Table 5 Comparison for laboratory data under treatment between increase and non-increase of serum potassium level

	Non-K increase	K increase	P
n	20	7	
Period (weeks)	4.5 (4-6)	5 (4-6)	0.34
Peak K (mEq/L)	4.4 (3.2-5.1)	4.9 (4.6-5.8)	<0.01
Δ K (mEq/L)	0.1 (−0.3-0.4)	0.7 (0.5-1.5)	<0.01
ALB_{4w} (g/dL)	4.0 (2.8-5.6)	4.1 (3.2-4.9)	0.49
$T\text{-}BIL_{4w}$ (mg/dL)	0.8 (0.4-1.7)	0.7 (0.3-2.0)	0.30
ALT_{4w} (IU/L)	23 (9-35)	11 (9-20)	<0.05
$Creatinin_{4w}$ (mg/dL)	0.8 (0.5-1.2)	0.9 (0.5-4.6)	0.62
$eGFR_{4w}$ (mL/min/1.73 m^2)	62 (39-99)	69 (8-106)	0.85
RVR, n (%)	4 (20)	3 (43)	0.33

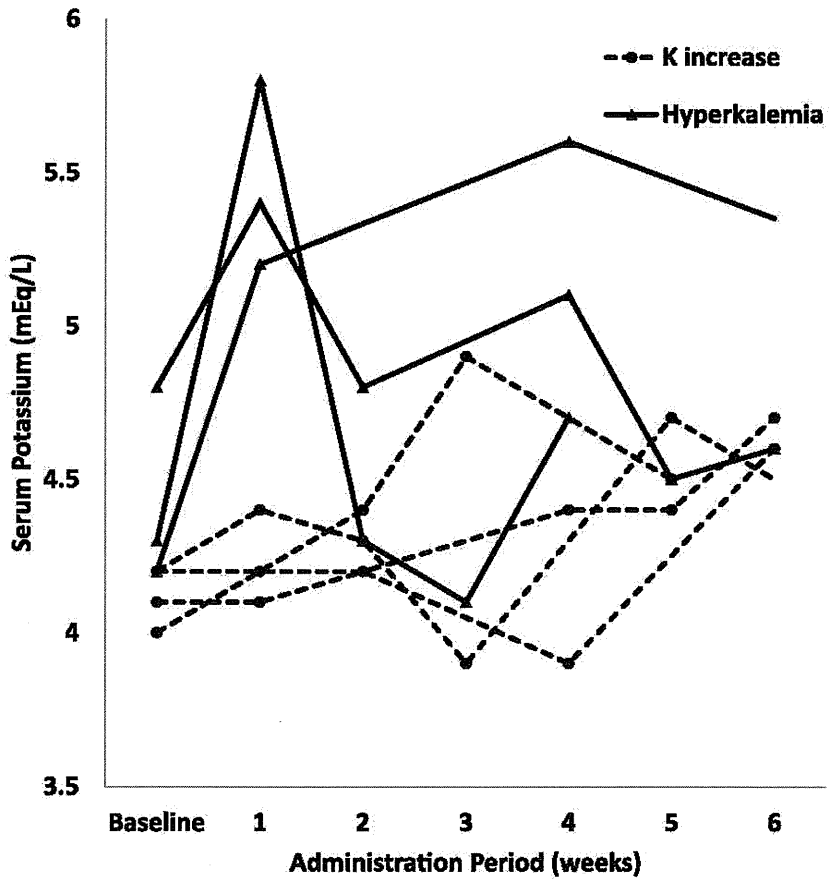

Fig. 1 Change of serum potassium levels under combination therapy with Daclatasvir and Asnaplevir in cases of K increase and Hyperkalemia
K increase; Δ K≧0.5 mEq/L, Hyperkalemia; both K≧5.1 mEq/L and Δ K≧0.5 mEq/L

が直接あるいは間接的に腎機能を低下させた可能性が示唆された．DCV・ASV 併用療法の国内臨床試験(第3相試験)は75歳以下，平均年齢62歳を対象とし，65歳以上の高齢者は40％であったが，本研究の対象症例は平均年齢70歳で，65歳以上の高齢者は81％と多く，今回の対象症例の高齢者傾向が，eGFR 低下の一因となった可能性があると考察する．またアンジオテンシンII受容体拮抗薬(Angiotensin II Receptor Blocker：ARB)使用時の高カリウム血症発症の予測には，eGFR よりも末期肝疾患モデル（Model for End-Stage Liver Disease：MELD)スコアが指標になるという報告があり[8]，腎機能だけでなく肝機能も高カリウム血症に影響を与える．本研究ではカリウム増加群と非増加群において，DCV・ASV 併用療法4週投与後のアルブミン低下，総ビリルビン上昇はなく，むしろカリウム増加群で ALT 値が有意に改善していた．有意差はなかったが，カリウム増加群で RVR 率がやや高い傾向にあったことが，ALT 値が低値となった一因の可能性があると考える．両群間での肝硬変の合併頻度は同等であり，肝障害，肝予備能低下による RAS 阻害剤使用時の血清カリウム上昇は否定的であるが，本研究は少数例，投与初期のみの検討であり，投与終了までの多数例を対象としたさらなる検討が必要である．

DCV・ASV は主として CYP3A で代謝され，ASV は CYP3A4 誘導作用を有するが[9][10]，使用していた RAS 阻害剤はいずれも CYP3A による代謝を介さないため[11]，CYP3A による相互作用により RAS 阻害剤の副作用が増強した可能性は低いと考える．しかし，DCV・ASV は肝細胞に取り込むトランスポーター OATP1B1, 1B3 の阻害作用があり，OATP1B1, 1B3 の基質であるスタチン系の薬剤は DCV・ASV 併用により血中濃度が上昇する可能性があり，併用注意薬となっている[9][10]．今回使用していた ARB のオルメサルタン，テルミサルタン，バルサルタンは OATP1B1 や 1B3 の基質となるため[12]，併用注意薬にはないが，DCV・ASV による OATP1B1, 1B3 の阻害作用により血中濃度が上昇する可能性があると考察する．高カリウム血症を呈した3例は DCV・ASV 開始1週後の早期に発症しており，OATP1B1, 1B3 を介した相互作用により RAS 阻害剤の血中濃度が上昇し，副作用が増強した可能性があると考える．

近年，CYP を介した薬物相互作用だけでなく，OATP, P-糖タンパク質などのトランスポーターによる薬物相互作用が重要視されるようになった[13]~[15]．C 型肝炎ウィルス(HCV)直接阻害剤(Direct acting antiviral agent：DAA 製剤)の多くは，P-糖タンパク質や OATP1B1, 1B3 などのトランスポーター阻害作用を有することが報告されている[9][10][16][17]．現在使用可能なシメプレビル，ASV だけでなく，今後発売される可能性のある Ledipasvir や Faldaprevir, ABT450 なども同様のトランスポーター阻害作用があると報告されている[9][10]．また，肝障害などの副作用が少ないと報告されている Sofosbuvir は CYP や OATP などの誘導，阻害作用はないが，腎排泄型の DAA 製剤であり，腎機能や腎排泄型の薬剤との併用に注意を要すると考えられる[16]~[18]．国内外の臨床試験においては併用薬，合併症，年齢の制限が厳しく，DAA 製剤による薬物相互作用に関連した有害事象の全貌は，市販後明らかになってくると考えられる．

