should be done in patients whose adhesions are mild. However, in patients with dense adhesion, reoperation carries the risk for secondary bowel injury (20), hard dense adhesions tend to be localized infection. So, effective drainage that formed a fistula was essential in Cases 1, 4, and 5. Chronic or persistent infection of enterocutaneous fistula, may require debridement and sleeve resection. Liver function and nutrition status may be attributable to healing of enterocutaneous fistula.

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特集 IFN治療はC型慢性肝炎の生命予後をどう変えたか

生命予後・死因からみたC型肝炎関連肝細胞癌切除例におけるインターフェロン治療の意義*

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はじめに

C型肝炎ウイルス(HCV)に起因する慢性肝疾患から発生する肝細胞癌(肝癌)では肝切除を施行しても多中心性再発が高頻度にみられるため長期間の無再発生存を得ることは困難である[1)~7)]．このためHCV関連肝癌の予後改善には肝癌治療後の多中心性再発対策が重要となる．さらにHCV関連肝癌症例では活動性肝炎の持続および肝繊維化の進行による肝不全に対する対策も必要である．インターフェロン(IFN)治療はHCV除去や肝炎鎮静化をもたらし，肝癌の発生を抑制させることが明らかとなっているが[8)~10)]，われわれは肝癌切除前後のIFN治療により術後再発が抑制できるだけでなく[11)~13)]，肝機能悪化を防ぐことにより肝癌切除後の成績が向上することを報告してきた[14)]．本稿では生命予後や死因からみたHCV関連肝癌切除例におけるIFN治療の意義について著者らの知見を中心に述べる．

HCV関連肝癌切除後の再発形式

本邦の肝癌はHCVおよびB型肝炎ウイルス(HBV)による慢性肝疾患を母地とするため，肝癌切除後の再発形式には転移再発だけでなく，高癌化病態である慢性肝疾患からの多中心性再発が存在する[1)~7)]．転移再発と多中心性再発の確実な鑑別診断は困難であるが，肝癌の多くは多段階発育を示し，高分化型肝癌では転移再発をきたすことがほとんどなく，原発性肝癌取扱い規約などの多中心性発癌の病理学的特徴から考えると再発病巣に高分化型肝癌組織がみられた場合，これらは多中心性再発と推察される[5)7)15)]．当科における高分化型肝癌切除後では再発病巣の多くで高分化型肝癌組織がみられ，その頻度は術後5年間で約50%に達する[6)]．HCV関連肝癌ではHBV関連肝癌と比較して多中心性再発が高頻度であり[4)7)]，HCV関連肝癌切除後では転移再発が多くみられる術後3年を経ても無再発生存率は長期間にわたって低下し続ける[2)~4)]．また，多中心性発癌および再発は持続性活動性肝炎を有する症例や肝繊維化の強い症例で多くみられることから[1)10)16)17)]，HCV関連肝癌切除後の多中心性再発抑制には活動性肝炎の沈静化が必要と

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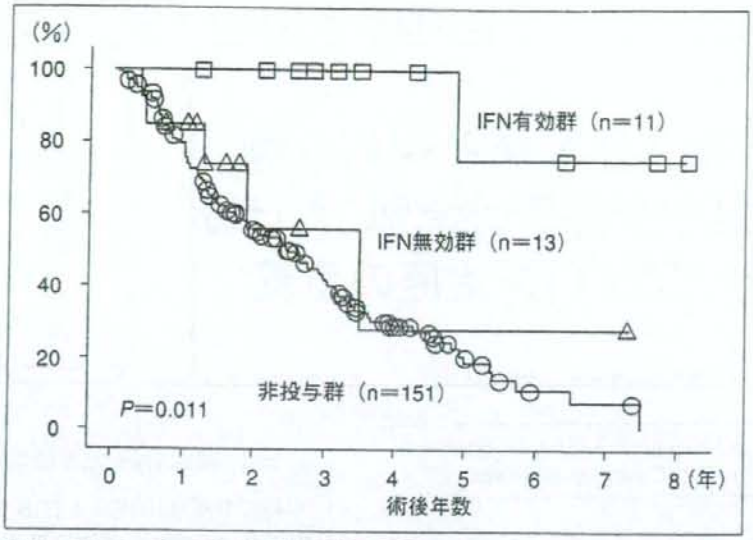

図1　インターフェロン(IFN)治療後に発見されたC型肝炎関連肝癌の術後無再発生存率

考えられる．

HCV関連肝癌切除例における インターフェロン治療の意義

IFN治療はHCV除去や活動性肝炎の沈静化をもたらし，HCV感染による慢性肝疾患からの発癌を抑制する[8)~10)]．しかしながら，HCV症例に対するIFN治療後に肝癌が発見されることが散見され，これら多くはIFN治療の施行前および施行中にすでに肝癌が発生していたが，画像診断では検出できなかったものと考えられる[18)]．われわれはIFN治療後に発見された肝癌に対して積極的に肝切除を施行しており，それら症例の術後無再発生存率はIFN非治療例と比較して有意に良好であることを明らかにしてきた[11)12)]．近年，HCV症例に対するIFN治療の増加に伴い，IFN治療後に発見された肝癌切除例も増加している．当科では1993年から2000年までに切除された両葉多発腫瘍もしくは門脈または肝静脈の1次分枝に血管侵襲を伴わなかったHCV関連肝癌(HCV抗体陽性，HBs抗原陰性)175例のうち24例に術前IFN治療が施行されていた．このうちIFN投与終了1年以上にわたって血清中HCV-RNAが消失もしくはHCV-RNAが陽性であってもAST/ALTが正常化していた11例では術後3年もしくは5年の無再発生存率が100%および75%と著しく向上していたが，IFN治療無効例では5年無再発生存率が28%とIFN非治療例の21%と差は認められなかった(図1)[12)]．このためHCVに対するIFN治療が有効であればIFN治療後肝癌が発見されても，肝切除を含めた根治治療後の成績向上が期待できると考えている．さらにわれわれは肝癌が5cm以下単発であり，血小板が5万/μl以上であった30例を対象としてHCV関連肝癌切除後のIFN治療による再発抑制の前向き試験を行ってきた[13)]．本試験はIFN治療15例にIFN-α 600万単位を2週連日投与した後，3回/週を14週さらに2回/週を88週投与し，IFN非治療15例と切除成績を比較したものであった．IFN治療終了後6か月での血液検査においてIFN治療群のうち2例でHCV-RNAが消失し，6例ではHCV-RNAは陰性化しなかったがAST/ALTが正常化していた．残りの7例はIFN治療が無効であった．肝切除後の無再発生存率をみるとIFN非治療群では無再発生存率は長期間にわたって低下し術3年後の無再発生存率は20%以下であったが，IFN治療群では術2年以降の再発を認めず術3年後の無再発生存率は60%以上であり(図2)，IFN治療によるHCV消失および肝炎鎮静化が根治治療後の多中心性再発を抑制可能であることを明らかにした．また，同試験の長期経過をみると，IFN治療群の累積生存率はIFN非治療群と比較して有意に高率であった[14)]

