表 12：３大学（広島・久留米・山口大学）調査における基礎データ

大学	患者数(人)	のべ入院回数	一患者平均入院回数
広島	500	623	3.25
久留米	741	1428	1.93
山口	678	1786*	2.63
全体	1919	4837	2.52

*山口大学症例では、消化器病態内科学および第二外科入院の２科に入院した患者が含まれ、一部重複してカウントされている。

表 13：３大学調査における初回治療一覧*

		全体	単発・3cm以下
総数		828	256
初回治療	肝切除	108	32
	経皮的局所療法(LAT)	202	117
	TACE+LAT	140	39
	化学的腫瘍塞栓術(TACE)	257	61
	動注化学療法	104	3
	対症療法	11	1
	不明	6	3

*過去に肝細胞癌の治療歴がないHCV陽性患者で半年以上の経過観察の可能であった患者のみ

表 14：治療による寛解率の３大学間比較

治療	山口大学		広島大学		久留米大学		範囲(率)	
	人数	率	人数	率	人数	率	最低	最高
肝切除術								
初回単発・小肝細胞癌	20/22	0.952	9/9	1.000	2/2	1.000	0.952	1.000
第2回入院以降	28/33	0.848	59/66	0.894	-		0.848	0.894
経皮的局所療法								
初回単発・小肝細胞癌	16/28	0.571	31/34	0.912	45/51	0.882	0.571	0.912
第2回入院以降	28/76	0.368	47/73	0.644	43/48	0.896	0.368	0.896
TACE+LAT								
第2回入院以降	25/71	0.352	52/88	0.591	9/15	0.600	0.352	0.600
化学的腫瘍塞栓術								
第2回入院以降	32/117	0.274	10/163	0.061	38/78	0.487	0.061	0.487
化学療法								
第2回入院以降	2/44	0.045	2/30	0.067	6/80	0.075	0.045	0.075

表 15：治療による寛解後の無再発期間の３大学間比較

治療	メジアン			平均期間*		
	Y大[1]	H大[2]	K大[3]	Y大[1]	H大[2]	K大[3]
肝切除術						
初回単発・小肝細胞癌	1089	1289	-	1716	1209	-
第2回入院以降	589	444	-	1200	1130	-
経皮的局所療法						
初回単発・小肝細胞癌	622	678	1185	786	975	1078
第2回入院以降	425	314	325	565	470	517
TACE+LAT						
第2回入院以降	344	379	218	448	500	232
化学的腫瘍塞栓術						
第2回入院以降	257	265	230	396	418	423
化学療法						
第2回入院以降	154	-	178	250	-	149

1. Y 大：山口大学　2. H 大：広島大学　3. K 大：久留米大学

* Restricted mean

Ⅱ　分担研究報告

厚生労働科学研究費補助金（肝炎等克服緊急対策研究事業）
分担研究報告書（平成17年度）

病期別にみた肝がん治療法の費用効果およびQOLの観点からみた有効性に関する研究

分担研究者；佐田通夫　久留米大学医学部内科学（二）講座　教授

研究テーマ；肝細胞癌の遠隔転移診断に対するＰＥＴの有用性の検討

研究要旨：＜背景＞肝細胞癌(HCC)の診断における ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (PET)の有用性は低いとされている．高分化型HCCはグルコース代謝が正常肝細胞に近く，FDGが集積しないためであるが，中分化型，低分化型，門脈腫瘍栓，遠隔転移巣に対するPETの陽性率は高く有用性も報告されている．
＜目的＞HCCの遠隔転移診断におけるPETの有用性を検討する．
＜対象と方法＞久留米大学病院を受診したHCC患者で，遠隔転移がすでに指摘されているか強く疑われる症例21例を対象とした．PET施行の前後2週間に胸部～骨盤部CT，骨シンチを施行し，1cm以上の病変を対象としてPETによる遠隔転移巣の検出率を検討した．
＜結果＞対象患者の背景は，男性/女性:16/5，HBV4例，HCV14例，NBNC3例．診断時の中央値は年齢64歳，AFP 278ng/ml(range3.5-94512.0)，L－3分画36.0%(range0-81.5)，DCP 427mAU/ml(range10-52074)であった．肝内病変は13/21例(55.6%)で集積を認めた．転移巣のPET陽性率は肺転移巣7/10（70%），リンパ節転移巣21/22（95.4%)，骨転移23/23（100%），その他7/8（87.5%）（横隔膜浸潤2/2，腹膜転移3/4，腎1/1，脾臓1/1），全遠隔転移巣では52/58(89.6%)の陽性率であった．また，PETにより他部位の悪性腫瘍（進行胃癌）が1例で指摘された。
＜結語＞HCCの遠隔転移巣の診断においてPETは高い陽性率を示した．HCCに対する生体肝移植が増加しているが，移植後，免疫抑制剤を使用中の遠隔転移による再発，他部位の悪性腫瘍の発生が大きな問題となる．移植前のPET検査により遠隔転移，他部位の悪性腫瘍を早期発見することが可能となれば，PETは移植前の検査として有用である可能性がある。

A. 研究目的

本邦に於ける肝細胞癌は、その多くがＣ型肝炎ウイルスやＢ型肝炎ウイルスによる慢性肝疾患を背景に発生する。肝細胞癌による死者は年間３万人以上であり、現在も増加傾向にある。

近年、肝細胞癌に対する治療法の進歩により肝臓内に限局する癌に対する治療成績は向上しつつあるが、肺や骨への遠隔転移を伴う高度に進行した肝細胞癌の予後は極めて不良である。肝細胞癌の遠隔転移の適切な評価は治療法の選択や患者のquality of lifeに多大な影響を与えるものであるが、これを迅速かつ正確に診断することに苦慮する場合も少なくない。

^{18}F -fluoro-2-deoxy-D-glucose positron

emission tomography (^{18}F -FDG-PET)は、非侵襲的に脳腫瘍、頸部悪性腫瘍、肺癌、膵臓癌、大腸癌などを早期に診断することが可能である。しかし、発生初期の高分化肝細胞癌ではFDGの取り込みが周囲の肝細胞と同程度のため検出率は低く、従来の画像診断装置と比べて優れているとは言い難い。一方、肝細胞癌の遠隔転移巣は通常分化度の低い腫瘍細胞で構成されるため^{18}F -FDG-PETで高率に検出出来ることが期待される。