DCV・ASV 併用療法開始前後で利尿剤，グリチルリチン製剤の新規開始や中止，減量したため除外された10症例の中にも高血圧症，糖尿病を合併し，RAS 阻害剤併用中に高カリウム血症を呈した1症例が含まれていた．高カリウム血症3例と併せて全例60歳以上の症例であった．実臨床においては高齢で合併症の多い C 型肝炎症例では併用薬が多く，併用薬の追加，減量，中止など複数の要因により血清カリウム値増加などの電解質異常をきたす可能性がある．日本における C 型慢性肝炎症例の平均年齢は上昇傾向にあり，60歳以上の高齢者の比率が70％を超えている[19]．本研究の対象症例においても約90％は60歳以上の高齢者であった．今後，DCV・ASV 併用療法の適用拡大，Sofosbuvir の発売などにより高齢者への DAA 製剤の使用頻度が増すことが予想される．合併症や併用薬の多い症例において DAA 製剤を使用する際には，肝障害や腎障害だけでなく電解質異常など予期せぬ副作用，有害事象の早期発見，迅速な対応のため，定期的に血液検査を行うなど慎重な経過観察が必要であると提唱する．

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本論文内容に関連する著者の利益相反：なし

The relationship between renin angiotensin system inhibitor and serum potassium increase during combination therapy with Daclatasvir and Asnaplevir for chronic hepatitis C

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To demonstrate the relationship between renin angiotensin system inhibitor (RASI) and serum potassium increase during combination therapy with Daclatasvir and Asnaplevir in 27 patients with chronic hepatitis C, we first categorized subjects according to the administration of RASI. We then evaluated a clinical characteristic, liver and renal function, serum potassium levels at the baseline and change of serum potassium levels under treatment. There were no significant differences in age, sex, liver and renal function, serum potassium levels at the baseline between groups. Serum potassium levels under treatment significantly increased in the RASI group, and hyperkalemia developed in three cases of the RASI group. The cases with serum potassium increase tended to be complicated with diabetes. It is necessary to be cautious with the serum potassium increase when we start Daclatasvir and Asnaplevir in chronic hepatitis C patients with concomitant use of RASI.

Key words: chronic hepatitis C　Daclatasvir・Asnaplevir　serum potassium increase　renin angiotensin system inhibitor　diabetes

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＜症例報告＞

Daclatasvir・Asunaprevir併用療法中に著明な血小板減少を来したC型慢性肝炎の一例

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新井　洋佑[1)]　佐藤　賢[2)]　山田　正信[2)]

要旨：症例は70歳代女性．C型慢性肝炎（HCV genotype 1b，低ウイルス量）につき当科通院中であった．過去4回のインターフェロン（IFN）治療歴があるが，いずれも著効は得られず，Daclatasvir（DCV）・Asunaprevir（ASV）併用療法を開始した．同薬内服18日目に急性胆嚢炎の疑いで当科入院となった．入院時に血小板数7.3万/μlとやや低値であったが，胆嚢炎症状が改善した後も血小板数が1.1万/μlまで低下し，血小板輸血を要した．血小板減少の原因としてDCV・ASVの影響が否定できず，同薬の内服は22日間で中止とした．中止後1週間ほどで血小板数は徐々に増加し，中止後24日で退院，中止後24週間での持続ウイルス陰性化も確認できた．HCV陽性患者における血小板減少は，IFNベースの治療時のみならず，IFNフリーのDirect Acting Antiviralsによる抗ウイルス治療時にも注意を要する副作用の一つと考えられるため，文献的考察を加え報告する．

索引用語：C型慢性肝炎　ダクラタスビル　アスナプレビル　副作用　血小板減少

はじめに

インターフェロン（IFN）フリーのC型慢性肝炎治療薬として本邦で初めて使用可能となったDaclatasvir（DCV）およびAsunaprevir（ASV）の併用療法は，高い抗ウイルス効果に加え，IFNと比較し重篤な副作用が少なく，忍容性が高いことも特長とされる[1)]．そのため，血球減少などが原因でIFN治療に不適格と判断されていた症例でも治療が可能となった．しかし，DCV・ASV投与症例の増加に伴い，高カリウム血症など[2)]，国内臨床試験ではさほど注目されていなかった副作用が問題となる症例もみられている．今回我々は，DCV・ASV併用療法中に著明な血小板減少を来したC型慢性肝炎の一例を経験したので報告する．

症　例

患者：70歳代女性．

主訴：発熱・右季肋部痛．

既往歴：脊柱管狭窄症，眼底出血，強迫性障害，高血圧症，びらん性胃炎，便秘症．

嗜好：飲酒歴；なし，喫煙歴；なし．

家族歴：特記すべきことなし．

現病歴：1991年，肝機能障害のため近医より当科紹介受診となり，C型慢性肝炎と診断された．1992年以降，計4種類のIFN製剤及びpeg-IFN製剤にて加療したがウイルス排除は得られなかった．2012年2月には肝S8に1.4 cm，S6に1.0 cmの肝細胞癌（HCC）を認め，経カテーテル的肝動脈化学塞栓療法および経皮的ラジオ波焼灼術にて治療した．2014年10月，MRIにてHCCの再発を認めないことを確認し，同年12月よりDCV・ASV併用療法を開始した（治療開始時の血液検査結果をTable 1に示す）．DCV・ASV内服15日目（第15日）頃より食思不振および嘔吐が出現し，第17日には39℃台の発熱も認めた．その後，右季肋部痛も出現したため第18日に当院救急外来を受診し，急性胆嚢炎の疑いで精査・加療目的に当科入院となった．

入院時現症：体温39.0℃，血圧114/77 mmHg，脈拍95回/分．意識清明．眼瞼血膜貧血なし，眼球結膜黄疸

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Table 1 The laboratory data before the start of the combination therapy with daclatasvir (DCV) and asunaprevir (ASV)

Hematology		Blood chemistry	
WBC	4600 /μl	TP	8.1 g/dl
Seg	27.6 %	Alb	4.3 g/dl
Lym	60.8 %	TTT	6.3 Unit
Mono	8.4 %	ZTT	13.9 Unit
Eosi	1.7 %	T.Bil	1.3 mg/dl
Baso	1.5 %	D.Bil	0.1 mg/dl
RBC	437×10⁴ /μl	AST	55 IU/l
Hb	14.0 g/dl	ALT	47 IU/l
Ht	43.2 %	LDH	230 IU/l
Plt	10.3×10⁴ /μl	ALP	313 IU/l
		GGT	17 IU/l
Coagulation		BUN	16 mg/dl
PT (%)	92 %	Cre	0.58 mg/dl
PT-INR	1.1	Na	143 mEq/l
APTT	31.2 sec	K	4.1 mEq/l
		Cl	106 mEq/l
Virus marker		T.Chol	156 mg/dl
HCV genotype	1b	Glu	144 mg/dl
HCV viral load	3.7 LogIU/ml		
Drug resistance mutation (PCR-Invader assay)			
L31	negative		
Y93	negative		
D168E/D168V	weakly positive		

Table 2 The laboratory data on admission

Hematology		Blood chemistry	
WBC	7600 /μl	TP	7.5 g/dl
Seg	82.0 %	TTT	4.9 Unit
Lym	8.8 %	ZTT	8.9 Unit
Mono	7.5 %	T.Bil	1.6 mg/dl
Eosi	1.2 %	D.Bil	0.5 mg/dl
Baso	0.4 %	AST	36 IU/l
RBC	442×10⁴ /μl	ALT	19 IU/l
Hb	14.0 g/dl	LDH	200 IU/l
Ht	42.0 %	ALP	249 IU/l
Plt	7.3×10⁴ /μl	GGT	19 IU/l
		BUN	12 mg/dl
Coagulation		Cre	0.63 mg/dl
PT (%)	60 %	Na	138 mEq/l
PT-INR	1.4	K	4.3 mEq/l
		Cl	104 mEq/l
		T.Chol	146 mg/dl
		Glu	101 mg/dl
		CRP	3.34 mg/dl
		PCT	1.42 ng/ml

なし．心音正常，呼吸音正常．腹部でグル音は正常も，右季肋部に自発痛および圧痛を認めた．筋性防御なし．

入院時血液検査所見（**Table 2**）：白血球数，ヘモグロビンは基準値内であったが，血小板数は7.3万/μlと軽度低下していた．PT(%)も60%に低下していた．生化学検査ではAST 36 U/l，CRP 3.34 mg/dl，PCT 1.42 ng/mlと上昇していた．血液培養及び便培養からは有意な菌発育は認められなかった．