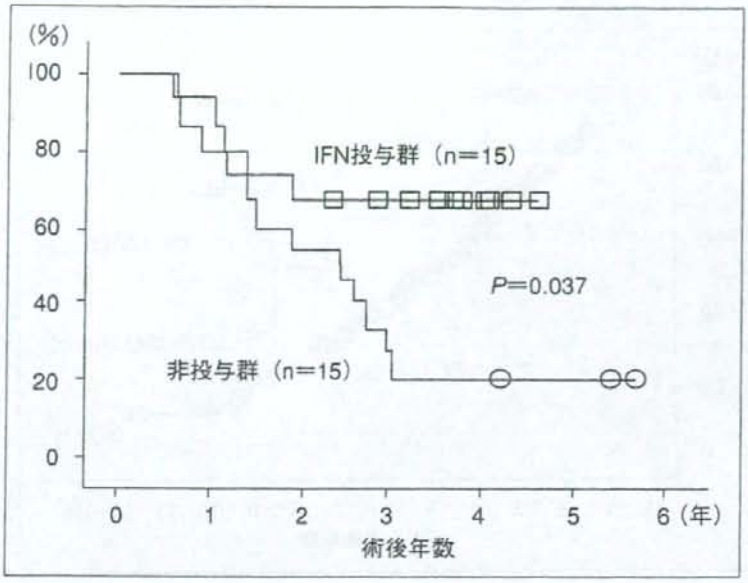

図2 C型肝炎関連肝癌切除後インターフェロン(IFN)治療有無別にみた術後無再発生存率

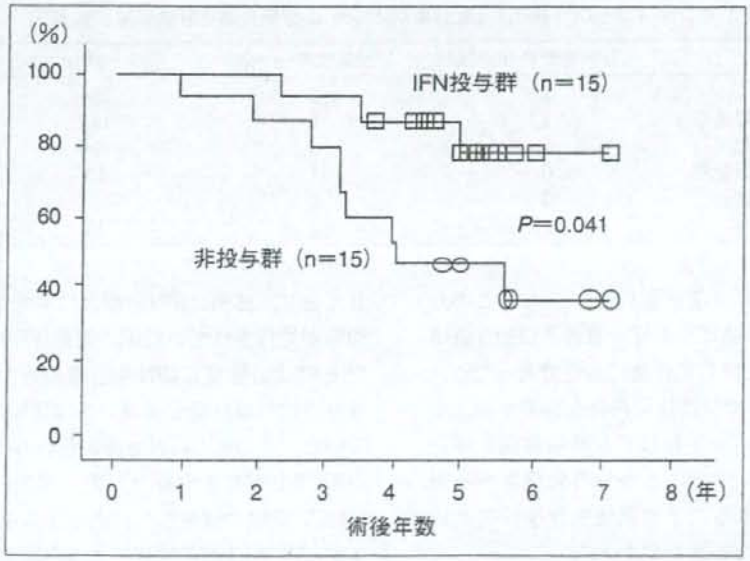

図3 C型肝炎関連肝癌切除後インターフェロン(IFN)治療有無別にみた術後累積生存率

(図3)．肝内再発はIFN治療群9例およびIFN非治療群13例でみられたが，再発病巣が3個以上であったものがIFN非治療群では6例であったのに対してIFN治療群では1例のみであった．IFNはNK細胞活性を高め，血管新生抑制作用を有し[19)20)]，さらにIFN自体が抗腫瘍効果を有するとの報告もみられるため[21)~23)]，これら細胞増殖抑制や免疫賦活作用により多中心性再発だけでなく転移再発も抑制できる可能性も考えられる．さらにIFN治療群では再発時および試験終了時の血清中アルブミン値，総ビリルビン値およびALT値が初回肝切除時より改善されたが，IFN非治療

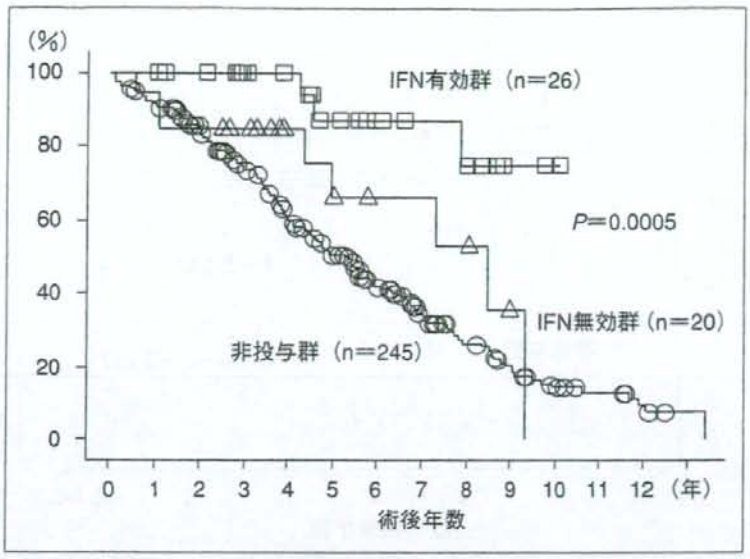

図4 インターフェロン(IFN)治療効果別にみたC型肝炎関連肝癌の術後累積生存率

表1 インターフェロン(IFN)治療効果別にみたC型肝炎関連肝癌切除例の死因

	IFN有効群(n=26)	IFN無効群(n=20)	非投与群(n=245)
死亡	3	8	164
肝臓関連死	1	6	144
癌死	1	5	134
肝不全死	0	1	10
術関連死	0	0	4
他病死	2	2	16

群では総ビリルビン値が悪化していた．このため，IFN治療群の総ビリルビン値およびALT値はIFN非治療群と比較して有意に良好であった[14]．つまりIFN治療群では術後無再発生存率が向上するのみならず，再発を有しても多発再発を抑制し，肝機能を温存することから再発病巣への根治治療を可能とすることで累積生存率の向上に寄与しているものと思われた．

インターフェロン治療はHCV関連肝癌切除例の死因をどうかえたか？

1990年から2002年末までに当科で切除されたHCV関連肝癌(HCV抗体陽性，HBs抗原陰性)478例のうち，JIS scoreが0～2であった291例を対象として経過観察を2003年末まで行い，HCV関連肝癌切除後の生命予後および死因に対するIFN治療の影響を検討した．IFN治療は46例に施行されており，29例はIFN治療後に発見された肝癌に切除が施行されていたが，術前IFNが無効であった6例は切除後にIFN再治療が行われていた．残りの17例は肝癌切除後のみにIFN治療が行われていた．その他のIFN治療が行われていなかった245例をIFN非治療群とした．また，IFN治療後にHCV-RNAの消失した17例とHCV-RNA陽性であるがAST/ALTが正常化した9例をあわせた26例をIFN治療有効群とし，IFN治療の効果のなかった20例を無効群と分類した．IFN治療群の累積5年生存率は78%であり，IFN非治療群の51%に比較し有意に高率であった($P=0.0002$)．IFN治療効果別の累積5年生存率はIFN治療有効群が87%ときわめて良好であり，IFN治療無効群でも66%とIFN非治療群の51%と比較して高率であった(図4，$P=0.0005$)．IFN非治療群のうち経過観察中に死亡した164例の死因は，肝癌死134例，

肝不全死(肝癌再発なく，肝機能悪化による死亡)10例，他病死16例，手術関連死亡4例であったが，IFN治療群では肝癌死6例，肝不全死1例，他病死4例で，肝臓関連死亡(肝癌死および肝不全死)の比率はIFN非治療群に比較し，IFN治療群では低値であった($P=0.0467$)．さらにIFN治療有効群26例では死亡した3例に肝不全死はみられず肝臓関連死亡は肝癌死した1例のみであり，IFN治療無効群およびIFN非治療群に比較し，IFN治療有効群では有意に肝臓関連死亡が減少していた($P=0.0158$, 表1)．以上よりHCV関連肝癌切除例おいてIFN治療が有効であれば，その投与時期に関わらず肝癌切除後の再発を抑制するのみでなく，肝臓関連死亡，とくに肝不全死を減少させ生命予後を延長させることが明らかとなった．これらの成績をもとに当科では進行肝癌例，肝機能不良例，高齢者などを除いてHCV関連肝癌切除例でも肝癌を伴わないHCV症例に対するIFN治療と同様に術後IFN治療を推奨している．

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特集 肝細胞がん患者にどう対応するか

4．外科的治療の進め方

2）術前・術後の補助療法はどこまで効果が期待できるか

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View Points !