今回は、肝細胞癌の遠隔転移巣の検出率を^{18}F -FDG-PET画像および^{18}F -FDG-PETとCTの合成画像とCT画像や骨シンチグラフィー画像での検出率と比較した。

B. 対象と研究方法

CT, MRI, 骨シンチグラフィーなどで遠隔転移を診断された肝細胞癌患者と画像診断にて遠隔転移は証明されなかったが腫瘍マーカーなどで遠隔転移の存在が強く疑われた肝細胞癌患者合計２１例。男性16例、女性5例。平均年齢６４歳。HBs 抗原陽性４例、HCV 抗体陽性14例。

（倫理面への配慮）

本研究は久留米大学病院の倫理委員会の承認を受け、患者さんに対して書面にてインフォームドコンセントを得た。

C. 研究結果

21例の患者のうち14例の遠隔転移はCT, MRI, 骨シンチグラフィーなど通常の画像診断にて診断できた。1 例は通常の画像診断およびPETいずれでも診断できなかった。PETによる肝内の肝細胞癌の診断率は55.6%。58個の総肝外転移結節のうち、PETで診断できたものは89.6%、CT単独で診断できたものが91.2%、PET ＋ CTの合成画像にて診断できたものは、98.2%であった。

１）肺転移

3症例で10結節をCTで診断でき、このうち70%の結節をPETでも検出できた。しかし、腫瘍径が10mm以下の多発した肺転移結節はPETでは検出できなかった。

２）リンパ節転移

5 症例で 22 結節を CT で診断でき、このうち96.4%の結節をPETでも検出できた。

３）骨転移

4症例16結節のうち、骨シンチグラフィーでは68.7%、PETではすべての結節が検出できた。骨シンチグラフィーでは陽性と認識した圧迫骨折２症例において、PETとMRIでは陽性とは認識しなかった。

４）他臓器癌

1例において、偶然PETにて進行胃癌の合併が発見できた。

病理組織学的検討

PETで検出できた肝内結節のうち4例において腫瘍生検を施行した。2 例は肝細胞癌と胆管細胞癌の混合型であり残りの 2 例は各々中分化、低分化肝細胞癌であった。PET陽性の転移結節のうち外科的に切除できた腹膜、横隔膜、肺の転移結節は中分化肝細胞癌であった。病理解剖

転移結節は中分化肝細胞癌であった。病理解剖を行えた１例は肝細胞癌と胆管細胞癌の混合型であった。

D. 考察

今回の検討において、PET による肝細胞癌の検出率は肝内結節では低かったが、肝外転移結節は比較的高率であった。これは、小型の肝内結節は高分化肝細胞癌が多く、正常肝細胞と高分化な肝癌細胞では糖代謝にそれほどの差が認められないためと考えられた。事実、PET にて検出できた肝内結節は肝細胞癌と胆管細胞癌の混合型もしくは、分化度の低い癌細胞であった。

肺転移結節の検出率は CT に比べ劣っていたが、リンパ節転移に関しては CT よりも感度が良好であった。また、骨転移に関しては PET 単独もしくは PET + CT の合成画像にて骨シンチグラフィーより高率に検出でき部位の同定も容易であった。

今後、PET による肝細胞癌の肝外転移巣の検索は治療法の決定および、肝移植の適否を決定する上で有用な検査法として用いることができると考えられた。

E. 結論

肝移植前の PET 検査により遠隔転移，他部位の悪性腫瘍を早期発見することが可能となれば，PET は移植前の検査として有用である可能性がある。

F. 健康危険情報

特記すべきものなし。

G. 研究発表

1. 論文発表

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H. 知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金

病期別にみた肝がん治療法の費用効果およびＱＯＬの観点からみた有効性に関する研究

分担研究報告書

再発肝癌患者の不安・抑うつに関連する身体・心理・社会的因子に関する研究

分担研究者　茶山一彰　広島大学医歯薬学総合研究科

研究要旨：肝細胞癌の再発が患者の心理状態に及ぼす影響を，前回治療後再入院した再発肝細胞癌患者を対象として横断的に調査した．HADSスコアによる検討から約４割の患者が精神症状を有し，何らかの心理的緩和ケアを必要とした．一方精神症状のない患者が高い「前向き」コーピング・スコアを持つ傾向が見られ，患者のQOLを高めるためには早期の精神症状の発見と治療の介入が必要と考えられた．

共同研究者
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A. 研究目的

がんの再発の宣告は，がん患者の全病期を通じて，もっとも強い心理的影響を及ぼすことが知られている．一方肝細胞癌はしばしば再発し，入退院の繰り返しを余儀なくされることも周知の事実である．そこでがんの再発が患者の心理状態に及ぼす影響を，前回治療後再入院した再発肝細胞癌患者を対象として横断的に調査した． HADS による患者の不安・抑うつ状態の scoring を primary endpoint とした．

B. 研究方法

画像診断または病理検査（組織診，細胞診）にて原発性肝細胞癌と診断されている広島大学病院消化器内科に入院中の患者で，年齢 18 才以上，がんの告知が行われている，研究の趣旨について文書によるインフォームド・コンセントが得られた 25 名を対象とした．

評価項目として，①社会医学的項目：肝癌の臨床病期，治療法，治療効果，学歴，職業，経済状態，家族構成等，②HADS (Hospital Anxiety and Depression Scale)：1983 年に Zigmond らにより作製された不安と抑うつについての 14 の質問からなる両者を測定する自己評価式質問紙法である．③Mac scale (Mental Adjustment to Cancer scale)：1983 年に Zigmond らにより作成された，がんに対する心理的態度の自己記入式調査票である．がん診断に対する心理的反応を，がんをどのように認識し，その脅威を軽減するためにどのように考えそして行動したかという２つの側面から調査し，そこから得られた臨床的知見をもとに作成された．40 の質問から構成されており，前向き，悲観・絶望，予期不安，あきらめ，逃避の５つの下位尺度に分類されている．④FRI (Family Relationships Index)：1984 年に Holahan らが，FES (Family Environment Scale) の 90 項目の中から人間関係性に関する３下位尺度，すなわち凝集性，表出性，葛藤性に関する 27 項目を抽出して構成したもの⑤EORTC QLQ-C30 Scoring (The European Organisation for Research and Treatment of Cancer quality of life questionnaire-C30)：1993 年に Aaronson らが国際的な臨床試験に参加するがん患者の QOL を評価するために作成された． 30 の質問から構成されており，機能と症状の下位尺度，その他の項目からなる．