入院後経過：絶食・補液・抗生剤投与を開始した．DCV・ASVのほか，常用薬（トコフェロールニコチン酸エステル，ファモチジン，ポラプレジンク，ゾルピデム酒石酸塩，酸化マグネシウム）の内服は継続とした．第20日の腹部CTでは胆嚢壁の肥厚及び少量の腹水貯留を認めたが，肝萎縮や脾腫は認めなかった．入院後，発熱や腹痛などの症状は徐々に改善したが，血小板減少が進行した．原因として抗生剤による薬剤性血小板減少を考慮し，以前使用し問題のなかったCEZに変更した．しかし，第22日には血小板数はさらに低下し2.5万/μlとなった．DCV・ASVの関与が否定でき

ないと考え，同2剤の投与を中止した．その他の常用薬は全て数年前から内服しており，被疑薬としては否定的と考えた．翌日（DCV・ASV中止後1日）には血小板数が1.1万/μlまで低下したため，血小板輸血を1日10単位行った．中止後2日の検査でも血小板数1.1万/μlと改善はみられなかった．同日の血清ALT値は86 IU/lに上昇していた．身体所見では硬口蓋に点状出血を認めた．中止後6日に骨髄穿刺を施行したところ，骨髄は低形成で，髄液検査での有核細胞数は1.0万/μl，巨核球数は3/μlと低下していた．塗沫標本でも巨核球はわずかに認めるのみで著明に減少していた（Fig. 1）．芽球等の増加や，細胞異型は認めなかった．末梢血塗沫標本では異型リンパ球が散在しており，好酸球が若干増加していた．造血能の評価のため胸腰椎MRIを施行したところ，下位胸椎～腰椎の骨髄でT2強調，T1強調高信号が斑状にみられた（Fig. 2）．高信号領域は一致しており，STIR法，T1 fat sat法では信号が抑制され，いずれも造血障害によるびまん性脂肪髄を示唆する所見であった．骨髄の染色体検査では異常を認めなかった（46, XX）．以上の血液学的検査結果から，急性の特発性血小板減少性紫斑病（ITP）は否定的で，DCV・ASVのいずれかもしくは両者による薬剤性血小板減少と考えた．入院時に疑われた急性胆嚢炎の影響も否定はできなかったが，画像・血液検査結果で胆嚢炎の所

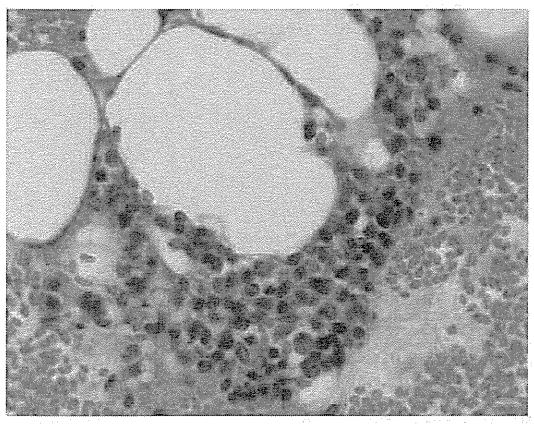

Fig. 1 The histopathological findings in a bone marrow specimen
The patient's bone marrow was relatively hypoplastic with a marked decrease in the number of megakaryocytes.

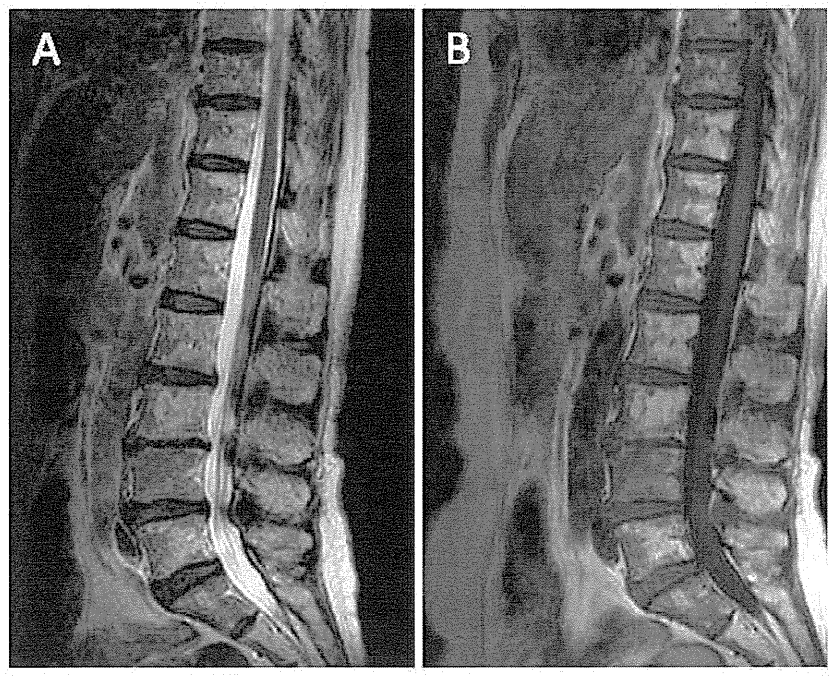

Fig. 2 The spinal MRI findings
Bone marrow MRI shows a patchy high signal in both T2 (A) and T1 (B) weighted images.

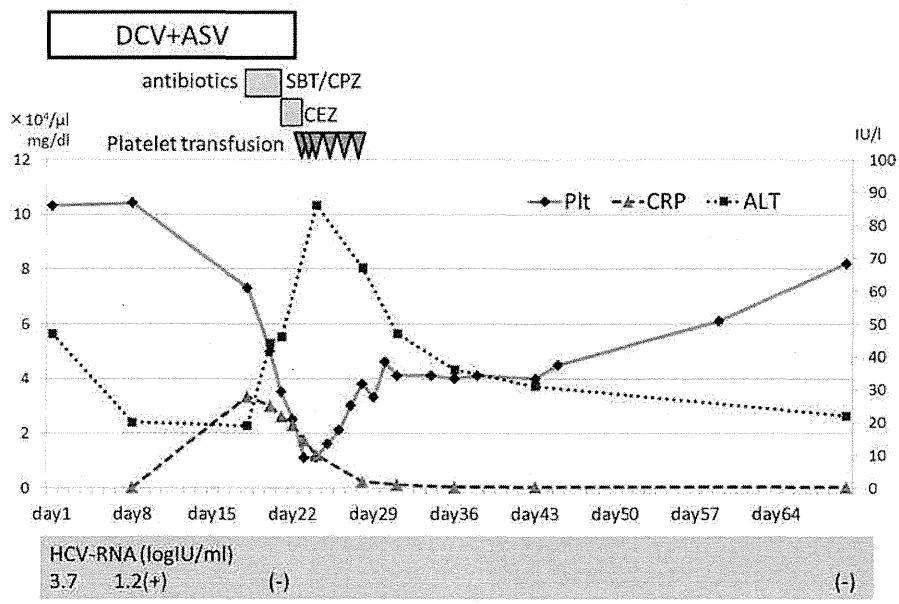

Fig. 3　The clinical course
A sustained virological response was achieved at 24 weeks after the discontinuation of the DCV and ASV combination therapy.