- 肝細胞がん治療後再発には転移再発と多中心性再発が含まれる。
- 術前肝動脈塞栓術の術後がん再発抑制に対する有効性は否定的である。しかし，術前肝動脈塞栓術により切除可能となる巨大肝がん症例がみられる。
- 術後肝動脈内抗がん薬注入療法の有効性は確立されていないが，がん再発の危険性が高い症例においては有用である可能性がある。
- C型肝炎関連肝細胞がん治療後インターフェロン療法はがん再発抑制効果を有し，予後向上効果が期待される。一方，B型肝炎関連肝細胞がん治療後インターフェロン療法により生存率が向上したと報告されている。
- 養子免疫療法の術後再発抑制効果や非環式レチノイドによる術後再発抑制効果および生存率向上効果が報告されている。

肝細胞がん治療後再発危険因子

- 肝細胞がん治療後再発危険因子のうち，腫瘍側因子では腫瘍径（大型），腫瘍分化度（低分化型），腫瘍数（多結節および肝内転移陽性），脈管侵襲（門脈侵襲，肝静脈侵襲），α-fetoprotein高値などが報告されている。また肝細胞がんの生物学的悪性度の指標としてDNA Ploidity，細胞増殖と関連するPCNA（proliferating cell nuclear antigen）の発現，ornithine decarboxylase活性亢進，テロメラーゼ活性高値などが報告されている。
- 宿主側の再発危険因子では高齢，輸血歴，多飲歴，持続性活動性肝炎，肝硬変や非がん部肝組織の増殖性亢進などが報告されており，また罹患肝炎ウイルスの病態によっても再発頻度や形式が異なる。
- 治療側の再発危険因子では非系統的切除，切除断端陽性などが報告されている。
- 肝細胞がんの補助療法としては上記の腫瘍側因子，宿主側因子，治療側因子に応じた方法が試みられている。

術前補助療法

1．肝動脈塞栓術

- 術前肝動脈塞栓療法の治療後予後改善効果に対する有効性は一定でなく[1~4]，がん再発抑制に関するrandomized controlled trial（RCT）研究ではその有効性は否定されている（**表1**）[5,6]。

表1 肝細胞がん切除後再発抑制（予防）策
(randomized controlled trial)

治療法	薬剤	無再発生存率	有意差
術前肝動脈塞栓術			
Wu（1995）[5]	DXR	40：50 （3年）	無
Yamasaki（1996）[6]	DXR	54：42 （3年）	無
術後動注療法			
Izumi（1994）[10]	DXR＋MMC	32：11.7（3年）	有
Kohno（1996）[11]	EPI＋経口 UFT	37：32（3年）	無
Lai（1998）[12]	CDDP＋EPI	18：48（3年）	無
Ueno（1999）[13]	CDDP＋MMC	72：28（3年）	有
Okuda（1999）[14]	CDDP＋5-FU	45.7：5.6（5年）*	有
Lau（1999）[15]	^{131}I-lipiodol	74.5：36（3年）	有
Ono（2001）[16]	EPI＋経口 HCFU	32：42（3年）	無
免疫療法			
Takayama（2000）[24]	養子免疫療法	48：33（3年）	有
その他の療法			
Muto（1996，1999）[25,26]	非環式レチノイド	77：40（4年）	有

DXR：塩酸ドキソルビシン/MMC：マイトマイシン C/EPI：塩酸エピルビシン/UFT：ユーエフティ®/HCFU：カルモフール/CDDP：シスプラチン/5-FU：フルオロウラシル．
＊累積生存率

- 術前肝動脈塞栓術による肝機能への影響，肝切除までの期間の延長や肝外再発の危険性が高くなる可能性が指摘されている[1,5,7]。
- 巨大肝がんに対して，術前肝動脈塞栓療法による腫瘍壊死や縮小効果によって切除可能となる場合があり，個々の症例に応じて適応を考える必要がある[1,8]。

2．門脈枝塞栓術

- 術前経皮経肝門脈枝塞栓術は肝機能不良例における切除率の向上や大量肝切除の安全性向上の点で有用である。術前経皮経肝門脈枝塞栓術の予後改善効果も報告されているが[9]，いまだ確立されるには至っていない。
- 大量肝切除例における安全性向上は臨床的に確立されており，一方，肝切除後肝不全は致命的である場合が少なくないため，術前経皮経肝門脈枝塞栓術の有用性に関するRCTを行うことは倫理的に困難であるとの指摘もある。

術後補助療法

1．化学療法

- 術後化学療法のうち予防的肝動脈内抗がん薬注入療法（肝動注療法）は，種々の薬剤を用いた報告がみられるものの，その有効性は確定していない。肝動注療法のRCTの結果も一定ではない[11~14,16]。
- 従来の研究成果からみると，進行癌など再発高危険群においては肝動注療法が有用であると推察され，今後，抗がん薬の組み合わせや対象症例の選択など，術後予防的肝動注療法の適応決定と治療法の改良が必要である。

表2 肝がん治療後インターフェロン療法の randomized controlled trial

報告者（年）	投与薬剤・方法	無再発生存率	累積生存率
C型肝炎関連肝細胞がん			
Ikeda（2000）[18]	β600万単位 2回/週36ヵ月	100：0（2年）	—
Kubo（2001，2002）[19,22]	α600万単位 連日2週，3回/週14週，2回/週88週	68：22（4年）	78：47（5年）
Shiratori（2003）[20]	α600万単位 3回/週48週	—	53：23（7年）
Lin（2003）[21]	α300万単位 3回/週24ヵ月 あるいは	53：10（4年）	
	α300万単位 10日/1ヵ月6ヵ月		
	10日/3ヵ月18ヵ月		
B型肝炎関連肝細胞がん	α1b300万単位 2回/週2週，	74：51（1年）	57：43（5年）
Sun（2006）[23]	500万単位 3回/週18ヵ月		

- ^{131}I-lipiodol 動注療法による肝切除施行後再発予防の RCT が行われた結果，投与群の無再発生存率が向上したと報告されているが[15]，その長期予後は報告されておらず，放射性同位元素を必要とする治療法は本邦ではなじまない。
- 全身化学療法について肝機能良好例では有用であるとの報告がみられるが，逆に肝機能が悪化し，予後が不良であったとの報告もあり，一定していない[12,16]。なお，経口抗がん薬の有効性を検討した研究は少なく，その評価は確定していない[17]。

2．抗ウイルス療法

- C型肝炎関連肝細胞がんにおける治療後インターフェロン投与試験（RCT）の結果，インターフェロン療法はがん再発抑制効果を有する（表2）[18~21]。
- C型肝炎関連肝細胞がん治療後インターフェロン療法はがん再発抑制に加えて，肝機能悪化の防止あるいは改善により，生存率を向上させる可能性がある[20,22]。
- しかしインターフェロン療法の適応の限界，効果不良例の存在，保険適用の制限などの問題点がある。
- B型肝炎関連肝細胞がん治療後インターフェロン療法によって生存率が向上したと報告されている[23]。