患者評価は１）文書同意の得られた患者に対して，調査担当者が診療録閲覧および簡単な面接を行い，患者用基本調査票を完成させ，２）調査担当者が HADS , MAC, FRI, EORTC QLQ-C30 を含む患者用質問票を患者に手渡し，記入していただくように依頼した．記入済みの質問票は後日調査担当者が訪室し，回収した．

C. 結果

今回の研究の対象になった23名の再発肝癌患者

の平均年齢は70±7才，男性12名，女性11名であった．臨床病期はstage Ⅰ 1名（4%），stage Ⅱ 6名（26%），stage Ⅲ 10名（43%），stageⅣ6名（26%）であった．選択された治療法は手術2名，経皮的局所療法1名，肝動注化学塞栓術（シスプラチン＋リピオドール）16名，リザーバー化学療法（5FU+IFN）4名であった．

平均の総HADSスコアは10.3±5.1（中央値 10；最小値3，最大値21）であった．HADSスコアから8例（35%）に適応障害が，1例（4%）に抑うつ状態が生じたと考えた．従って今回対象となった9例（39%）に精神症状が出現し，心理的緩和ケアが必要であったと考えられた．臨床病期別に見ると何らかの症状が出現したのは，stage Ⅱ 6名中2名（33%），stage Ⅲ 10名中3（30%），stageⅣ6名中4名（67%）であった．

MAC scaleによるコーピング・スコアを適応障害または抑うつ状態の生じた8例（有症状群）と生じなかった15例（無症状群）に分けて比較したところ，患者の「前向き」コーピング・スコアは有症状群で42±6.7，無症状群で55±7.6と無症状群で高い傾向にあった．また患者の「悲観・絶望」コーピングスコアは有症状群で12.8±3.2，無症状群で6.5±2.4と有症状群で高い傾向にあった．また家族の「凝集性」スコアと患者の「前向き」コーピング・スコアとの間には，有症状群，無症状群とも相関する傾向が見られた．

D. 考察

今回の我々の検討では，約４割の患者が精神症状を有し，何らかの心理的緩和ケアを必要とした．この結果はこれまでの他部位の癌患者に対する報告と同様に，患者の心理状態，精神的苦痛度が過小評価されていることを示している．

HADS スコアにより，今回検討した患者を精神症状の有無の２群に分別したところ，無症状群で fighting sprit などの「前向き」コーピング・スコアが高くなる傾向が見られた．すなわち精神症状出現時のケアマネージメントひいては癌患者の精神症状出現の早期の認識，が患者の QOL の改善に必要であると考えられた．

また家族の「凝集性」と患者の「前向き」コーピング・スコアとの間には相関する傾向が見られ，家族機能の重要性が示唆された．

E. 結論

再発肝癌患者の約4割に何らかの心理的緩和ケアを必要とする精神症状が存在した．精神症状のない患者が高い「前向き」コーピング・スコアを持つ傾向が見られ，患者のQOLを高めるためには早期の精神症状の発見と治療の介入が必要と思われた．

F. 健康危機情報

特になし

G. 研究発表

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H. 知的財産権の出願・登録状況

特になし

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

雑誌

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Ⅳ．研究成果の刊行物・別刷

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Prognostic factors in patients with advanced hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy

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Background. The prognosis of patients with advanced hepatocellular carcinoma (HCC) is poor. We aimed to clarify the prognostic factors in patients with advanced HCC receiving hepatic arterial infusion chemotherapy (HAIC). ***Methods.*** Forty-four HCC patients were treated with HAIC, using low-dose cisplatin (CDDP) and 5-fluorouracil (5-FU) with/without leucovorin (or isovorin). Of these 44 patients, 15 received low-dose CDDP and 5-FU, and 29 received low-dose CDDP, 5-FU, and leucovorin or isovorin. Prognostic factors were evaluated by univariate and multivariate analyses of patient and disease characteristics. ***Results.*** Of all patients, 5 and 12 patients respectively, exhibited a complete response (CR) and a partial response (PR) (response rate, 38%). The response rate (48.3%) in the low-dose CDDP and 5-FU with leucovorin/isovorin group was significantly better than that (20%) in the low-dose CDDP and 5-FU group ($P = 0.002$). The 1-, 2-, 3-, and 5-year cumulative survival rates of the 44 patients were 39%, 18%, 12%, and 9%, respectively. The regimen using low-dose CDDP and 5-FU with leucovorin/isovorin tended to improve survival rates ($P = 0.097$). Univariate and multivariate analyses showed the same variables—the Child-Pugh score ($P = 0.013$, $P = 0.018$), α-fetoprotein (AFP) level ($P = 0.010$, $P = 0.009$), and therapeutic effect after HAIC ($P = 0.003$, $P = 0.01$), respectively, to be significant prognostic factors. ***Conclusions.*** Patients who had advanced HCC with favorable hepatic reserve capacity and a lower AFP level were suitable candidates for HAIC. Moreover, the regimen using low-dose CDDP and 5-FU with leucovorin/isovorin may be suitable for advanced HCC patients, because of the improvement in the response rate and survival compared with the low-dose CDDP and 5-FU regimen without leucovorin/isovorin.

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Key words: advanced hepatocellular carcinoma, hepatic arterial infusion chemotherapy, biochemical modulator, prognostic factor

Introduction

The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, especially for patients with portal vein tumor thrombosis (PVTT).[1–4] Almost all patients with advanced HCC die within several months of diagnosis. Therefore, patients with unresectable HCC are usually treated with hepatic arterial infusion chemotherapy (HAIC). HAIC, with several anticancer agents[4–6] and a combination of antiproliferative agents,[7,8] is useful for patients with advanced HCC. However, there are not yet any standard chemotherapeutic regimens for advanced HCC.