見はさほど強くなく，かつ自覚症状も比較的速やかに改善したため，血小板減少を引き起こす原因とは考えにくいと判断した．DCV・ASV中止後1週間ほどで血小板数は緩徐な上昇傾向を示し，血小板輸血も不要となった．血清ALT値も徐々に改善した．DCV・ASV中止後24日で退院となり，その後も血小板数は10万/μl前後，血清ALT値は基準値内を推移し，治療中止後24週間での持続ウイルス陰性化（SVR24）を確認した（経過表 Fig. 3）．

考　察

IFNをベースとしたC型慢性肝炎治療の進歩により，SVRを得られる症例が増加した一方[3]，IFNの副作用で治療困難な症例も多く存在する[4]．治療前に血小板が低値の症例では，脾臓摘出術や部分脾動脈塞栓術を併用した治療が試みられているが[5]，実際には治療導入を断念せざるを得ない症例も多い．IFNフリーのC型慢性肝炎治療薬として本邦で初めて使用可能となったNS5A阻害剤であるDCVおよびNS3/4A protease阻害剤であるASVの併用療法は，その抗ウイルス効果の高さとともに，副作用が軽微で忍容性が高いことも特長である[1]．現在は治療前のウイルス学的検査にてNS5A領域のL31/Y93アミノ酸変異を認めないC型慢性肝炎・代償性肝硬変症例で広く投与されている[6]．

DCVおよびASVは細胞毒性が弱い薬剤であり[7]，同2剤の併用により，抗ウイルス効果としては相加あるいは相乗効果が得られるが，毒性の増強はみられないとされる[8]．実際，DCV・ASVの併用療法で比較的頻度の高い副作用は鼻咽頭炎や血清AST・ALT値の上昇などで，多くの副作用は対症療法や経過観察で対応可能である．重篤な肝機能異常を生じた際には同薬の投与中止を余儀なくされるものの，中止後に肝機能異常は速やかに改善し，そのようなケースでもSVRを得られることが多い[1]．本例ではDCV・ASV投与が22日間という短期間で中止となったが，SVRが得られた．国内臨床試験の結果，肝機能異常のためにDCV・ASV併用療法の中止を要した症例における，肝機能異常の発現日は治療開始27～123日とされ[9]，そのうち多くの症例（phase-3試験では中止10例のうち8例）でSVRが得られている[1]．本例でも血清ALT値の上昇を認めたが，その発現は血小板数低下が出現した後であった．本例においてDCV・ASVの短期間投与でSVRが得られた

理由としては，治療前の HCV ウイルス量が比較的低値だったことに加え，何らかの原因により DCV・ASV の血中濃度が上昇し，強い抗ウイルス効果が得られたことなども考えられる．

DCV・ASV は共に，CYP3A4 で代謝され，ASV は OATP1B1 及び 2B1 の基質でもある．これらの酵素で代謝される薬剤もしくは基質となる薬剤のうち一部は，血中濃度の上昇を呈する恐れがあり併用禁忌もしくは併用に注意が必要である[10]．本例では DCV・ASV の併用禁忌薬や併用注意薬の使用はなかった．しかし，CYP3A4 の活性には個体差が大きいとされ[11]，本例でその活性が低下していた可能性は否定できない．本例では同じ CYP3A4 で代謝されるゾルピデム酒石酸塩を常用していたが，同薬の持ち越し効果や副作用は認められなかった．

C 型慢性肝炎・肝硬変に対する抗ウイルス治療に伴う血小板減少は，IFN を含むレジメンでは比較的高頻度でみられた副作用である．IFN が血小板減少の主因となるため，IFN の投与量を調節することで対応が可能となることが多く[12]，IFN の添付文書でも血小板数による減量・中止基準が明記されている．欧米の報告では，血小板減少が重篤な場合はトロンボポエチン受容体作動薬である eltrombopag の投与も有用とされる[13][14]．一方，DCV・ASV 併用療法では，国内第 2 相試験及び第 3 相試験の統合解析における血小板数の推移で治療開始後に grade4 の血小板減少（2.5 万/μl 未満）を認めた症例は全 255 例のうち 2 例であった．本例のように著明な血小板減少を認めるのは比較的稀と考えられる[10]．本薬剤の適応症として非代償性肝硬変は認められていないが，血小板数に投与開始時の制限はなく，中止基準も示されていない．

薬剤による血小板減少の発生機序を大別すると，薬剤により惹起された免疫学的機序のため血小板破壊が亢進する場合と，薬剤の作用で骨髄抑制が起こり骨髄巨核球の血小板産生が低下する場合の 2 通りがある[15]．前者（血小板破壊の亢進）の原因薬剤としてはキニーネ，キニジンなどが有名で，被疑薬の中止でも改善が得られない場合の治療法として血小板輸血，副腎皮質ステロイド投与，γグロブリン大量投与，血漿交換などがある．後者（血小板産生の低下）では更に，抗腫瘍薬剤使用時のように骨髄細胞が総じて抑制される場合と，巨核球系のみが抑制される場合がある．本例の髄液検査では有核細胞数や巨核球数の著明な低下を認めた．検体採取時に末梢血が混入した可能性も否定はできなかったが，脊椎 MRI を施行し，造血障害によるびまん性脂肪髄を裏付ける所見が得られている．本例では巨核球系が特に強く抑制されており，骨髄所見で巨核球の無形成を認めた．著明な血小板減少を呈するが貧血や白血球減少は目立たず，「無巨核球性血小板減少症（AAMT）」に近い病態であったと考える[16]．しかし，当初，血小板輸血に対する反応も乏しかったことを考慮すると，他の複数の病態が関与し著明な血小板減少を来した可能性も示唆される．

C 型慢性肝炎は時に ITP を合併することがあり，IFN 治療が有効であると報告されている[17]．一方，ITP 合併の C 型慢性肝炎症例に対し Direct Acting Antivirals (DAAs) を投与し，SVR が得られたものの ITP の悪化を認めた症例の報告もあり[18]，ITP 合併症例での DAAs 使用は一定の注意が必要と考える．本例では，血小板輸血を行っても減少に歯止めがかからない場合や，重篤な出血症状の恐れがある場合には，ITP や AAMT の治療方針に準じてステロイド投与を行い[19]，それでも改善がみられない場合にトロンボポエチン受容体作動薬を投与する方針としていた．実際には，全経過中の出血症状としては硬口蓋の点状出血を認めたのみで，DCV・ASV の中止後に徐々に血小板数が上昇に転じたため，新たな薬剤の投与は要さなかった．

結　語

DCV・ASV 併用療法中に著明な血小板減少を来した C 型慢性肝炎の一例を経験した．血小板減少は IFN ベースの治療時のみならず，IFN フリーの DAAs による抗ウイルス治療時にも注意を要する副作用の一つと考えられた．

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本論文内容に関連する著者の利益相反：なし

A case of chronic hepatitis C accompanied by marked thrombocytopenia during combination therapy with daclatasvir and asunaprevir

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The patient was a 70-year-old woman with chronic hepatitis C with genotype 1b and a low viral load. She had previously undergone treatment with several interferon regimens but could not achieve sustained virologic response (SVR). Treatment was initiated with a combination of daclatasvir (DCV) and asunaprevir (ASV). On the 18th day of treatment, she was admitted with suspected acute cholecystitis. Her platelet count was slightly low and continued to decrease after the improvement of acute cholecystitis. She required a platelet transfusion. From the clinical course and the laboratory data, we suspect that the patient experienced drug-induced thrombocytopenia due to DCV/ASV. The patient's platelet count showed gradual improvement one week after the discontinuance of DCV/ASV. She subsequently achieved SVR. We should pay attention to the possibility of drug-induced thrombocytopenia not only in patients who receive interferon regimens but also in those who receive interferon-free regimens with direct acting antivirals.

Key words: chronic hepatitis C　daclatasvir　asunaprevir　adverse effect　thrombocytopenia

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Percutaneous radiofrequency ablation for hepatocellular carcinoma located in the caudate lobe of the liver

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Abstract

Aim : **This study aimed to evaluate the effectiveness and safety of radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) located in the caudate lobe of the liver.**

Patients and methods : **Between 2012 April and 2014 February, 142 patients with HCC meeting the Milan criteria were enrolled in this study. Of these patients, nine patients had HCC located in the caudate lobe (caudate group). Six of the nine cases were located in the Spiegel lobe, two cases were located in the paracaval portion and one case was located in the caudate process. We evaluated the local recurrence rate and RFA-related complications in the caudate group and non-caudate group.**

Results : **The local recurrence rate in the caudate group was 12.5% at 1 year and 12.5% at 2 years, while the local recurrence rate in the non-caudate group was 14.9% at 1 year and 29.0% at 2 years ; there were no significant differences between the groups. No complications were observed in the caudate group, and minor complications were observed in six patients (4.5%) in the non-caudate group. No major complications or mortalities were observed in either group, and the complication rates were not significantly different between the groups (P = 1).**

Conclusions : **RFA for HCC in the caudate lobe and the non-caudate lobe has equivalent effectiveness and safety. RFA is a promising treatment option for HCC arising in the caudate lobe.** (Acta gastroenterol. belg., **2015**, 78, **267-273**).

