hotte SJ, Hirte HW. BAY 43-9006: early clinical data in patients with advanced solid malignancies. *Curr Pharm Des* 2002; **8**: 2249–53.
8 Huynh H, Nguyen TT, Chow KH *et al*. Overexpression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: Its role in tumor progression and apoptosis. *BMC Gastroenterol* 2003; **3**: 19.
9 Pang R, Poon RTP. Angiogenesis and antiangiogenic therapy in hepatocellular carcinoma. *Cancer Lett* 2006; **242**: 151–67.
10 Strumberg D, Richly H, Hilger RA *et al*. Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J Clin Oncol* 2005; **23**: 965–72.
11 Moore M, Hirte HW, Siu L *et al*. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. *Ann Oncol* 2005; **16**: 1688–94.
12 Awada A, Hendlisz A, Gil T *et al*. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumors. *Br J Cancer* 2005; **92**: 1855–61.
13 Tong FK, Chow S, Hedley D. Pharmacodynamic monitoring of BAY 43-9006 (Sorafenib) in phase I clinical trials involving solid tumor and AML/MDS patients, using flow cytometry to monitor activation of the ERK pathway in peripheral blood cells. *Cytometry B Clin Cytom* 2006; **70**: 107–14.
14 Ratain MJ, Eisen T, Stadler WM *et al*. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**: 2505–12.
15 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.
16 The Liver Cancer Study Group of Japan. Primary liver cancer in Japan: Clinicopathologic features and results of surgical treatments. *Ann Surg* 1990; **211**: 277–87.
17 Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002; **35**: 519–24.
18 Minami H, Kawada K, Ebi H *et al*. A phase I study of BAY 43-9006, a dual inhibitor of Raf and VEGFR kinases, in Japanese patients with solid cancers. *J. Clin. Oncol. 2005 Proc. Am. Soc. Clin. Oncol.* 2005; **23** (Suppl.): 207s (abstract 3062).
19 Therasse P, Arbuck SG, Eisenhauer EA *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
20 Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma: A prospective randomized trial. *Cancer* 1988; **62**: 479–83.
21 Yeo W, Mok TS, Zee B *et al*. A randomized phase III study of doxorubicin versus cisplatin/interferon α-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005; **97**: 1532–8.
22 Kaneko Y, Shibuya M, Nakayama T *et al*. Hypomethylation of c-myc and epidermal growth factor receptor genes in human hepatocellular carcinoma and fetal liver. *Jpn J Cancer Res* 1985; **76**: 1136–40.
23 Hung WC, Chuang LY, Tsai JH *et al*. Effects of epidermal growth factor on growth control and signal transduction pathways in different human hepatoma cell lines. *Biochem Mol Biol Int* 1993; **30**: 319–28.
24 Thoma MB, Dutta A, Brown T *et al*. A phase II open-label study of OSI-774 (NSC 718781) in unresectable hepatocellular carcinoma. *Proc Am Soc Clin Oncol* 2005; **23**: 317S.
25 Philip PA, Mahoney MR, Allmer C *et al*. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005; **23**: 6657–63.
26 Ramanathan RK, Belani CP, Singh DA *et al*. Phase II study of lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase 1 and 2 (Her2/Neu) in patients (pts) with advanced biliary tree cancer (BTC) or hepatocellular cancer (HCC): A California Consortium (CCC-P) Trial. *Proc Am Soc Clin Oncol* 2006; **24**: 181S.
27 Schwartz JD, Schwartz M, Lehrer D *et al*. Bevacizumab in unresectable hepatocellular carcinoma (HCC) for patients without metastasis and without invasion of the portal vein. *Proc Am Soc Clin Oncol* 2006; **24**: 213S.
28 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**: 1898–903.