We previously designed a new regimen using cisplatin (CDDP), 5-fluorouracil (5-FU), and leucovorin. Leucovorin is a biochemical modulator of 5-FU.[9–11] We reported the usefulness of HAIC using low-dose CDDP and 5-FU with leucovorin in patients with advanced HCC. In addition, we found that the response rate and survival for the low-dose CDDP and 5-FU with leucovorin regimen were significantly better than those for the low-dose CDDP and 5-FU-alone regimen, in a randomized study.[12] Furthermore, we investigated the efficacy of our regimen with high-dose leucovorin, using isovorin, which is an active form of leucovorin. We reported that there were no significant differences in the response rate, the survival rate, and the toxicity between low-dose leucovorin and high-dose leucovorin.[13] In the current study, we investigated the factors that influenced survival by applying univariate and multivariate analyses to 44 patients with advanced HCC treated with HAIC using low-dose CDDP and 5-FU with/without leucovorin (or isovorin).

Table 1. Clinical characteristics of 44 patients with hepatocellular carcinoma

Clinical characteristics	
Sex (male/female)	38/6
Age (younger than 65 years/66 years and older)	28/16
HCV (+/−)	32/12
Child-Pugh (A/B)[a]	29/15
Previous treatment (yes/no)	35/9
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	24/20
Plasma concentration of DCP (<1000 mAU/ml/≧1000 mAU/ml)	27/17
Maximum tumor size (<50 mm/≧50 mm)	22/22
Tumor stage (II/III/IV A/IV B)[b]	6/16/19/3
Grade of portal invasion (Vp 0/1/2/3/4)[c]	23/3/4/7/7
Leucovorin or isovorin (yes/no)	29/15
Additional therapy (yes/no)	20/24

HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin; Vp, portal tumor thrombosis
[a] Child-Pugh stage
[b] According to the Liver Cancer Study Group of Japan
[c] Portal invasion. Vp1, tumor thrombus in a third or more of the peripheral branches; Vp2, in the second branch; Vp3, in the first branch; Vp4, in the trunk

Patients and methods

Patients

Forty-four patients with unresectable HCC who were admitted to the Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, were enrolled in the current study between July 1997 and March 2002. Disease was considered unresectable when there was locally advanced disease too extensive for resection, bilobar disease, extrahepatic metastasis, or PVTT. Of these 44 patients, 15 patients underwent HAIC using low-dose cisplatin (CDDP) and 5-FU, and 29 underwent HAIC using low-dose CDDP and 5-FU with leucovorin or isovorin. The diagnosis of HCC was made by imaging studies and was based on elevated serum levels of α-fetoprotein (AFP) and/or des-γ-carboxyprothrombin (DCP).

Patients were asked to give their written informed consent to enter the study, which was approved by the Institutional Review Board of Yamaguchi University Hospital.

Table 1 summarizes the clinical profiles of the 44 HCC patients treated by HAIC. They included 38 men and 6 women, with an average age of 62.3 years (range, 32–79 years). Thirty-two patients were infected with hepatitis C virus (HCV), 11 were infected with hepatitis B virus (HBV), and 1 was not infected with either HCV or HBV. Thirty-five patients had previously undergone treatment for HCC (surgery, percutaneous ethanol injection,[14] percutaneous hot water injection therapy,[15] percutaneous microwave coagulation therapy,[16] percutaneous radiofrequency ablation therapy,[17] transcatheter arterial embolization,[18] or transcatheter arterial chemoembolization[19]). Tumor stage and PVTT grading were determined according to the criteria of the Liver Cancer Study Group of Japan.[20,21] PVTT grading was based on the location of the tumor thrombus in the peripheral portal vein: Vp1, tumor thrombus in a third or more of the peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in the first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein. Tumor staging was done using the Liver Cancer Study Group of Japan criteria, based on the following three conditions (T factor): solitary, <2 cm in diameter, or no vessel invasion. Stage I was defined as fulfilling the three conditions (T1), stage II as fulfilling two of the three conditions (T2), stage III as fulfilling one of the three conditions (T3), stage IV A as fulfilling none of the three conditions (T4) with no distant metastasis or any T factor with lymph node metastasis, and stage IV B as any T factor with distant metastasis.

Technique of catheter placement

A 5-French heparin-coated catheter (Anthron P-U Catheter; Toray Medical, Tokyo, Japan) was inserted intraluminally from the right femoral artery or the subclavian artery with a subcutaneously implanted reservior, and was positioned in the proper or common hepatic artery. The gastroduodenal artery and the right gastric artery were occluded with steel coils as required to prevent gastroduodenal injury from the anticancer agents. The entire procedure was performed with the patient under local anesthesia. To prevent occlusion of the device, it was filled with 5 ml (5000 units) of a heparin solution every 2 weeks.

Chemotherapeutic regimen

Patients received repeated arterial infusions of chemotherapeutic agents via the injection port. Of the 29 patients who received low-dose CDDP, 5-FU, and leucovorin or isovorin, 9 patients received low-dose CDDP, 5-FU, and leucovorin (12 mg/body), 15 received low-dose CDDP, 5-FU, and isovorin (12.5 mg/body), and 5 received low-dose CDDP, 5-FU, and isovorin (6.25 mg/body). One course of chemotherapy consisted of the daily administration of CDDP (10 mg/body, on days 1 to 5) and leucovorin or isovorin (12 mg leucovorin or 12.5 mg or 6.25 mg isovorin, on days 1 to 5) followed by 5-FU (250 mg/body, on days 1 to 5). Days 6 and 7 were rest days. In the 15 patients who received low-dose CDDP and 5-FU, the same regimen was followed, except for the administration of leucovorin or isovorin. In principle, patients were to receive four serial courses of chemotherapy. Both CDDP and 5-FU were administered by a mechanical infusion pump, set at 1 and 5 h, respectively. Either leucovorin or isovorin was administered at 10 min. As an antiemetic, the serotonin antagonist ondansetron hydrochloride was administered intravenously.