Key words : hepatocellular carcinoma, radiofrequency ablation, caudate lobe.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide (1). It is the fifth most common malignant disease in men and the eighth most common malignant disease in women (1). Current options for curative treatment of HCC consist of surgical resection, liver transplantation and radiofrequency ablation (RFA). However, HCC arising in the caudate lobe is considered to be difficult to treat with curative therapy because of its location, between the right and left lobes of the liver, near the hepatic hilus and the inferior vena cava. Surgical resection for HCC in the caudate lobe carries a high surgical risk because it is associated with significantly higher intraoperative blood loss and longer operative time than that in other locations (2,3). Although RFA is a local curative therapy (4,5), RFA for HCC in the caudate lobe is thought to be a contraindication because of the deep tumor location from the body surface, presence of adjacent large vessels, such as the portal vein trunk and inferior vena cava, and difficulty in performing safe puncture of the tumors. Some reports have described the therapeutic outcomes of RFA for HCC in the caudate lobe (6-10), reporting that RFA for HCC in the caudate lobe carries a high local recurrence rate (6,7). Previous authors have also discussed the possibility of the heat sink effect of the inferior vena cava and the restricted puncture approach (7) and concluded that it was necessary to pursue a revised method to reduce local recurrence (7).

In the present study, we evaluated the local recurrence rate and incidence of RFA-related complication for HCC in the caudate lobe compared to that observed in other locations.

Patients and methods

Patient eligibility

Between 2012 April and 2014 February, 142 patients with HCC participated in this study. All patients were treated at Isesaki Municipal Hospital. Of these patients, nine patients had HCC in the caudate lobe. The inclusion criteria were as follows : (a) ineligible for surgical resection/liver transplantation or patient refusal for surgery ; (b) Eastern Cooperative Oncology Group performance status, grade 2 or less ; (c) a single tumor ≦ 5 cm in diameter or three or fewer tumors ≦ 3 cm in diameter ; (d) Child-Pugh class A or B ; (e) no extrahepatic metastasis ; (f) no vascular invasion ; (g) platelet count ≧ 50,000/mm^3 ; (h) prothrombin activity ≧ 50%. The exclusion criteria were as follows : (a) tumors not visualized on ultrasonography ; (b) refractory ascites ; (c) enterobiliary reflux ; (d) total bilirubin level ≧ 3 mg/dl ; (e) other active malignancy that may affect the patient prognosis.

The diagnosis of HCC was established based on findings of nodular enhancement in the arterial phase and wash out in the delayed phase on dynamic computed tomography (CT) and/or dynamic magnetic resonance imaging (MRI) according to the AASLD guidelines (11).

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When the nodules were not typical on CT or MRI imaging, we performed a liver biopsy and diagnosed it based on the results of a histological examination.

All RFA procedures were performed percutaneously using ultrasonographic guidance. We performed RFA alone or in combination with transarterial chemoembolization (TACE). In principle, HCC lesions were treated with RFA combined with TACE when measuring 2 cm larger or exhibiting contact with major vessels in the caudate group. Informed consent was obtained from all patients.

RFA procedure

We performed RFA with the patient in the supine or head up position in all cases. We continuously monitored the heart rate, blood pressure and saturation of oxygen during treatment. One gram of cefazolin sodium was intravenously administered before the RFA procedure to prevent infectious disease. A local anesthetic (1% lidocaine) was injected from the site of insertion in the skin and liver surface along the planned puncture line. We incised the skin with a small lancet and inserted the 17-G cool tip needle with a 2- or 3-cm exposed tip (Covidien, Mansfield, MA, USA) into the tumor area with ultrasound guidance. During treatment, all patients were treated with conscious sedation via the intravenous injection of 15 mg of pentazocine hydrochloride. When the patients complained of intolerable pain, we intravenously administered an additional 15 mg of pentazocine hydrochloride. The ablation time ranged from 3-12 min per procedure. When the roll off temperatures were under 60°C after ablation, then we increased the ablation time until we obtained a roll off temperature above 60°C. After ablation, we withdrew the needle and evaluated the degree of tract needle bleeding using Color Doppler imaging. When we detected continuous tract needle bleeding, we ablated the bleeding point at the surface of the liver. This process was repeated until the entire tumor was adequately ablated.

Approaches for RFA

We identified two approaches to insert the ablation needle into the HCC in the caudate lobe. The first is the epigastric approach (EA), in which the ablation needle is transfixed from the lateral segment to the targeted HCC via the lesser omentum. In this approach, we evaluated the vessels between the lateral segment and caudate lobe using color Doppler imaging and CT or MRI and carefully placed the ablation needle forward to the target the HCC lesion because it exits the liver once and may potentially penetrate any major vessel in the trans-omental tract. The second method is the right costal approach (RCA), in which the ablation needle is transfixed from the right lobe of the liver to the targeted HCC lesion. We mainly used the epigastric approach. When the HCC was located in the paracaval portion or caudate process and we could not find the puncture route via the epigastric approach, we used the right costal approach.

Assessment of ablation and follow-up schedule

One to three days after RFA, dynamic CT with a 3-5 mm section thickness was performed to evaluate the RFA procedure. When the ablated area was large enough to cover the pretreatment HCC area on arterial and portal venous phase images, we defined such case as complete ablation. When complete ablation was not obtained, the RFA procedure was repeated until complete ablation was achieved.

In order to detect HCC recurrence earlier, we performed dynamic CT or dynamic MRI every 3-4 months. The serum alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) levels were measured every 1-3 months. Local tumor recurrence was defined as the appearance of enhancement in the arterial phase around the ablation area.

Statistical analysis

The statistical analyses were performed with the EZR graphical interface (12). Student's *t*-test was used to compare continuous data following a normal distribution, and Welch's t test was used to compare data without a normal distribution. Fisher's exact test was employed to compare categorical data. The local tumor recurrence rate was calculated according to the Kaplan Meier method. A P value of < 0.05 was considered to be statistically significant.

Results

We divided the 142 consecutive patients with HCC into two groups according to the tumor location, the caudate group (n = 9) and non-caudate group (n = 133). The characteristics of the caudate and non-caudate groups are summarized in Table 1 and Table 2. In the caudate group, six HCCs were located in the Spiegel lobe, two were located in the paracaval portion and one was located in the caudate process according to the Kumon classification (13). In the caudate group, five patients were male and four patients were female. In the non-caudate group, 73 patients were male and 61 were female. The mean age of the patients was 69.0 ± 9.4 years (caudate group), 71.5 ± 7.5 years (non-caudate group), respectively. The etiology of HCC was HBV/HCV/other in 1/5/3 patients (caudate group) and 5/111/18 patients (non-caudate group), respectively. The Child-Pugh class was A/B in 8/1 patients (caudate group) and 105/29 patients (non-caudate group), respectively. All characteristic parameters in the caudate group and non-caudate group showed no significant differences between the groups, except for the serum level of total bilirubin.