3．免疫療法

- 肝がん切除後養子免疫療法の RCT によりがん再発抑制効果が認められたが，生存率を有意に向上させるまでには至っていない[24]。

4．その他の治療法

- 肝がん治療後再発抑制に対する非環式レチノイドにより再発が抑制され，生存率が向上したと報告されている[25,26]。現在，全国的な trial が行われている。
- 生存率向上に対する分枝鎖アミノ酸長期投与の効果はみられなかった[27]。

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Chemoprevention of spontaneous development of hepatocellular carcinomas in fatty liver Shionogi mice by a cyclooxygenase-2 inhibitor

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Cyclooxygenase 2 (COX-2) and retinoid X receptor α (RXRα) are suggested to have roles in carcinogenesis. COX-2 inhibitors have been reported to suppress growth of hepatocellular carcinoma (HCC) cell lines *in vitro*. However, little is known about the preventive effect of these drugs on spontaneous hepatocarcinogenesis *in vivo*. Etodolac exists in a racemic mixture containing S- and R-etodolac. S-etodolac is responsible for COX-2 inhibitory activity and R-etodolac is related to the downregulation of RXRα. Here, the effect of etodolac on spontaneous development of HCC in fatty liver Shionogi mice is evaluated. Etodolac was administered at a low (2 mg/kg) or high (10 mg/kg) dose three times a week for 16 months starting at the age of 3 months. The development of HCC was suppressed slightly in the high-dose group, and suppressed markedly in the low-dose group, although the development of fatty liver was not inhibited in either group. Plasma prostaglandin E_2 levels were also decreased significantly in the low-dose group, consistent with the suppression of HCC. The expression of RXRα and proliferating cell nuclear antigen in non-tumorous liver tissues was decreased significantly in both the low-dose and high-dose groups. These findings show that etodolac treatment at an optimum dose suppresses hepatocarcinogenesis *in vivo*, and may be useful for preventing the development of HCC in humans. (*Cancer Sci* 2006; 97: 768–773)

Hepatocellular carcinoma is a common malignancy worldwide, accounting for approximately 6% of all human cancers and up to 1 million deaths per year.[1,2] Epidemiological studies and clinical observations have indicated that some medicines, such as vitamin A, vitamin K2 and interferon-α, have chemopreventive effects for hepatocarcinogenesis.[3–5] Because these medicines are not enough to prevent hepatocarcinogenesis in humans, other efficient preventive tools are needed urgently.[6]

The use of COX-2 inhibitors is associated with a reduced development of certain types of tumors, such as colorectal cancer and prostate cancer.[7–9] COX-2 inhibitors suppress the growth of human HCC implants in nude mice and lung metastasis of HCC in F344 rats, and show preventive effects on chemically induced hepatocarcinogenesis in rats.[6,10–13] We reported previously that a specific COX-2 inhibitor, etodolac ([±]-1,8-diethyl-1,3,4,9,-tetrahydropyrano-[3,4-b] indole-1-acetic acid), decreases the levels of PGE_2 and inhibits the expression of PCNA in several HCC cell lines *in vitro*.[14] Etodolac exists in a racemic mixture containing S- and R-etodolac. S-etodolac has been shown to possess COX-2 inhibitory activity and R-etodolac was recently reported to bind RXRα and to inhibit the development of prostate cancer.[15–17] RXRα, which plays an important role in regulating cell proliferation and differentiation, is expressed abundantly in the liver and is involved in hepatic steatosis and hepatocarcinogenesis in HBV and HCV infection in humans.[18–20] However, little is known about the chemopreventive effect of COX-2 inhibitors on spontaneous hepatocarcinogenesis *in vivo*.

Fatty liver Shionogi mouse is an inbred strain that shows neither hyperphagia nor obesity but has an abnormal triglyceride accumulation in hepatocytes after birth.[21,22] Fifty percent of the mice show fatty liver grade I and II 9 weeks after birth, and all mice develop fatty liver grade III and IV after 15 weeks.[21] FLS mice develop severe fatty liver (hepatic steatosis) and chronic HCC under normal conditions, in which the incidence of HCC is reached to 52% at 16 months of age.[22] To explore the mechanism involved and to find a specific and effective medicine for the prevention of hepatocarcinogenesis, we studied the effect of a COX-2 inhibitor, etodolac, on spontaneous development of HCC in FLS mice.

Materials and Methods

Animals and experimental design

Thirty male FLS mice aged 2 months were obtained from Aburahi Laboratories, Shionogi Company (Shiga, Japan).

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Abbreviations: BW, bodyweight; COX-2, cyclooxygenase-2; E-HD, high-dose treatment group; E-LD, low-dose treatment group; FLS, fatty liver Shionogi; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PCNA, proliferating cell nuclear antigen; PGE_2, prostaglandin E_2; RT-PCR, reverse transcription–polymerase chain reaction; RXRα, retinoid X receptor α.

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They were housed, one per cage, under specific pathogen-free conditions in a 12 : 12 h L : D cycle at 23 ± 1°C and 50 ± 10% humidity, and fed a standard CE-2 diet (CLEA Japan, Tokyo, Japan) and tap water *ad libitum*. The mice were divided randomly into three groups of 10 mice each. All animals received humane care and all experiments followed the Guidelines for Animal Experimentation of the Japanese Association for Laboratory Animal Science.[23] Two doses of etodolac (Nihon Shinyaku Company, Tokyo, Japan) were used: 2 mg/kg BW for the E-LD group and 10 mg/kg BW for the E-HD group. Etodolac was dissolved in 100% ethanol and diluted to suitable concentrations with a 5% aqueous solution of arabic gum. The solutions of etodolac were given to mice by oral gavage, three times per week (Monday, Wednesday and Friday) for 16 months from age 3–18 months. The control group was treated with the same amounts of 0.7% ethanol and 5% arabic gum. The mice were observed weekly for BW, skin damage and general condition. The animals that were still alive at 18 months were anesthetized with diethyl ether and blood was collected from the heart. The livers were immediately removed and weighed. Tumor nodules that had developed were measured for diameter and cut for formalin fixation and paraffin embedding or frozen storage.

Measurement of prostaglandin E_2

Prostaglandin E_2 levels in the plasma were assayed using the PGE_2 High Sensitivity Immunoassay Kit (R & D Minneapolis, MN, USA) as described previously.[14]

Histological examination

Tumor and non-tumorous liver tissues were fixed in 10% neutral-buffered formalin, embedded in paraffin, cut into sections 5 μm thick, and stained with hematoxylin and eosin. The classification of liver histology was based on the criteria described by Frith and Ward.[24]

Immunohistochemical analysis

Paraffin sections from HCC and non-tumorous liver tissues were deparaffinized in xylene, rehydrated with graded concentrations of ethanol, and treated with antibodies against COX-2, RXRα and PCNA, as described previously.[25] All antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA) and used at a dilution of 1/100. The RXRα-positive and PCNA-positive cells were counted microscopically in five high-power fields at magnitude × 400. The labeling index of RXRα and PCNA was expressed as the proportion of cells with positive RXRα and PCNA nuclear activity.