Evaluation

Tumor regression was assessed by computed tomography during angiography (CTA)[22] and/or by digital subtraction angiography (DSA) after the initial treatment. The response criteria defined by the Liver Cancer Study Group of Japan were used. Complete response (CR) was defined as disappearance of the tumor and no evidence of new lesions for at least 4 weeks. Partial response (PR) was defined as a greater than 50% decrease in the tumor and no evidence of new lesions for at least 4 weeks. Minor response (MR) was defined as a less than 50% decrease in the tumor and a greater than 25% decrease and no evidence of new lesions for at least 4 weeks. No change (NC) was defined as a less than 25% decrease in the tumor and no evidence of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a greater than 25% increase in the tumor and evidence of new lesions for at least 4 weeks.

Additional therapy

In principle, the treatment course was repeated several times unless the tumor progressed during the therapy. We tried to perform additional therapies, such as microwave coagulation therapy (MCT);[16] percutaneous radiofrequency ablation therapy (RFA);[17] transcatheter arterial chemoembolization (TACE),[19] using epirubicin HCL, mitomycin C, and lipiodol; operation; and chemotherapy, using other drugs (epirubicin HCL, mitomycin C) after evaluation of the effects of this study. Of 20 patients who received additional therapies, 9 patients were responders (CR + PR) and 11 were nonresponders (MR + NC + PD). Of the responders, 2 patients were treated with RFA, 4 were treated with TACE, 2 were treated with RFA and TACE, and 1 was treated with MCT and TACE. Of the nonresponders, 1 patient was treated with MCT, 1 was treated with RFA and operation, 4 were treated with TACE, and 5 were treated with chemotherapy.

Statistical analysis

The data values were expressed as means ± SDs. Statistical analyses were performed using the unpaired *t*-test, and the Mann-Whitney *U*-test as appropriate. Univariate analysis, to identify predictors of survival, was performed by the Kaplan-Meier method[23] and compared by the log-rank test. Thirteen variables were assessed for survival, including sex, age (younger or older than 65 years), the presence of hepatitis-C antibody (HCV-Ab), hepatic reserve capacity (Child-Pugh score A or B[24]), the presence of previous therapy for HCC, AFP level (<1000 or ≧1000 ng/ml), DCP level (<1000 or ≧1000 mAU/ml), maximum tumor size (<50 or ≧50 mm), PVTT rating (Vp0-1 or Vp2-4), tumor stage (stage II, III or stage IV-A, IV-B), therapeutic effect after HAIC (CR, PR or MR, NC, PD), use of leucovorin or isovorin (yes or no), and additional therapy (yes or no). The multivariate analysis was done by the Cox proportional hazards model with stepwise selection. Survival was confirmed up to August 31, 2003. Statistical significance was defined as a P value of less than 0.05.

Results

Response to therapy

Of the 44 patients, 5 (11%), 12 (27%), 2 (5%), 12 (27%), and 13 (30%) patients exhibited CR, PR, MR, NC, and PD, respectively (response rate [patients with CR + PR/all patients], 38%). In the low-dose CDDP and 5-FU with leucovorin/isovorin group (29 patients), 4 (14%), 10 (34.5%), 2 (7%), 10 (34.5%), and 3 (10%) patients exhibited CR, PR, MR, NC, and PD, respectively (response rate, 48.3%). In the low-dose CDDP and 5-FU group (15 patients), 1 (7%), 2 (13%), 0 (0%), 2 (13%), and 10 (67%) patients exhibited CR, PR, MR, NC, and PD, respectively (response rate, 20%). The response rate in the low-dose CDDP and 5-FU with leucovorin/isovorin group was significantly better than that in the low-dose CDDP and 5-FU group ($P = 0.002$; Mann-Whitney *U*-test; Table 2). There were no statisti-

Table 2. Clinical responses to therapy

	CR	PR	MR	NC	PD	Response rate
Low-dose CDDP and 5-FU with leucovorin/isovorin (n = 29)	4	10	2	10	3	48.3% *
Low-dose CDDP and 5-FU (n = 15)	1	2	0	2	10	20% *
Total no. of patients (n = 44)	5	12	2	12	13	38%

* P = 0.002 (Mann-Whitney U-test)
CR, complete response; PR partial response; MR, minor response; NC, no change; PD, progressive disease

Table 3. Clinical characteristics of patients treated with low-dose CDDP and 5-FU with leucovorin/isovorin, or low-dose CDDP and 5-FU

Clinical characteristics	Low-dose CDDP and 5-FU with leucovorin/isovorin (n = 29)	Low-dose CDDP and 5-FU (n = 15)	P value
Sex (male/female)	26/3	12/3	0.376
Age (younger than 65 years/66 years and older)	19/10	9/6	0.718
HCV (+/−)	19/10	13/2	0.135
Child-Pugh (A/B)[a]	19/10	10/5	0.939
Previous treatment (yes/no)	25/4	10/5	0.128
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	20/9	4/11	0.008
Plasma concentration of DCP (<1000 mAU/ml/≧1000 mAU/ml)	17/12	10/5	0.603
Maximum tumor size (<50 mm/≧50 mm)	18/11	4/11	0.026
Tumor stage (II/III/IV A/IV B)[b]	6/10/12/1	0/6/7/2	0.141
Grade of portal invasion (Vp 0/1/2/3/4)[c]	16/2/3/3/5	7/1/1/4/2	0.656
Additional therapy (yes/no)	12/17	8/7	0.450

HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin; Vp, portal tumor thrombosis
[a] Child-Pugh stage
[b] According to the Liver Cancer Study Group of Japan
[c] Portal invasion. Vp1, in a third or more of the peripheral branches; Vp2, in the second branch; Vp3, in the first branch; Vp4, in the trunk

cally significant differences in the clinical characteristics between the two groups, except for AFP level and maximum tumor size (Table 3).