Local recurrence rate

Local recurrence was observed in two nodules in the caudate lobe at 4.8 and 27.1 months after RFA treatment. In the non-caudate group, local recurrence was observed

Table 1. — **Characteristic of the nine patients with HCC in the caudate lobe of the liver**

Case	Age/sex	Diameter (cm)	Location	Vascular contact	Combination With TACE	Puncture approach	Number of session	Length of needle	Follow up (month)
1	64/M	2.1	Spiegel	None	No	EA	1	2 cm	29.3
2	68/M	2.9	Paracaval	PVT	Yes	EA	1	2 cm	27.2
3	64/F	2.2	Spiegel	IVC	Yes	EA	1	2 cm	26.7
4	73/F	4.5	Caudate process	IVC, PVT	Yes	RCA	1	3 cm	25.8
5	68/M	3.9	Spiegel	IVC, PVT	Yes	EA	2	2 cm	20.2
6	53/M	1.8	Paracaval	IVC	Yes	EA	2	2 cm	13.3
7	80/F	0.7	Spiegel	IVC	No	EA	1	2 cm	4.8
8	66/M	1.8	Spiegel	PVT	No	EA	2	2 cm	2.1
9	85/F	3.0	Spiegel	None	Yes	EA	1	3 cm	13.5

TACE, trans arterial chemoembolization ; PVT, portal vein trunk ; IVC, inferior vena cava ; EA epigastric approach, RCA ; right costal approach.

Table 2. — **Characteristics of the patients and tumors in the caudate group and non-caudate group**

Case (n)	Caudate group (N = 9)	Non-caudate group (N = 134)	*P*-value
Age (mean ± SD, years)	69.0 ± 9.4	71.5 ± 7.5	0.336*1
Sex (Male / Female)	5 / 4	73 / 61	1.0*2
ECOG PS 0 / 1 / 2	6 / 2 / 1	67 / 63 / 4	0.493*3
Etiology (HBV / HCV / others)	1 / 5 /3	5 / 111 / 18	0.382*3
Child-Pugh classification A / B	8 / 1	105 / 29	1.0*2
Total bilirubin, median (range) (mg/dl)	0.67 (0.50-0.86)	0.69 (0.29-2.02)	< 0.001*4
AST (mean ± SD, IU/l)	40.5 ± 24.6	51.5 ± 22.2	0.255*1
ALT (mean ± SD, IU/l)	37.4 ± 32.5	42.5 ± 27.4	0.613*1
Albumin (mean ± SD, g/dl)	3.67 ± 0.43	3.59 ± 0.47	0.603*1
Platelet (mean ± SD, /mm^3)	12.9 ± 5.7	9.9 ± 4.5	0.07*1
PT, median (range) (%)	87 (73-92)	85 (52-133)	0.273*4
Tumor size, median (range) (cm)	2.2 (0.7-4.5)	1.8 (0.7-4.7)	0.135*4
Number of tumor (mean ± SD)	1.44 ± 0.72	1.26 ± 0.52	0.32*1
Follow up period (mean ± SD , month)	16.6 ± 7.1	14.7 ± 7.0	0.051*1
Combined TACE (yes / no)	6 / 3	84 / 50	1.0*2
Number of RFA session 1 / 2 / 3	5 / 3 / 0	134 / 22 / 1	0.148*2
AFP, median (range) (ng/ml)	15 (2-2373)	16 (7-2878)	0.414*4
DCP, median (range) (mAU/ml)	23 (3-3097)	19 (15-550)	0.765*4

ECOG PS, Eastern Cooperative Group Performance Status ; HBV, hepatitis B virus ; HCV, hepatitis C virus ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; TACE, transarterial chemoembolization ; AFP, α-fetoprotein ; DCP, des-γ-carboxy prothrombin .
*1 Student's *t*-test, *2 Fisher's exact test, *3 Mann-Whitney U test, *4 Welch's *t*-test.

in 35 cases. The cumulative local recurrence rate in the caudate group was 12.5% and 12.5% at 1 and 2 years, respectively (Fig. 1), while that in the non-caudate group was 14.9% and 29% at 1 and 2 years, respectively. There were no significant differences in the local recurrence rates between the caudate group and the non-caudate group ($P = 0.875$).

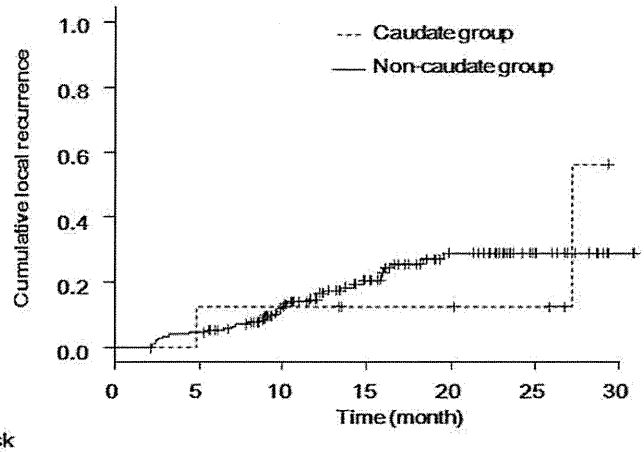
Representative cases

Epigastric approach

Figure 2 shows a representative case of the epigastric approach (Case 9). Dynamic computed tomography (CT) revealed HCC of 3.0 cm in diameter in the Spiegel lobe. Trans-arterial chemoembolization (TACE) was performed before RFA. Percutaneous RFA was then performed five days after chemoembolization. We used the epigastric approach because there were no major vessels in the puncture route.

Right intercostal approach

Figure 3 shows a representative case of the right intercostal approach (Case 4). Dynamic magnetic resonance imaging (MRI) revealed HCC of 4.5 cm in diameter in the caudate process of the caudate lobe. The HCC lesion was adjacent to the portal vein trunk and inferior vena



Number at risk							
caudate group	9	7	7	5	5	4	0
Non-caudate group	170	162	121	69	40	16	2

Fig. 1. — Cumulative local recurrence rates. There were no significant differences in the local recurrence rates between the caudate group and the non-caudate group ($P = 0.875$).

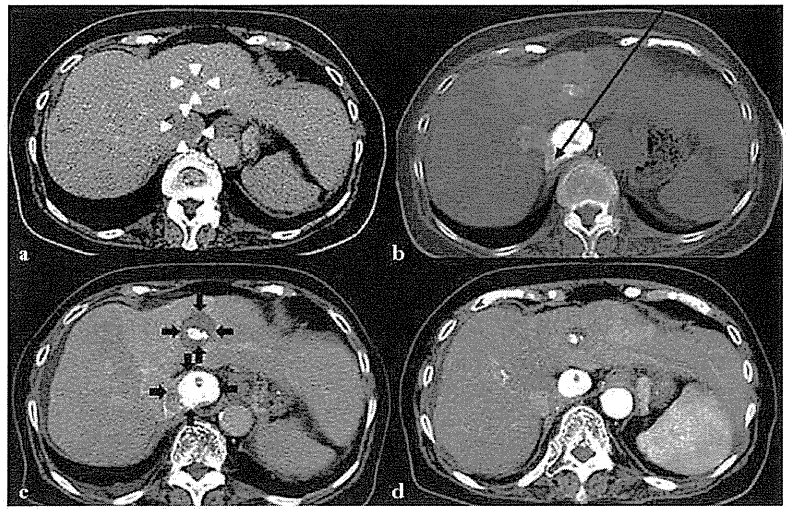


Fig. 2. — Case 9 (a) Dynamic computed tomography (CT) showed two hepatocellular carcinoma (HCC) lesions 3.0 cm in diameter in the Spiegel lobe and 1.2 cm in diameter in segment 3. An assay for hepatitis C antibodies was positive. (b) Transarterial chemoembolization was performed. (c) Percutaneous radiofrequency was performed five days after chemoembolization. We used the epigastric approach because there were no major vessels in the puncture route. Dynamic CT was performed three days after RFA. The tumor was surrounded by hypo-attenuating non-enhancing areas. (d) No local recurrence has been observed for 13.5 months after RFA.
(△) viable tumor. (→) puncture route. (⬆) coaguoblated area.

cava. We were unable to find the puncture route via the epigastric approach, because the lateral segment showed atrophy. Therefore, we used the right intercostal approach after TACE. No local recurrence has been observed for 25.8 months after RFA.