RNA extraction and reverse transcription–polymerase chain reaction

Total RNA was extracted from liver tissues using Isogen (Nippon Gene, Toyama, Japan), and mRNA was prepared using an Oligotex-dT30 mRNA Purification Kit (Takara Bio, Otsu, Japan) according to the manufacturer's instructions. cDNA was synthesized using random 9-mers and an RNA PCR Kit (version 2.1; Takara). The primers for polymerase chain reaction were as follows: COX-2 forward, 5′-GGTCT GGTGC CTGGT CTGAT GATG-3′; COX-2 reverse, 5′-GTCCT TTCAA GGAGA ATGGT GC-3′;[9] RXRα forward, 5′-CTTTG ACAGG GTGCT AACAG AGC-3′; RXR α reverse, 5′-ACGCT TCTAG TGACG CATAC ACC-3′;[26] β-actin forward, ATGGT GGGAA TGGGT CAGAA GGAC-3′; and β-actin reverse, 5′-CTCTT TGATG TCACG CACGA TTTC-3′.[27] cDNA amplification was carried out under the conditions 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min, using β-actin as an internal control. The products were analyzed on a 3% NuSieve 3 : 1 agarose gel (FMC BioProducts, Rockland, ME, USA), stained with ethidium bromide and photographed under ultraviolet light.

Statistical analysis

Statistical analysis for the development of HCC was carried out using the Student's *t*-test or Fisher's exact test. Values are expressed as mean ± SE. $P < 0.05$ was considered statistically significant.

Results

Effects of etodolac on HCC development

Histological findings of fatty liver and HCC spontaneously developed in the liver of 18-month-old FLS mice are shown in Fig. 1A,B. The expression of COX-2 protein in the non-tumorous liver tissues was determined by immunohistological staining (Fig. 1C,D). The mRNA expression of COX-2 was confirmed by RT-PCR (Fig. 1E).

The incidence of HCC was evaluated after the administration of etodolac. The total numbers of HCC nodules were 11 in the control group (10 mice), 0 in the E-LD group (eight mice) and three in the E-HD group (nine mice). The numbers of mice that developed HCC were 5, 0 and 3 in the control, E-LD and E-HD groups, respectively. Development of HCC was suppressed completely by the administration of low-dose etodolac. The administration of high-dose etodolac also showed a suppressive effect, although it was not statistically significant (Table 1).

All of the 27 mice used in the present study developed fatty liver from grades II to IV at the end of experiments with no remarkable difference in the degree of fatty or inflammatory changes. A small number of mice in each group developed yellow nodules of 1–2 mm in diameter and reddish cysts, which were identified microscopically as fatty nodules and peliosis hepatis, respectively (data not shown). Liver cirrhosis was not observed in any of the mice. Liver weights also did not show significant differences among the control, E-LD and E-HD groups (data not shown). One mouse in the E-HD group died at the age of 17 months, and two mice in the E-LD group died at 13 and 14 months. No HCC was found in these mice and the cause of death was not clear.

Except for the livers, no abnormal findings were observed macroscopically in heart, lung, kidney, intestines and large vessels in any of the FLS mice. Five mice in the E-HD group had skin damage, including depilation and rash, and two among them had skin ulcers. The mean BW of mice at 18 months of age were 37.9 ± 1.11 g ($n = 10$), 36.88 ± 1.2 g ($n = 8$) and 35.56 ± 0.93 g ($n = 9$) in the control, E-LD and E-HD groups, respectively. No significant difference was found in BW among the control, E-LD and E-HD groups.

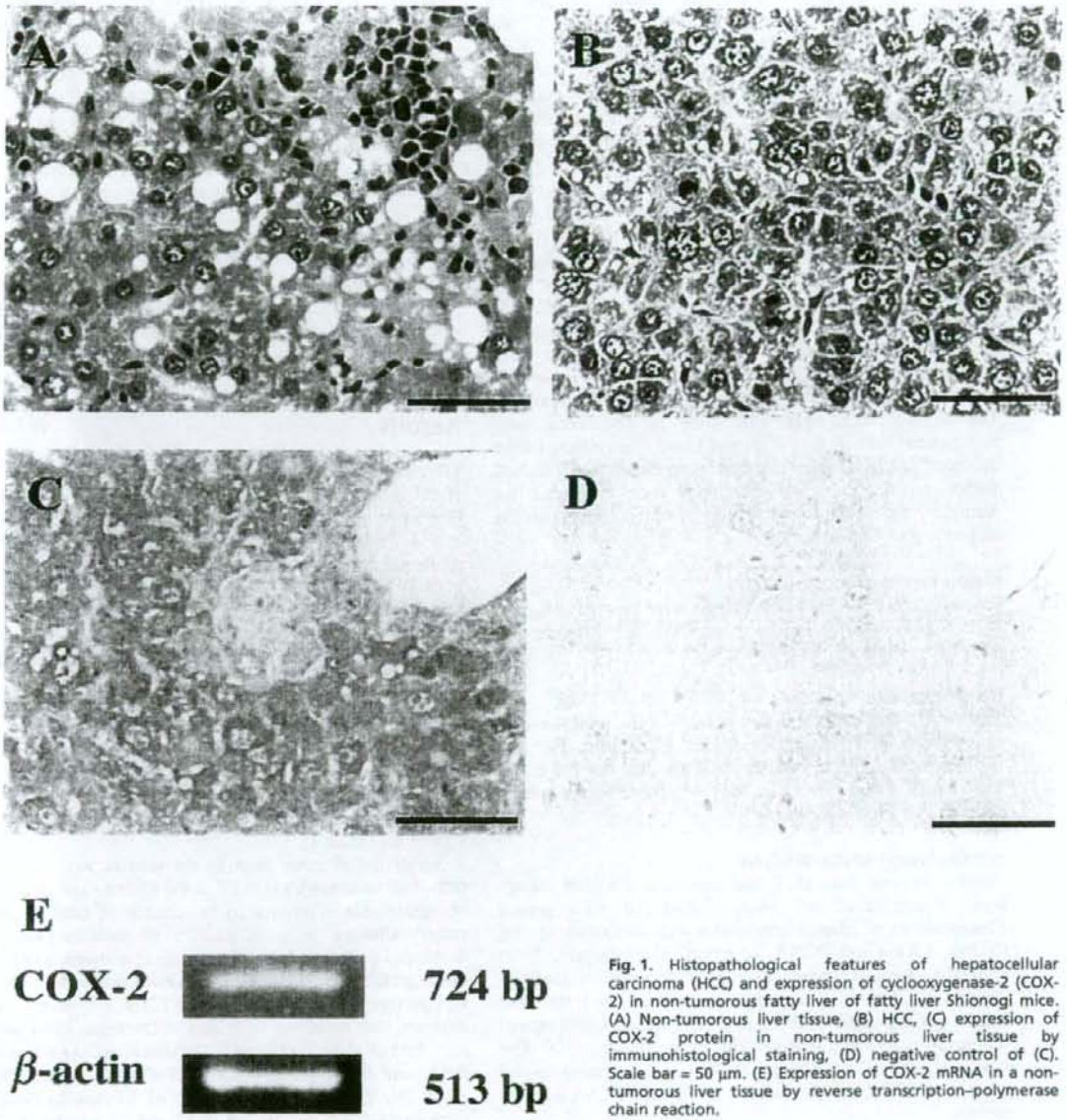

Fig. 1. Histopathological features of hepatocellular carcinoma (HCC) and expression of cyclooxygenase-2 (COX-2) in non-tumorous fatty liver of fatty liver Shionogi mice. (A) Non-tumorous liver tissue, (B) HCC, (C) expression of COX-2 protein in non-tumorous liver tissue by immunohistological staining, (D) negative control of (C). Scale bar = 50 μm. (E) Expression of COX-2 mRNA in a non-tumorous liver tissue by reverse transcription–polymerase chain reaction.