ELSEVIER

Critical Reviews in Oncology/Hematology 67 (2008) 8–15

CRITICAL REVIEWS IN
Oncology
Hematology
incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Growth factors as therapeutic targets in HCC

Junji Furuse *

Department of Internal Medicine, Medical Oncology, School of Medicine, Kyorin University, 6-20-2, Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan

Accepted 26 February 2008

Contents

Abstract

Despite various effective local treatments for hepatocellular carcinoma (HCC), some patients do not meet the treatment criteria because of extrahepatic metastases or macroscopic vascular invasion at the time of their diagnosis. Furthermore, many patients treated with successful local treatments develop recurrences after treatment. Although these patients receive systemic treatment including chemotherapy, HCC is generally recognized as a chemo-resistant tumor. Recently, new molecular targets have been confirmed and various targeted agents are now being investigated for the treatment of HCC. Epidermal growth factor receptor (EGFR) is frequently expressed in human hepatoma cells, and EGF may be one of the mitogens that are needed for the growth of hepatoma cells. HCC is generally hypervascular, and vascular endothelial growth factor (VEGF) promotes HCC development and metastasis. Various inhibitors targeting EGFR and/or VEGF, VEGF receptor (VEGFR) have been developed as treatments of HCC. In phase-II studies of these growth factor inhibitors, the response rates are relatively low; however, high rates of disease control, enabling a good time to progression, have been achieved. Recently, a randomized phase III trial of sorafenib versus placebo conducted in patients with advanced HCC demonstrated the beneficial effects of this drug on the time-to-progression and overall survival of the patients, and the drug could become established as the standard chemotherapeutic agent for advanced HCC. Further clinical trials using biologic agents are warranted to prolong the survival in HCC patients.

Keywords: Hepatocellular carcinoma; Epidermal growth factor receptor; Vascular endothelial growth factor

1. Introduction—etiology and treatment strategy

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide [1], with approximately 500,000 new cases per year. There are globally some discrepancies in the incidence and etiology of HCC. Almost 80% of patients with HCC arise in Asia and Africa [2]. In Japan, approximately 34,000 patients died of primary liver cancer, and it is 11.6% of cancer deaths and the fourth mortality of malignancy [3]. The incidence of HCC is approximately 43/100,000 population, and about 50,000 new HCC patients annually arise [3]. Most patients with HCC have chronic liver disease, especially liver cirrhosis, and it is mainly due to hepatitis virus infection. However, there is definitely difference in etiology among regions. Hepatitis B virus (HBV) is very common in east and South-East Asia and Africa; more than 80% HCC patients have HBV infection [2]. On the other hand, hepatitis C virus

* Tel.: +81 422 47 5511; fax: +81 422 44 1858.
E-mail address: jfuruse@kyorin-u.ac.jp.

1040-8428/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.critrevonc.2008.02.009

(HCV) is common in Japan, and HCV antibody is observed in 72% of Japanese HCC patients [4]. The incidence of HCV infection is also increasing in the United States and European countries, and the incidence of HCC is rising [5].

The treatments are classified to local and systemic therapy. Various treatment modalities such as surgery, ablation, transcatheter arterial chemoembolization (TACE), and liver transplantation, are available as local therapeutic approach. The treatments for HCC are selected according to the tumor stage, the grade of liver dysfunction, and performance status [4,6]. The local approaches yield good outcomes in patients with earlier stage disease. Since rigorous screening of at-risk patients is carried out and many early-stage HCC patients are identified, large numbers of patients probably undergo surgery or regional therapy in Japan. In other parts of the world, the majority of HCC patients may have advanced disease at the time of diagnosis.

Despite successful these local therapies above, many patients develop recurrences or progression after treatments. Some patients do not meet the indication criteria of local therapies at the time of their diagnosis, such as extrahepatic metastases. Although these patients receive systemic treatment including chemotherapy, HCC is generally recognized as a chemo-resistant tumor. Recently, some growth factors and various signal transduction pathways have been identified, and various targeted agents are now being investigated as the treatment of HCC. They control processes of cell proliferation and survival and specialized functions such as angiogenesis. Dysregulated signaling pathways contribute to malignant transformation in human cells. In this paper, recent progress in treatments using growth factor targeted agents for HCC is reviewed.