Survival and prognostic factors

The cumulative survival rates of the 44 patients are shown in Fig. 1. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 39%, 18%, 12%, 9%, and 9%. The median survival duration of the 44 patients treated with HAIC was 9.4 months (range, 1.9–68.5 months). The cumulative survival rates of patients treated with low-dose CDDP and 5-FU with leucovorin/isovorin, or low-dose CDDP and 5-FU, are shown in Fig. 2. The regimen using low-dose CDDP and 5-FU with leucovorin/isovorin tended to improve survival rates, although there was no significant difference between the two groups (P = 0.097).

Three of the 13 factors analyzed by univariate analysis showed prognostic significance—the Child-Pugh score (P = 0.013), AFP level (P = 0.010), and therapeutic effect after HAIC (P = 0.003; Table 4). The cumulative survival rates of patients by Child-Pugh score, AFP levels, and therapeutic effect after HAIC are shown in

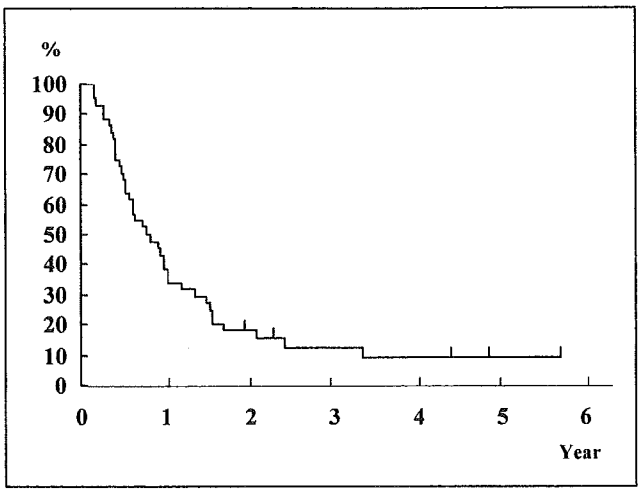

Fig. 1. Cumulative survival of 44 patients with advanced hepatocellular carcinoma treated with hepatic arterial infusion chemotherapy. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 39%, 18%, 12%, 9%, and 9%, respectively

Table 4. Factors influencing cumulative survival of patients: univariate analysis

Factors	*P* value
Sex (male/female)	0.873
Age (younger than 65 years/66 years and older)	0.872
HCV (+/−)	0.439
Child-Pugh (A/B)[a]	0.013
Previous treatment (yes/no)	0.942
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	0.010
Plasma concentration of DCP (<1000 mAU/ml/≧1000 mAU/ml)	0.354
Maximum tumor size (<50 mm/≧50 mm)	0.732
Tumor stage (II/III/IV A/IV B)[b]	0.288
Grade of portal invasion (Vp 0–1/Vp 2–4)[c]	0.622
Therapeutic effect (CR or PR/MR, NC, or PD)	0.003
Leucovorin or isovorin (yes/no)	0.097
Additional therapy (yes/no)	0.107

HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin; Vp, portal tumor thrombosis

[a] Child-Pugh stage

[b] According to the Liver Cancer Study Group of Japan

[c] Portal invasion. Vp1, in a third or more of the peripheral branches; Vp2, in the second branch; Vp3, in the first branch; Vp4, in the trunk

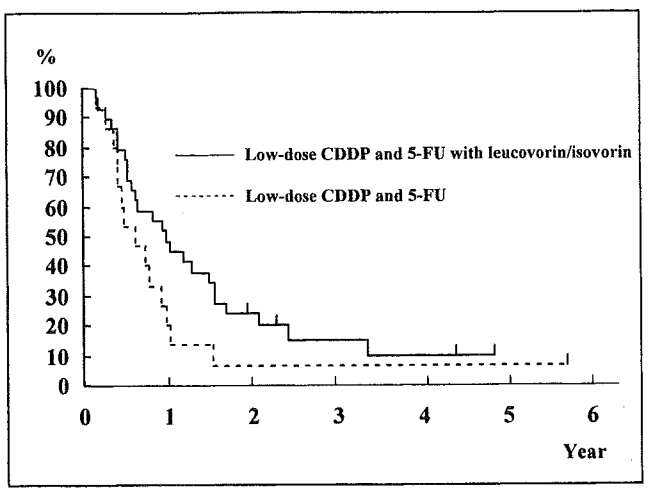

Fig. 2. Cumulative survival rates are shown for patients treated with low-dose cisplatin (*CDDP*) and 5-fluorouracil (*5-FU*) with leucovorin/isovorin, or low-dose CDDP and 5-FU. The 1-, 2-, 3-, and 4-year cumulative survival rates for low-dose CDDP and 5-FU with leucovorin/isovorin were 48%, 24%, 15%, and 10%, respectively. The median survival duration was 11.8 months. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates for low-dose CDDP and 5-FU were 20%, 7%, 7%, 7%, and 7%, respectively. The median survival duration was 7.3 months. There was no significant difference between the two groups ($P = 0.097$)

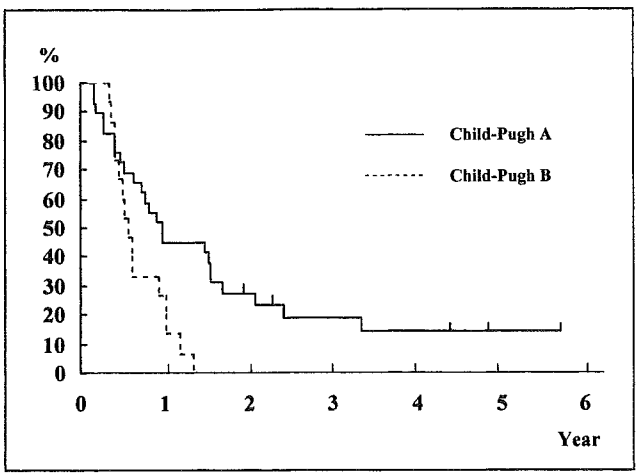

Fig. 3. Cumulative survival rates of patients by Child-Pugh score are shown. For patients with Child-Pugh A score, the 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 45%, 28%, 19%, 14%, and 14%, respectively. The median survival duration was 11.6 months. For those with Child-Pugh B score, the 1- and 2-year cumulative survival rates were 27% and 0%, respectively. The median survival duration was 6.7 months. There was a significant difference between the two groups ($P = 0.013$)

Figs. 3, 4, and 5, respectively. Multivariate analysis showed the same variables—the Child-Pugh score ($P = 0.018$), AFP level ($P = 0.009$), and therapeutic effect after HAIC ($P = 0.01$), to be independent predictors of mortality (Table 5).

