厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

進行・再発肝細胞癌に対する動注化学療法と分子標的薬併用による新規治療法の確立を目指した臨床試験（PhaseIII）ならびに効果を予測するbiomarkerの探索研究

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研究要旨：外科的切除、局所壊死療法および肝動脈化学塞栓療法が適応とならない進行肝細胞癌患者を対象としたソラフェニブとLow-doseFPによる肝動注化学療法の併用療法のソラフェニブ単独治療に対する優越性を確認する前向き、無作為化、非盲検、多施設共同、並行群間、第III相、比較臨床試験

A. 研究目的

外科的切除、局所壊死療法および肝動脈化学塞栓療法が適応とならない進行肝細胞癌患者を対象とし、ソラフェニブと低用量シスプラチン／フルオロウラシル肝動注の併用療法における全生存期間（OS）の延長をプライマリエンドポイントとして標準的治療であるソラフェニブ単独治療に対する優越性を検証する。

B. 研究方法

外科的切除、局所壊死療法および肝動脈化学塞栓療法が適応とならない進行肝細胞癌患者に文書で同意を取得したうえで、ソラフェニブ単独治療群あるいはソラフェニブと Low-doseFP による肝動注化学療法の併用療法のどちらかの治療法へ無作為に割り付けを行い、プロトコールを順守して治療を施行する。プライマリエンドポイントは全生存期間（OS）とする。無増悪期間（TTP）、無増悪生存期間（PFS）、客観的奏効率（ORR）、腫瘍マーカーの変化（Tumor markers）、および安全性（Safety）を比較する。さらには付随研究として効果予測因子となるバイオマーカーを探索する。

（倫理面への配慮）

本試験に関係する研究は、ヘルシンキ宣言および「臨床研究に関する倫理指針」（平成２０年厚生労働省告示第４１５号）に従って実施している。なお、本試験は手稲渓仁会病院の諮問機関である当院倫理委員会（Ethics Committee）で審査され、手稲渓仁会病院の院長と倫理委員会から承認文書で承認済みである。

C. 研究結果

H24 年 12 月 16 日現在、全国で 136 例の症例が組み入れられ本試験を実施中である。当院では H24 年から参加したため現時点では登録症例がないが、現在、症例組み入れの準備中である。

D, E.　考察ならびに結論

本試験の解析により進行肝癌の治療に対する新たな選択肢が科学的に証明され、患者さんに福音となることが期待される。

Ｇ．研究発表

1.　学会発表

第48回日本肝臓学会総会　2012．6．8　金沢　ワークショップ16

肝癌に対するＲＦＡの長期予後とＶナビによる最新の治療支援について

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第16回日本肝臓大会　2012．10．10　神戸

ワークショップ1

非Ｂ非Ｃ型肝癌の現状と今後の展開

辻　邦彦、友成暁子、山崎大

H. 知的所有権の出願・取得状況

　なし

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Ⅳ. 研究成果の刊行物・別刷

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FGF3/FGF4 Amplification and Multiple Lung Metastases in Responders to Sorafenib in Hepatocellular Carcinoma

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The response rate to sorafenib in hepatocellular carcinoma (HCC) is relatively low (0.7%-3%), however, rapid and drastic tumor regression is occasionally observed. The molecular backgrounds and clinico-pathological features of these responders remain largely unclear. We analyzed the clinical and molecular backgrounds of 13 responders to sorafenib with significant tumor shrinkage in a retrospective study. A comparative genomic hybridization analysis using one frozen HCC sample from a responder demonstrated that the 11q13 region, a rare amplicon in HCC including the loci for *FGF3* and *FGF4*, was highly amplified. A real-time polymerase chain reaction–based copy number assay revealed that *FGF3/FGF4* amplification was observed in three of the 10 HCC samples from responders in which DNA was evaluable, whereas amplification was not observed in 38 patients with stable or progressive disease ($P = 0.006$). Fluorescence *in situ* hybridization analysis confirmed *FGF3* amplification. In addition, the clinico-pathological features showed that multiple lung metastases (5/13, $P = 0.006$) and a poorly differentiated histological type (5/13, $P = 0.13$) were frequently observed in responders. A growth inhibitory assay showed that only one *FGF3/FGF4*-amplified and three *FGFR2*-amplified cancer cell lines exhibited hypersensitivity to sorafenib *in vitro*. Finally, an *in vivo* study revealed that treatment with a low dose of sorafenib was partially effective for stably and exogenously expressed *FGF4* tumors, while being less effective in tumors expressing *EGFP* or *FGF3*. *Conclusion:* *FGF3/FGF4* amplification was observed in around 2% of HCCs. Although the sample size was relatively small, *FGF3/FGF4* amplification, a poorly differentiated histological type, and multiple lung metastases were frequently observed in responders to sorafenib. Our findings may provide a novel insight into the molecular background of HCC and sorafenib responders, warranting further prospective biomarker studies. (HEPATOLOGY 2012;00:000-000)

Abbreviations: 5FU, 5-fluorouracil; CGH, comparative genomic hybridization; DMEM, Dulbecco's modified Eagle's medium; EGFR, epidermal growth factor receptor; FBS, fetal bovine serum; FFPE, formalin-fixed, paraffin-embedded; FISH, fluorescence in situ *hybridization; HCC, hepatocellular carcinoma; IC_{50}, 50% inhibitory concentration; mRNA, messenger RNA; PCR, polymerase chain reaction; PIVKA-II, protein induced by vitamin K absence or antagonist-II; RPMI-1640, Roswell Park Memorial Institute 1640; RT-PCR, reverse-transcription PCR.*

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