Complications

There were no major complications or mortalities related to the RFA procedure in either group. No minor complications were observed in the caudate group. In the

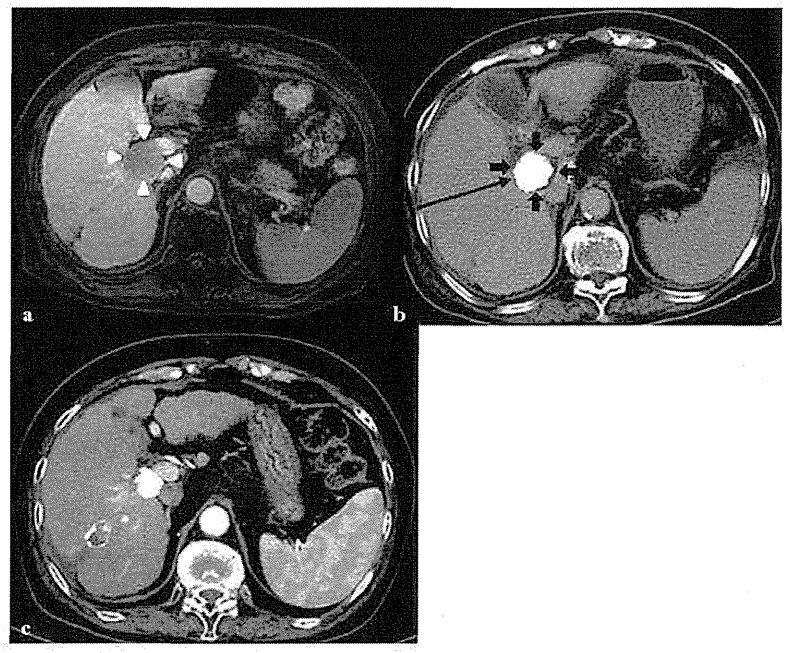


Fig. 3. — Case 4. (a) Dynamic magnetic resonance imaging (MRI) revealed hepatocellular carcinoma (HCC) 4.5 cm in diameter in the caudate process of the caudate lobe. The HCC lesion was adjacent to the portal vein trunk and inferior vena cava. (b) We performed transarterial chemoembolization (TACE) plus radiofrequency ablation (RFA). We were unable to detect the puncture route via the epigastric approach, because the lateral segment showed atrophy. Therefore, we used the right intercostal approach. The tumor was surrounded by hypoattenuating, non-enhancing areas on dynamic computed tomography (CT). (c) No local recurrence has been observed for 25.8 months after RFA.
(△) viable tumor ; (→) puncture route ; (⬆) ablated area.

non-caudate group, there were minor complications in six patients (4.5%), including sub-segmental hepatic infarction in five patients (3.75%) and biloma in one patient (0.76%). All complications were improved with conservative therapy and did not require additional therapy or longer hospitalization. The incidence of RFA-related complications in the groups was not significantly different ($P = 1$).

Discussion

This study suggests that percutaneous RFA for HCC in the caudate lobe of the liver is an effective and safe treatment. In the present study, the local recurrence rate of RFA for HCC in the caudate lobe of the liver was not significantly higher than that in the non-caudate lobe. The caudate lobe is located in the central liver around large vessels deep from the hepatic surface. Therefore, for HCC in the caudate lobe, it is thought to be difficult and dangerous to puncture the nodule from the skin using RFA. However, this study showed no complications or mortalities in the caudate group.

Hepatic resection is a curative therapy, although hepatic resection for HCC arising in the caudate lobe is associated with significantly higher intraoperative blood loss and a longer operative time than that arising in non-caudate regions (2,3). As a result, hepatic resection for HCC in the caudate lobe is a high-risk procedure. In the present study, local recurrence in the caudate group was observed in two nodules in the caudate lobe at 4.8 and 27.1 months after RFA treatment, respectively. The cumulative local recurrence rate in the caudate group was 12.5% and 12.5% at 1 and 2 years, respectively. Kariyama *et al.* (6), Nishigaki *et al.* (7) and Fujimori *et al.* (8) reported local recurrence rates of 12% at 2 years, 22.3% at 4 years and 13.5% at 3 years, respectively, which is similar to our data (See Table 3). Nishigaki *et al.* (7) reported that the local recurrence rate of RFA alone for HCC in the caudate group is significantly higher than that in the non-caudate group. They reported that the location in the caudate lobe of the liver is an independent risk factor for local recurrence according to a multivariate analysis (7). However, there were no significant differences in the local recurrence rates between the caudate group and non-caudate groups in this study. A possible explanation for this discrepancy may the differences in both patient and tumor characteristics. Comparing the patients and tumor characteristics between our and their study, the

Table 3. — **Previous reports concerning RFA for HCC in the caudate lobe of the liver**

Author	Kariyama K. (6)	Nishigaki Y. (7)	Seror O. (9)	Fujimori M. (10)	This study
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Cancer	HCC	HCC	HCC and colon metastases	HCC	HCC
Number of cases	50	20	10	20	9
RFA indication	milan criteria	Solitary	NA	Solitary ≦ 5 cm	milan criteria
tumor size	1.5 cm (median)	1.7 ± 0.5 cm (mean ± SD)	4.1 cm (median)	≦ 3 cm 14 case 3.1-5.0 cm 6 case	2.2 cm (median)
Treatment	RFA alone or TACE plus RFA	RFA alone	RFA alone	TACE plus RFA	RFA alone or TACE plus RFA
Type of guidance	US	US	US and CT	CT	US
Follow up period (mean)	18 month	NA	11.4 month	NA	16.6 month
Local recurrence rate	12% at 2 years	22.3% at 4 years	3/10 nodule	13.5% at 3 years	12.5% at 2 years
Complication	No major complication	No major and minor complication	Major in 1 case and minor in 1 case	Major in 2 cases and minor in 3 cases	No major and minor complication

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; NA, not available; TACE, transarterial chemoembolization; US, ultrasonography; CT, computed tomography.

median size of HCC treated in our study was 2.2 cm and the mean size of HCC in their study was 1.7 cm ± 0.5 cm in the caudate group (See Table 3). In the control group, we evaluated single tumors of ≦ 5 cm in diameter or three or fewer tumors of ≦ 3 cm in diameter in the non-caudate group. On the other hand, they evaluated solitary tumors of less than 3 cm in diameter in the non-caudate group. Several authors have reported that the tumor size is an independent risk factor for local recurrence (14,15). Therefore, the differences in the tumor size may have affected the results of our and their studies.

With respect to reducing the local recurrence rate of RFA, the effectiveness of preceding TACE prior to RFA is controversial. Shibata *et al.* (16) reported that combined RFA plus TACE and RFA alone have equivalent effectiveness for the treatment of small (≦ 3 cm) HCCs. However, in patients with intermediate-sized lesions (diameter, 3.1-5 cm), RFA plus TACE is more effective than RFA alone for extending the ablated area in fewer treatment sessions and needle insertions and decreasing the rate of local tumor progression (17). Peng *et al.* (18) reported that the efficacy of sequential TACE-RFA is better than that of RFA alone for HCC measuring 5 cm in diameter or smaller. They also reported that, in their subgroup analyses, the recurrence-free survival and overall survival rates were better in the sequential TACE-RFA group than in the RFA alone group with tumors measuring 3.1-5.0 cm in diameter. Therefore, preceding TACE before RFA was found to be a better treatment than RFA alone when performing RFA for HCC measuring 3.1-5.0 cm in diameter. Although it is not easy to detect the feeding artery on angiograms and TACE is performed for HCC arising in the caudate lobe (19), preceding TACE before RFA for HCC arising in the caudate lobe is also a better treatment with less complications for reducing the number of punctures. In the present study, all three patients with HCC measuring 3 cm larger in the caudate group were treated with RFA combined with TACE, and no local recurrence was observed.