Causes of death

Five patients remained alive throughout the entire observation period, and 39 patients died. Thirty patients (77%) died of cancer-related disease. Of these, 28 died of tumor extension and 2 died of tumor rupture. Four patients (10%) died of gastrointestinal bleeding and 3 (8%) died of liver failure. Two patients (5%) died of pneumonia.

Table 5. Factors influencing cumulative survival of patients: multivariate analysis

Factors	Hazard ratio	95% CI	*P* value*
Child-Pugh (A/B)	2.474	1.168–5.242	0.018
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	2.492	1.251–4.965	0.009
Therapeutic effect (CR or PR/MR, NC, or PD)	2.614	1.259–5.430	0.01

*Cox proportional hazards model with stepwise selection
AFP, α-fetoprotein; CI, confidence interval

Table 6. Causes of death

	Low-dose CDDP and 5-FU with leucovorin/isovorin (n = 29)	Low-dose CDDP and 5-FU (n = 15)	Total no. of patients (n = 44)
Alive	4 (CR, 2; PR, 1; NC, 1)	1 (CR, 1)	5
Dead	25 (CR, 2; PR, 9; MR, 2; NC, 9; PD, 3)	14 (PR, 2; NC; 2, PD, 10)	39
Cancer-related disease	18 (CR, 2; PR, 5; MR, 1; NC, 7; PD, 3)	12 (PR, 1; NC, 1; PD, 10)	30 (77%)
Primary cancer-related	15 (PR, 4; MR, 1; NC, 7; PD, 3)	12 (PR, 1; NC, 1; PD, 10)	
Metastatic cancer-related	3 (CR, 2; PR, 1)	0	
Gastrointestinal bleeding	3 (PR, 1; NC, 1; MR, 1)	1 (NC, 1)	4 (10%)
Liver failure	2 (PR, 1; NC, 1)	1 (PR, 1)	3 (8%)
Pneumonia	2 (PR, 2)	0	2 (5%)

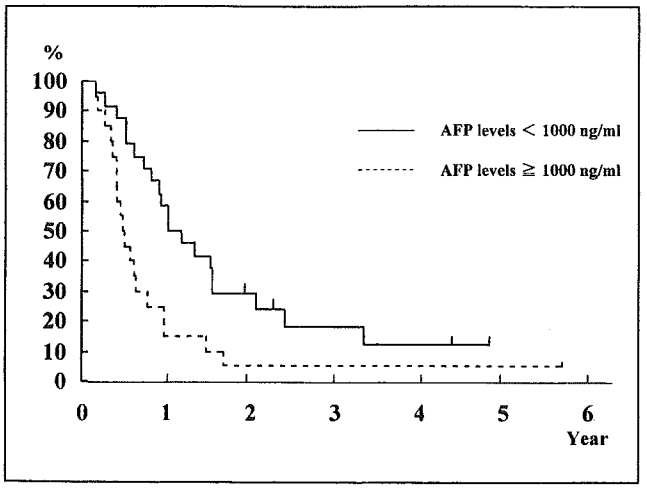

Fig. 4. Cumulative survival rates of patients by α-fetoprotein (*AFP*) level are shown. For patients with an AFP level of less than 1000 ng/ml, the 1-, 2-, 3-, and 4-year cumulative survival rates were 58%, 29%, 19%, 18%, and 12%, respectively. The median survival duration was 12.3 months. For those with an AFP level of 1000 ng/ml or more, the 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 15%, 5%, 5%, 5% and 5%, respectively. The survival duration was 5.8 months. There was a significant difference between the two groups (P = 0.010)

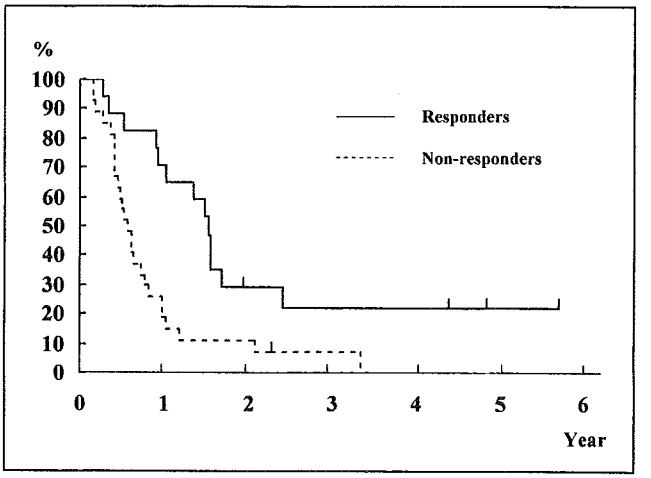

Fig. 5. Cumulative survival rates of patients by therapeutic effect after hepatic arterial infusion chemotherapy (HAIC) are shown. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates of responders (complete response [CR] + partial response [PR]) were 71%, 29%, 22%, 22%, and 22%, respectively. The median survival duration was 18.4 months. The 1-, 2-, and 3-year cumulative survival rates of non-responders were 19%, 11%, and 7%, respectively. The median survival duration was 6.7 months. There was a significant difference between the two groups (P = 0.003)

We compared causes of death between the low-dose CDDP and 5-FU with leucovorin/isovorin group and the low-dose CDDP and 5-FU group (Table 6). In the low-dose CDDP and 5-FU with leucovorin/isovorin group, 4 patients remained alive and 25 died. Of the 4 patients who were alive, 2 had CR; 1, PR; and 1, NC after HAIC. Eighteen patients (72%) died of cancer-related disease. Of these patients, 15 died of primary cancer-related disease and 3 of metastatic cancer-related disease. Of the 15 patients who died of primary

cancer-related disease, 4 had PR; 1, MR; 7, NC; and 3, PD after HAIC. Of the 3 patients who died of metastatic cancer-related disease, 2 had CR and 1, PR. Three patients (12%) died of gastrointestinal bleeding. Of these 3, 1 had PR; 1, NC; and 1, MR. Of the 2 patients (8%) who died of liver failure, 1 had PR and 1, NC. Two patients (8%) with PR after HAIC died of pneumonia.