Table 1. Incidence of hepatocellular carcinoma (HCC) in fatty liver Shionogi mice

Group	No. mice	Etodolac (mg/kg)	Grade of steatosis			No. HCC nodules	No. mice that developed HCC
			II	III	IV		
Control	10	0	0	4	6	11	5 (50%)
E-LD	8	2	1	2	5	0*	0*
E-HD	9	10	0	3	6	3	3 (33%)

*$P < 0.05$ by Fisher's exact test. Grades of classification are according to the size and distribution pattern of the vesicles in the hematoxylin–eosin-stained sections.[24] E-HD, high dose of etodolac; E-LD, low dose of etodolac.

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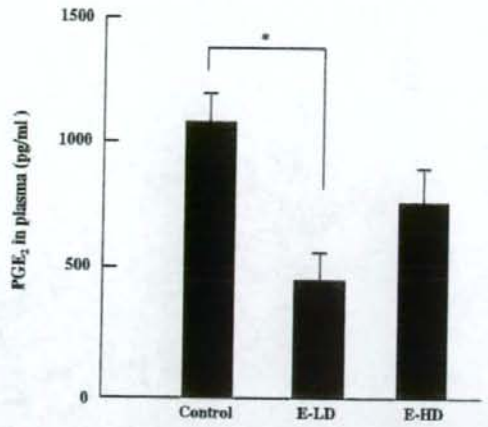

Fig. 2. Effect of etodolac on plasma prostaglandin E_2 (PGE_2) levels in fatty liver Shionogi mice. A marked decrease in plasma PGE_2 levels was observed after low-dose (2 mg/kg bodyweight) administration of etodolac (E-LD). E-HD, high-dose (10 mg/kg bodyweight) administration of etodolac. *$P < 0.05$. Bars indicate ±SE of mean.

Plasma PGE_2 levels after etodolac administration

The activity of etodolac can be estimated by analyzing the concentration of PGE_2 in the plasma. The concentrations of PGE_2 in the plasma were 1010.15 ± 120.22 pg/mL ($n = 10$), 443.33 ± 116.99 pg/mL ($n = 8$) and 773.8 ± 137.67 pg/mL ($n = 9$) in the control, E-LD and E-HD groups, respectively. We found that the plasma levels of PGE_2 of the E-LD group, but not the E-HD group, were significantly lower than in the control group ($P < 0.05$) (Fig. 2).

Effects of etodolac on RXRα expression

Hepatocarcinogenesis in FLS mice has been attributed to chronic inflammation in fatty liver. Therefore, we investigated the effects of etodolac administration on hepatocytes in non-tumurous fatty liver of FLS mice. In prostate cancer, R-etodolac has been shown to bind to RXRα, inducing its degradation via ubiqutin and the proteasome-dependent pathway.[17] Analysis by immunohistological staining showed that the expression of RXRα in hepatocytes in non-tumorous liver tissues was significantly lower in E-LD (10.98 ± 0.87% $n = 6$) and E-HD (11.65 ± 1.72% $n = 4$) groups than in the control group (27.28 ± 2.91% $n = 5$) ($P < 0.01$; Fig. 3A–C). In contrast, semiquantitative RT-PCR analysis showed identical expression of RXRα mRNA among non-tumorous liver tissue of the control, E-LD and E-HD groups (Fig. 3D). These findings suggest that etodolac binds to RXRα and induces its degradation in the non-tumorous liver of FLS mice.

Effects of etodolac on PCNA expression

Proliferating cell nuclear antigen is expressed throughout the cell cycle, except during G_0 phase, and plays an important role in cell proliferation. The labeling index of PCNA in the non-tumorous liver tissues of the E-LD (2.15 ± 0.11%, $n = 8$) and E-HD groups (2.2 ± 0.27%, $n = 9$) was significantly lower than the control group (3.13 ± 0.26%, $n = 10$) ($P < 0.05$, Fig. 4). These findings show that the growth of hepatocytes in non-tumorous tissue was inhibited by etodolac administration.

Discussion

Fatty liver Shionogi mice develop serious fatty liver and HCC with age, providing a good animal model to study hepatocarcinogenesis from fatty liver *in vivo*.[21,22] Using FLS mice, we here examined the *in vivo* effects of a COX-2 inhibitor, etodolac, on spontaneous development of HCC.

Etodolac exists in a racemic mixture. S-etodolac possesses activity to inhibit COX-2, which catalyzes the conversion of arachidonic acid to PGE_2.[15,16] COX-2 and PGE_2 have been reported to be involved in carcinogenesis of the colon, prostate and liver.[7–9,28–30] Etodolac has been reported to reduce aberrant crypt foci in rat colon, and another selective COX-2 inhibitor, NS-398, has been reported to reduce rat colon carcinogenesis.[31–33] In the present study, we found that etodolac was effective in inhibiting PGE_2 synthesis and HCC development in FLS mice, particularly at a low concentration. A similar observation has been reported for aspirin, where a low dose has a better preventive effect than a high dose in human colorectal cancer.[7] On the other hand, NS-398 has been shown to inhibit aberrant crypt foci in F344 rats in a dose-dependent manner.[32]

In the present study, we observed that the plasma concentration of PGE_2 was higher in the E-HD group than in the E-LD group. The plasma concentration of PGE_2 was lower in the E-HD group than in the control group (not significantly). The plasma levels of etodolac in mice in the E-HD group were approximately five times higher than those in mice in the E-LD group (data not shown). Our previous study using HCC cell lines showed that PGE_2 generation by etodolac is not inhibited in a dose-dependent manner. Rather, PGE_2 levels in the culture medium were higher with the high-dose treatment than with the low-dose treatment.[14] The inhibition of PGE_2 generation by NS-398 was also dose-independent at doses higher than 100 mM in some HCC cell lines.[34] The dose-independency of plasma PGE_2 suppression by etodolac *in vivo* is compatible with these findings in the *in vitro* experiments. However, the precise mechanism of dose-independency has not yet been clarified. Another suggested explanation is that the higher levels of PGE_2 in the E-HD group may be attributable to adverse effects of a high dose of etodolac. Severe skin damage developed in mice in the E-HD group. This could be responsible for loss of the preventive effect of COX-2 inhibitor on HCC in the E-HD group. Furthermore, in the present study, the plasma PGE_2 levels were consistent with the HCC incidences. These data suggest that PGE_2 plays an important role in the development of HCC in FLS mice. The 2 mg/kg dose of etodolac three times a week used in this study is less than the usual dose in humans (200 mg orally twice a day), and no side effects were observed in this group. Thus, we consider that administration of a low dose of COX-2 inhibitor should be sufficient for liver cancer prevention in humans. Furthermore, it is necessary to evaluate the efficacy of etodolace doses lower than 2 mg/kg to elucidate the optimum dose for liver cancer prevention.