No complications were observed in the caudate group, and major complications requiring additional therapy or longer hospitalization were absent in both groups. Minor complications were observed in six patients (4.5%) in the non-caudate group and improved with conservative therapy. There were no statistical differences between the groups. In past studies, major complications were observed in 0-10% of cases, and all types of complications were observed in 0%-25% of cases (See Table 3). The low complication rates noted in our study were achieved by careful advancing the ablation needle and avoiding the vital strictures and vessels. A careful examination of the puncture needle line in epigastric approach (EA) and right costal approach (RCA) before RFA is important for avoiding serious complications.

A limitation of this study is the retrospective design with a small number of patients and the short follow-up period. In conclusion, our findings suggest that RFA for HCC in the caudate lobe and the non-caudate lobe has equivalent effectiveness and safety and that RFA is a promising treatment option for HCC arising in the caudate lobe. When encountering HCC lesions measuring 3 cm in diameter or larger in the caudate lobe, RFA combined with TACE may be a better treatment for reducing the local recurrence rates.

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Hepatology Research

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Original Article

Safety and efficacy of balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma

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Aim: Balloon-occluded transcatheter arterial chemoembolization (B-TACE) using a microballoon catheter was performed to administrate miriplatin, and the early therapeutic efficacy and safety of the procedure were evaluated.

Methods: Out of 158 patients who received miriplatin using B-TACE for hepatocellular carcinoma, 49 patients with a single lesion at either stage I or II (according to the Liver Cancer Study Group of Japan) were evaluated in comparison with 48 matched patients who received miriplatin using conventional TACE (C-TACE).

Results: The mean total dose and median dose of miriplatin in each group were 32.5 ± 31.7 mg and 20 mg (C-TACE) and 50.1 ± 31.3 mg and 40 mg (B-TACE), respectively ($P < 0.01$). The treatment effect (TE) on the target nodule classified as TE4, TE3, TE2 or TE1 was 39.6%, 33.3%, 25.0% and 2.1%, respectively, in the C-TACE group, and 55.1%, 38.8%, 4.1% and 2.0%, respectively, in the B-TACE group. Therefore, the TE was significantly higher in the B-TACE group ($P < 0.05$). Although abdominal blood tests revealed adverse, increased levels of serum alanine aminotransferase (ALT) in a significantly higher number of B-TACE-treated patients, serum ALT levels returned to baseline levels in all patients within 1 month. There were no significant differences in clinical symptoms between the two groups.

Conclusion: Compared with C-TACE, B-TACE significantly improved cancer nodule control, and it was satisfactory in terms of safety. B-TACE is an effective procedure that enhances the effects of catheterization with miriplatin.

Keywords: balloon-occluded transcatheter arterial chemoembolization, hepatocellular carcinoma, miriplatin

INTRODUCTION

IN TRANSCATHETER ARTERIAL chemoembolization (TACE) for hepatocellular carcinoma (HCC), greater improvement of local control is achieved with better uptake of lipiodol (Lipiodol Ultrafluid; Terumo, Tokyo, Japan).[1] Balloon-occluded TACE (B-TACE), in which a microballoon catheter is used for TACE, is considered to improve the uptake of lipiodol into cancer nodules, as compared with conventional TACE (C-TACE).[2,3] Meanwhile, miriplatin (MIRIPLA; Dainippon Sumitomo Pharma, Osaka, Japan), which has high affinity for lipiodol, locally remains in tumors for a long period of time and thereby exerts prolonged antitumor effects but is minimally transferred to the systemic circulation. Based on these pharmacokinetic characteristics, miriplatin has recently been reported to be highly effective and safe.[4–6] In this study, we performed B-TACE to administrate miriplatin and evaluated the early therapeutic efficacy and safety of this procedure.

METHODS

A TOTAL OF 158 patients received miriplatin using B-TACE for HCC at our hospital between November 2011 and November 2013. Of these 158 patients, 49 with a single lesion at either stage I or II were included

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Table 1 Patient and tumor characteristics

		B-TACE ($n=49$)	C-TACE ($n=48$)	
Age	Median (range)	71.9 (62–84)	69.9 (54–91)	n.s.
Sex	(M/F)	33/16	34/14	n.s.
Etiology	(HBV/HCV/NBNC)	1/41/7	4/36/8	n.s.
Child–Pugh grade	(A/B/C)	36/13/0	37/11/0	n.s.
Stage	(I/II/III)	16/33/0	22/26/0	n.s.
Tumor size (mm)	Median (range)	29 (8–73)	24.5 (14–90)	n.s.
Portal vein invasion		0	0	n.s.
Miriplatin dose (mg)	Median (range)	40 (10 120)	20 (5–120)	$P<0.01$

B-TACE, balloon-occluded transcatheter arterial chemoembolization; C-TACE, conventional transcatheter arterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B, non-C; n.s., not significant.

in this study in comparison with 48 matched patients who received miriplatin using C-TACE (Table 1). All patients received information on the study and provided fully informed, written consent. The clinical study was approved by the hospital ethics committee and was performed in accordance with the internationally accepted ethical standards for human experimentation.

The indications for B-TACE were that the patients had no indications for hepatectomy/radiofrequency ablation. Each patient met the following criteria: a single cancer nodule was identified; the nodule was tumor stage I or II according to the staging system of the Liver Cancer Study Group of Japan;[7,8] there was no evidence of portal vein invasion; the patient had a Child–Pugh classification of A or B; adequate hematological function (white blood cell count ≥3000/μL, blood platelet count ≥50 000/μL, hemoglobin level ≥9.5 g/dL), adequate hepatic function (aspartate aminotransferase and alanine aminotransferase [ALT] levels ≤5-fold above maximum normal levels, serum bilirubin level <3 mg/dL, serum albumin level ≥3 g/dL), adequate renal function (serum creatinine ≤maximum normal levels); and an Eastern Cooperative Oncology Group performance status of 0–2 were recorded. B-TACE was performed according to the procedure reported by Irie *et al.*[2,3] Specifically, a microballoon catheter (Attendant [Terumo] or Logos [Piolax, Kanagawa, Japan]) was inserted into the tumor-feeding artery as peripherally as possible, and positioned in the subsegmental branch or segmental branch of the artery. The balloon was dilated to occlude the artery, and miriplatin was then administrated. It was injected until sufficient filling of the cancer nodule or overflow into the intrahepatic collateral pathway was observed. Subsequently, an embolic agent (Gelpart; Nihonkayaku, Tokyo, Japan) was injected into the blood vessel until a mold-like structure was formed, so long as permitted by the liver reserve capacity.

Conventional TACE was performed according to the following procedure. A microcatheter (Progreat; Terumo) was inserted into the tumor-feeding artery as peripherally as possible, and positioned in the subsegmental branch or segmental branch of the artery. Miriplatin was then administrated until the arterial blood flow reduced. Subsequently, an embolic agent was injected until the blood flow stopped.

The treatment effect (TE) on the target nodule was determined on computed tomography performed 1 month after treatment according to the Response Evaluation Criteria in Cancer of the Liver in the fifth supplementary edition of General Rules for the Clinical and Pathological Study of Primary Liver Cancer issued by the Liver Cancer Study Group of Japan.[9] The TE was defined as follows: TE4, disappearance or 100% necrosis of all treated tumors; TE3, more than 50% reduction in tumor size and/or more than 50% necrosis; and TE1, more than 25% increase in tumor size regardless of the necrotic effect. TE2 was defined as a response not qualifying for classification as TE4, TE3 or TE1. Safety was assessed according to the Japanese translation of the Common Terminology Criteria for Adverse Events version 4.0 by the Japan Clinical Oncology Group/Japan Society of Clinical Oncology.[10]

The Mann–Whitney *U*-test was used for comparisons between the two groups.

RESULTS

THE MEAN TOTAL dose and the median dose of miriplatin were 32.5 ± 31.7 mg and 20 mg, respectively, in the C-TACE group, and 50.1 ± 31.3 mg and