In the low-dose CDDP and 5-FU group, 1 patient was still alive and 14 patients had died. The surviving patient had CR after HAIC. Twelve patients (86%) died of primary cancer-related disease but none died of metastatic cancer-related disease. Of these 12 patients, 1 had PR; 1, NC; and 10, PD after HAIC. One patient (7%) who had NC after HAIC died of gastrointestinal bleeding. One patient (7%) with PR died of liver failure.

Discussion

The prognosis of advanced HCC remains poor, especially for patients with PVTT.[1-4] Recently, progress in implantable drug delivery systems has made possible the repeated arterial infusion of chemotherapeutic agents for patients with advanced HCC.

We previously designed a new regimen using CDDP, 5-FU, and leucovorin.[12] CDDP and leucovorin can amplify the effect of 5-FU.[9-11,25,26] We thought that they acted as double biochemical modulators for 5-FU. In a randomized study, we demonstrated the efficacy of our regimen, although we investigated only a small number of patients. The response rate for low-dose CDDP and 5-FU with leucovorin was significantly better than that for low-dose CDDP and 5-FU (56% vs 20%; $P = 0.022$). In addition, survival with low-dose CDDP and 5-FU with leucovorin was significantly better than that with low-dose CDDP and 5-FU ($P = 0.033$). We also investigated the efficacy of our regimen with high-dose leucovorin (about two times as much as the previous dose), using isovorin, which is an active form of leucovorin.[13] We reported that there were no significant differences in the response rate (56% vs 53%; $P = 0.71$) and the survival rate ($P = 0.29$) between low-dose leucovorin and high-dose leucovorin. After these studies, we have used a dose of isovorin of 6.25 mg per day in our regimen.

Hepatic arterial infusion chemotherapy (HAIC) is useful for patients with advanced HCC.[4-8] However, little has been established regarding the prognostic factors after HAIC.[27] In the current study, we investigated the factors that influenced survival by applying univariate and multivariate analyses to the 44 patients with advanced HCC treated with HAIC using low-dose CDDP and 5-FU with/without leucovorin (or isovorin).

Univariate analysis demonstrated that three factors; namely, the Child-Pugh score ($P = 0.013$), AFP level ($P = 0.010$), and therapeutic effect after HAIC ($P = 0.003$), influenced the prognosis (Table 4). However, the grade of portal invasion did not influence the prognosis ($P = 0.622$). Although previous studies have documented that PVTT is an important prognostic factor that influences survival in patients with HCC,[28-30] it was not a prognostic factor in our current study. We think that HAIC changed the prognostic factors of advanced HCC. Ando et al.[27] reported the efficacy of HAIC using low-dose CDDP and 5-FU for 48 patients having advanced HCC with PVTT. In their study, the therapeutic effect and hepatic reserve capacity (Child classification[31]) were identified as significant prognostic factors by univariate analysis, and multivariate analysis identified only the therapeutic effect as being significantly related to survival. Our study demonstrated by multivariate analysis that the Child-Pugh score ($P = 0.018$), AFP level ($P = 0.009$), and therapeutic effect after HAIC ($P = 0.01$) were significant prognostic factors, as they were on univariate analysis. Except for the AFP level, our results were the same as those in the report by Ando et al.[27] Previous reports have demonstrated that AFP is one of the prognostic factors in patients with HCC.[32-35] The importance of the AFP level as a prognostic factor for HCC has been shown in a report from the Center of the Liver Italian Program (CLIP) investigators.[2] Hanazaki et al.[36] reported, similarly to our result, that an AFP value of 1000 ng/ml or more was an independent unfavorable factor affecting survival after hepatic resection for HCC with hepatitis C virus infection. On the other hand, DCP and the grade of portal invasion were not prognostic factors in our univariate analysis in the present study ($P = 0.354$, $P = 0.622$). Koike et al.[37] have reported that DCP is a useful factor indicating a predisposition for the development of portal venous invasion. Therefore, AFP may influence the tumor characteristics of HCC, differing from DCP, which is related to portal venous invasion. We consider that AFP may be a useful parameter for determining survival when advanced HCC is treated with HAIC. Recently, AFP L3 was reported to be a useful prognostic factor in patients with HCC.[38,39] Although we did not measure AFP L3 in our study, we think that further investigation of it is required to determine its usefulness as a prognostic factor in patients with advanced HCC receiving HAIC.

The regimen using low-dose CDDP and 5-FU with leucovorin/isovorin tended to improve survival rates, although there was no significant difference between the groups with our two regimens ($P = 0.097$). However, four patients who had PR after HAIC with low-dose CDDP and 5-FU with leucovorin/isovorin died: gastrointestinal bleeding (1 patient; survival period, 4.1

months), hepatic failure (1 patient; survival period, 11.4 months), and pneumonia (2 patients; survival periods, 3.2 months and 6.4 months). We think that the reason why there was no significant difference in the survival between the two groups was the short survival periods of the four patients. Although there were only slight differences in the clinical characteristics between the two groups, the response rate in the low-dose CDDP and 5-FU with leucovorin/isovorin group was significantly better than that in the low-dose CDDP and 5-FU group ($P = 0.002$). Therefore, low-dose CDDP and 5-FU with the addition of a biochemical modulator appears to be a useful regimen for advanced HCC.

Ando et al.[27] reported that additional therapy following HAIC might be an option for prolongation of survival. In our study, additional therapy tended to improve survival rates, although it was not a significant prognostic factor on univariate analysis ($P = 0.107$). However, additional therapy following HAIC may be found to be a significant prognostic factor in studies with a large number of patients with advanced HCC.

In conclusion, patients who had advanced HCC with favorable hepatic reserve capacity and lower AFP level were suitable candidates for HAIC. Moreover, the regimen using low-dose CDDP and 5-FU with leucovorin/isovorin may be suitable for advanced HCC patients because of the improvement in the response rate and survival compared with the low-dose CDDP and 5-FU regimen without leucovorin/isovorin.

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