Recently, R-etodolac has been reported to bind specifically to RXRα and prevent prostate cancer.[17] In the present study,

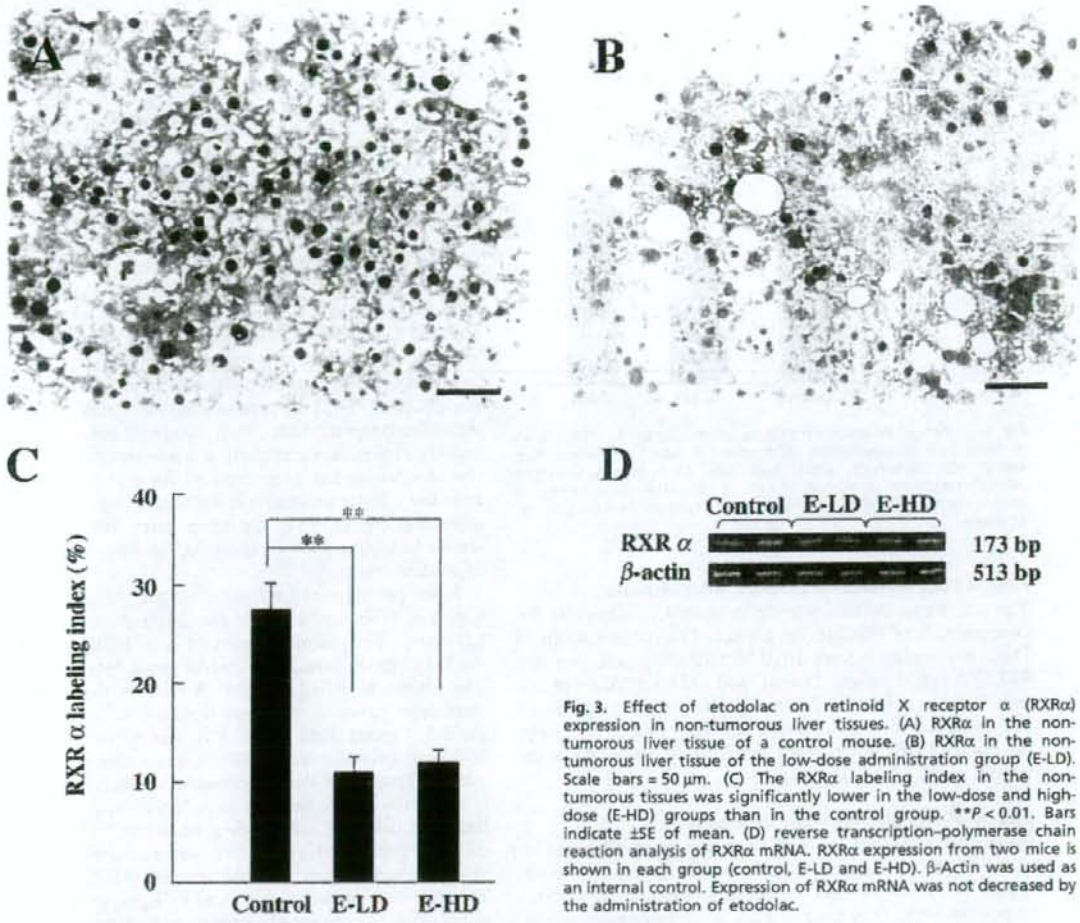

Fig. 3. Effect of etodolac on retinoid X receptor α (RXRα) expression in non-tumorous liver tissues. (A) RXRα in the non-tumorous liver tissue of a control mouse. (B) RXRα in the non-tumorous liver tissue of the low-dose administration group (E-LD). Scale bars = 50 μm. (C) The RXRα labeling index in the non-tumorous tissues was significantly lower in the low-dose and high-dose (E-HD) groups than in the control group. $^{**}P < 0.01$. Bars indicate ±SE of mean. (D) reverse transcription–polymerase chain reaction analysis of RXRα mRNA. RXRα expression from two mice is shown in each group (control, E-LD and E-HD). β-Actin was used as an internal control. Expression of RXRα mRNA was not decreased by the administration of etodolac.

we found significant decreases in RXRα protein expression in non-tumorous liver tissue in both the E-LD and E-HD groups, whereas RXRα mRNA expression was almost similar among the control, E-LD and E-HD groups. These results suggest that the degradation of RXRα induced by R-etodolac is also responsible for the preventive effect of hepatocarcinogenesis in FLS mice.

Hepatitis C virus stimulates the expression of COX-2 via oxidative stress.[35] HCV core protein induces fatty liver by binding to the DNA-binding domain of RXRα.[20] High levels of COX-2 and RXRα expression in hepatocytes may be involved in hepatocarcinogenesis following HBV and HCV infection.[18–20,36,37] Vitamin A has been reported to inhibit hepatocarcinogenesis by dephosphorylating RXRα.[38] Our results showed that both PGE_2 and RXRα levels were decreased by etodolac, indicated that etodolac may be useful for the prevention of HCC caused by HBV and HCV.

We have reported that COX-2 inhibitors (etodolac and NS-398) suppress PCNA expression and induce cell cycle arrest in HCC cell lines.[14,34] In the present study, we found that PCNA expression in non-tumorous fatty liver was significantly lower in both the E-LD and E-HD groups compared with the control group. The PCNA labeling index showed no difference between the E-LD and E-HD groups. Similar results have been reported with NS-398 in F344 rats.[32,33] These results suggest that low-dose administration of etodolac is sufficient to suppress cell cycle progression in FLS mice.

The present results suggest that low-dose administration of etodolac has a strong chemopreventive effect against hepatocarcinigenesis by inhibiting COX-2 activity, and RXRα and PCNA expression in mice. The prevention of hepatocarcinogenesis *in vivo* by COX-2 inhibitor may be caused by the primary suppression of malignant transformation from hepatocytes or inhibition of the growth of HCC cells in early stages, which have already developed in the liver but can not be detected as tumors. Etodolac may also prove to be of value in the prevention of HCC in humans.

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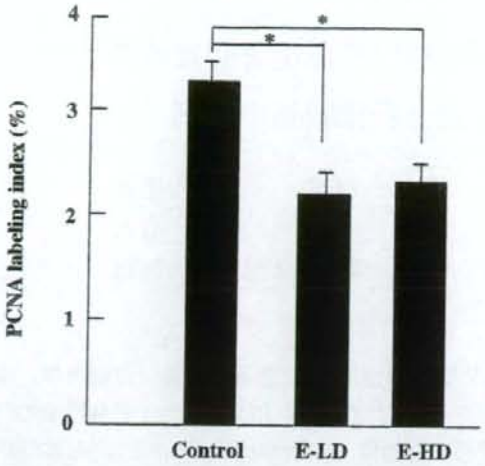

Fig. 4. Proliferating cell nuclear antigen (PCNA) labeling index in non-tumorous liver tissues. The PCNA labeling index was significantly suppressed by low-dose (E-LD) and high-dose (E-HD) administration of etodolac. *$P < 0.05$. Bars indicate ±SE of mean.