2. Systemic chemotherapy for hepatocellular carcinoma

Systemic chemotherapy is applied for patients with advanced HCC to which local treatments are not able to be indicated. TACE refractory stage is also considered candidates for chemotherapy. In various reports on chemotherapy for HCC, anthracycline antitumor antibiotic agents such as doxorubicin and mitoxantrone have been considered as the basis of chemotherapy [7,8]. Furthermore, cisplatin and/or fluorouracil have been used as combination chemotherapy [9–12]. The response rate ranges from 14% to 26%, and the median overall survival (OS) varies from 8.9 to 11.6 months in combination chemotherapies of fluorouracil/mitoxantrone/cisplatin (FMP), epirubicine/cisplatin/fluorouracil (ECF), and cisplatin/interferon α-2b/doxorubicin/fluorouracil (PIAF). Doxorubicin has been considered a referential arm in randomized clinical trials for HCC based on comparison trial between doxorubicin and supportive treatment [9]. Despite better response in phase III trials of combination chemotherapy compared to doxorubicin, no standard chemotherapy has currently been identified that can clearly prolong survival; for example, recent phase III trial of doxorubicin versus PIAF failed to show survival benefit (response rate: 10.5% for doxorubicin and 20.9% for PIAF, $p = 0.058$; median OS: 6.8 months for doxorubicin and 8.7 months for PIAF, $p = 0.83$) [13].

In Japan, various regimens of hepatic arterial infusion chemotherapy have been tried for very advanced stage HCC such as extensive portal vein tumor thrombus, and some regimens were reported to have response rate of more than 40% [14,15]. However, no standard regimen has currently been identified that can clearly prolong survival based on prospective large clinical trials.

1.1. Epidermal growth factor

Cell regulation is controlled by secreted polypeptide molecules called growth factors such as epidermal growth factor (EGF) and transforming growth factor (TGF)-α. There are four different human EGF receptors, human epidermal growth factor receptor (HER) 1–4, and EGF receptor exists as monomers and consists of extracellular domain and intracellular domain. When EGF binds to EGF receptor, a dimerization loop of EGF receptors is induced at first. Then, tyrosine-kinase intracellular domain is activated and it serves as docking sites for intracellular signaling molecules that bind to phosphotyrosine. It leads various pathways to cancer cell proliferation, invasion, metastasis, angiogenesis, and inhibition of apoptosis [16,17]. EGFR/HER1 is frequently expressed in human hepatoma cells or HCC, and EGF may be one of the mitogens that are needed for the growth of hepatoma cells [18–21]. The ligand for EGFR/HER1 has different effects on different human hepatoma cell lines, and its role might be more important in poorly differentiated hepatoma cells than in the well-differentiated ones [18]. Increased expression of TGF-a and EGFR also occur frequently in human HCC, and the detection of greater staining in more highly differentiated portions of the tumors suggested that increased expression of TGF-α and EGFR/HER1 might be related to the early stages of human hepatocarcinogenesis [20]. Thus, in patients with HCC, the EGFR/HER1 blockade possible reduces HCC development and/or delays the disease progression.

In cellular signalings, various sites of EGF receptor can be targets of treatments for cancer. Regarding development of agents inhibiting the tyrosine kinase activity, there are a variety of strategies targeting both the extracellular and intracellular domains [22]. Small molecule compounds, which directly inhibit tyrosine phosphorylation, have been investigated for HCC. So far, erlotinib and lapatinib have been reported in clinical trials for HCC (Table 1). Overexpression of EGFR/HER1 was observed in 52–71% of the patients with HCC in phase-II studies of erlotinib or cetuximab [23,24,27]. The response rate to erlotinib was relatively low, but the DCR was significant (43–59%), and the 6-month progression-free survival rate was 28–32% [23,24]. In these trials, the disease control rate (DCR), defined as the sum of the CR + PR + SD