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＜症例報告＞

UFT，etodolac，ビタミンK_2経口投与後著明に改善した門脈腫瘍塞栓を伴う進行肝細胞癌の1例

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要　旨：症例は78歳，女性．肝機能障害(HCV抗体陽性)にて近医通院中に全身倦怠感，体重減少，腫瘍マーカー(AFP，PIVKA-II)高値がみられたため当科に紹介された．各種検査で門脈腫瘍塞栓を伴う進行肝細胞癌と診断した．治療前の評価はPerformance Status 2，日本肝癌研究会のTNM分類Stage IV-A，Child-Pugh分類A，Liver damage Bであった．CLIP scoreは4，JIS scoreは3点であった．治療として経口抗癌剤であるUFTを投与した．治療開始より2カ月後にCTにて明らかな腫瘍の縮小を確認できた．また5カ月後には腫瘍マーカーは正常化し，その後は上昇傾向を認めず，現在(治療開始後2年2カ月)に至るまで正常値を維持している．治療効果の総合評価はPRであった．本例はUFT投与が奏効したと考えられるが，UFTとほぼ同時期にetodolac，ビタミンK_2を投与しており，etodolacとビタミンK_2がUFTの抗癌作用に何らかの影響を与えた可能性も否定できないと考えている．

索引用語：UFT　etodolac　cyclooxygenase-2阻害剤　ビタミンK_2　進行肝細胞癌

はじめに

一般的に進行肝細胞癌に対しては経口抗癌剤単独投与では治療効果は低いが，著効例の報告もある．今回当科においてuracil-tegafur (UFT)投与後に著明な効果を認めた進行肝細胞癌の1例を経験した．また同時期にcyclooxygenase-2 (COX-2)阻害薬，ビタミンK_2を併用しており，これらの抗癌作用の可能性に関しても文献的考察を加え報告する．

症　例

症例：78歳，女性．

主訴：全身倦怠感と体重減少．

現病歴：入院の約4年前よりHCV抗体陽性と軽度肝機能障害を指摘され，近医にてウルソデオキシコール酸(UDCA)と強力ネオミノファーゲンCの投与を不定期にうけていた．入院の3カ月前より全身倦怠感が出現し，血液検査にてalpha-fetoprotein (AFP)とprotein-induced by vitamin K absence or antagonist II (PIVKA-II)の高値がみられたため近医より紹介され当科に来院．来院時には体重減少(−5 kg/3カ月)を認めた．

既往歴：特記事項なし．

輸血歴：なし．

合併症：58歳頃より慢性気管支炎，高血圧．

家族歴：特記事項なし．

生活歴：飲酒歴なし．タバコ，20本×30年．

入院時現症：身長153 cm，体重43 kg，血圧145/72 mmHg，脈拍60/分，整，体温36.6°C，意識は清明．眼瞼結膜に貧血なく，眼球結膜に黄染を認めなかった．手掌紅斑を認めた．くも状血管拡張は認めなかった．心，肺に異常所見なし．腹部は平坦，軟で腹水を認めず．肝は正中線上に4横指，右季肋下に2横指触知した．右季肋部から右側腹部に軽度の圧痛と自発痛を認めた．

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Table 1　Laboratory data on admission

Hematology		**Blood chemistry**		Hyaluronic acid	350 ng/ml
RBC	$432\times10^4/\mu l$	TP	7.5 g/dl	Collagen type IV 7S	7.4 ng/ml
Hb	12.1 g/dl	Alb	3.5 g/dl		
Plt	$12.7\times10^4/\mu l$	T. Bil	0.7 mg/dl	ICG R_{15}	16%
WBC	4,200/μl	AST	46 U/l		
PT	77%	ALT	18 U/l	**Tumor markers**	
CRP	(−)	ALP	208 U/l	AFP	2220 ng/ml
		γ-GTP	53 U/l	PIVKA II	1590 mAU/ml
Virus markers		ChE	84 U/l	CEA	4.2 ng/ml
HBs Ag	(−)	T. Chol	180 mg/dl		
HBc Ab	(−)	TG	76 mg/dl	**Bone mineral density**	
HCV Ab	(+)	NH_3	27 μmol/l	%Young Ref.	54.6%
HCV RNA	over 850 KIU/ml	FBS	78 mg/dl	T score	−3.34
		HbA1c	4.9%		

入院時検査所見（Table 1）：貧血はなく，プロトロンビン時間（PT）は77%であった．HCV抗体は陽性で，腫瘍マーカーはAFP 2220 ng/ml，PIVKA-II 1590 mAU/mlと高値で，CEAは正常であった．生化学所見ではアルブミン（Alb）は3.5 g/dl，総ビリルビン0.7 mg/dl，AST 46 U/l，ALT 18 U/lであった．線維化マーカーとしてヒアルロン酸は350 ng/ml，IV型Collagen 7Sは7.4 ng/mlと高値を示し，ICG停滞率15分値は16%であった．骨粗鬆症があり骨密度値は若年成人平均値に比して54.6%であった．

入院時腹部CT所見（Fig. 1 A, B）：単純CTでは肝右葉を中心に全体にlow density areaが広がっており，これは造影CT早期相にて不整に造影された．また後期相にて門脈に一致してwash outされるlesionがみられ，腫瘍が肝右葉を中心にび漫性に存在し門脈本幹まで広がっていると考えられた．

入院時腹部MRI所見：T1強調画像にて周囲の肝組織より低信号，T2強調画像にて高信号の病変が右葉を中心に描出された．またこの病変は門脈右枝から左枝umbilical portion，門脈本幹まで進展していた．

入院時上部消化管内視鏡所見：下部食道にF2〜3，Red color（RC）サイン陽性の食道静脈瘤がみられた．

臨床経過：腹部造影CT，MRI，腫瘍マーカーなどの検査所見より肝細胞癌と診断した．治療前の評価として，Performance Status（PS）は2，日本肝癌研究会のTNM分類はStage IV-A，Child-Pugh分類は6点のA，Liver damageはBであった．またCLIP score[1]は4で，JIS score[2]は3点であった．局所治療，外科手術，肝動脈塞栓療法の適応ではなく，また定期的通院も充分できないとのことでUFT 300 mg/日の投与を開始した．これとほぼ同時期に右側腹部痛に対してetodolac，骨粗鬆症に対してビタミンK_2（menatetrenone）45 mg/日を投与した．また以前よりUDCA，ACE阻害剤（imidapril hydrochloride），カルシウム拮抗剤（diltiazem）を服用されていたので継続した．

治療開始1カ月後の単純CTではほとんど変化はみられなかったが，造影CT早期相では造影効果がやや弱くなり，後期相でのwash outも不明瞭になった．治療開始2カ月後には単純CTおよび造影CTにて，右葉のび漫性の肝細胞癌は不明瞭化がみられ，門脈内の腫瘍は残るものの明らかな縮小を認めた（Fig. 1 C, D）．

治療後の腫瘍マーカーの動きに関しては，PIVKA-IIは治療開始2カ月後には正常化（1590 mAU/mlから14 mAU/ml）し，AFPも治療開始5カ月後には正常化（2220 ng/mlから5.3 ng/ml）した．その後は上昇傾向を認めず，現在（治療開始後2年2カ月）に至るまで正常値を維持している（Fig. 2）．

治療前にみられたF2から3，RCサイン陽性の食道静脈瘤は，治療開始3カ月後にはF1から2となりRCサインは見られなくなった（この間とくに食道静脈瘤に対して直接的な治療は行っていない）．臨床症状に関しては治療開始1カ月後より徐々に全身倦怠感が軽快し，体重も徐々に増加してきた．

副作用としては治療開始3.5カ月後に血小板数減少（12.7万/μlから6.2万/μl）と白血球数減少（4200/μlから2700/μl）が最も強くみられたが，その後はUFTの減量に伴い回復傾向を示した．治療開始3カ月後に上部消化管内視鏡にて胃潰瘍瘢痕（S1）がみられたが，外来での投薬のみで対応し重篤な症状の出現はなかった．