B　研究方法

対象は、次のモデル作成群と検証群の２群とした。モデル作成群は、当大学附属病院に肝細胞癌の診断で入院し 2003 年７月１日から 2004 年３月 31 日までに退院となった患者のべ 260 名(男性 197 名、年齢 68.0±0.48 才(50～85 才)、入院日数 23.6±1.2 日(１～175 日)、同期間に複数回入院同一患者の 52 名)であり、この中で入院期間が５日未満のもの、情報に欠損のあるものは対象外とし、最終的に 238 例を解析対象とした。検証群は、2002 年７月１日から 10 月 31 日までの期間に同様に肝細胞癌の診断で入院したのべ 93 症例(男性 68 名,年齢 69±才(21～81 才)、平均入院日数 28.8±2.2 日(３～125 日)、同期間に複数回入院同一患者の７名)の中で入院期間が５日未満のもの、情報に欠損のあるものを除く 80 例を最終対象とした。

この検討における医療費は、保険支払いの立場での入院基本料などの Hospital fee を含む診療報酬請求額および Hospital fee を除く入院期間中の一つ一つの診療行為からの医事点数を加算した診療行為請求額とした。

データの集計および解析は次のような手順で行った。

1.　個々の症例について入院期間および入院中の診療行為の明細、最終的な診療報酬請求額をレセプト請求データから抽出した。さらに診療行為の明細と医事点数を掛け合わせ入院基本料などのいわゆる Hospital fee を除いた診療行為のみの診療行為請求額を算定した。

2.　慢性肝炎および肝硬変症における抗炎症基礎治療、肝硬変症の非代償性合併症、すなわち、腹水・浮腫、肝性昏睡、食道静脈瘤に対する治療、さらには肝細胞癌の特異的治療、すなわち、手術、経皮的エタノール注入(PEIT 療法)、抗ガン剤とリピオドール(およびスポンゼル)による血管塞栓術(Chemolipiodol 療法)、化学療法(塞栓剤を用いない動注化学療法など)などに用いられる代表的な薬剤や診療行為に着目し(表 1)、個々の症例の診療行為の明細からそれぞれの合併症に対する治療の有無、個々の肝細胞癌治療実施の有無の判定を行った。尚、放射線療法(体外照射)については実施された患者数が４人と少なく最終的な検討対象には入れなかった。

3.　２で得られた合併症や個別の肝細胞癌治療行為の有無により一入院期間における診療報酬請求額および診療行為請求額に差があるかどうかを検定するために単変量解析を行った。さらに、それらの請求額に対する入院日数および合併症の有無や肝細胞癌治療法の種別との関連を多変量解析にて検討した。

統計解析は、StatFlex (アーテック社)を用いて、合併症ならびに肝細胞癌の治療行為別(要因)に入院あたりの診療報酬請求額との関連を Mann-Whitney 検定を用いて $P<0.05$ を有意水準として検討した(単変量解析)。また、診療報酬請求額、診療行為請求額を従属変数とし、入院日数と非代償性肝硬変症の腹水などの３合併症、手術、PEIT、TACE、Chemolipidol 療法、化学療法の肝細胞癌に対する５種類の治療法、そして抗炎症基礎療法についての有(1)、無(0)を説明変数とした重回帰分析を行った。この際、変数の正規化のため、あらかじめ分布型の解析を行い、入院中の診療報酬請求額、診療行為請求額、入院日数に対してそれぞれ、0.36 乗、0.48 乗、0.2 乗の Box-Cox 変換を行った。最適な重回帰モデルは変数増減法により、$P<0.05$ であればモデルの中に組み込み、$P<0.15$ であればモデル内に残す条件で最も大きな調整済み R2 を持つ回帰式を選択した。

C　研究結果

モデル作成群の 238 名の肝細胞癌患者における入院日数および診療報酬請求額の平均および標準誤差は、それぞれ 24.3±1.2 日、93,0138±61,173 円であった。実施された合併症および肝細胞癌に対する治療頻度の内訳は表２のごとくであった。その中で、Chemolipiodol 療法を除いてそれぞれの治療が実施された群はされなかった群と比較して入院日数は長く、診療報酬請求額は高かった。特に、浮腫・腹水、肝性脳症、食道静脈瘤に対する治療および手術、化学療法が実施された群は平均医療費が 100 万円を超える請求額となっていた。また、単変量解析では、抗炎症基礎治療における入院日数と診療報酬請求額、および PEIT 療法、Chemolipiodol 療法

の診療報酬請求額以外では、合併症のある群、肝細胞癌治療がされた群で有意に入院日数が長く、診療報酬請求額も高かった。
入院日数と診療報酬請求額の間では、Spearman の順位相関にて 0.78 と高い相関は示した。また、合併症、肝細胞癌の診療行為別に診療報酬請求額および診療行為請求額と入院日数の相関をみると前者では 0.712～0.924 と高い正の相関を認め、後者でも 0.433～0.690 と中等度の相関を認めた。(表３)
診療報酬請求額に対する多変量解析(表４)では、t 値より入院日数が診療報酬請求額に影響する最も大きな要因であったことは相関が高かったことと一致するものである。入院日数以外には、手術、Chemolipiodol 療法や化学療法などが有意に影響するものであったが、肝硬変症の非代償期の合併症である肝性脳症や腹水・浮腫などは有意ではなかった。すなわち、診療報酬請求額に対してこれらの要因の寄与度は、入院日数が最も有意で、次に肝細胞癌に対する治療の寄与度が有意であったが、肝硬変症の合併症における寄与度は高くないという結果であった。一方、入院日数に依存する入院基本料などの Hospital fee を除いた診療行為請求額に対する多変量解析では(表 5)では、 t 値から入院日数、手術、Chemolipiodol 療法が同程度の寄与度になっていたが、肝硬変症の合併症項目は唯一、腹水・浮腫が有意となっているのみで、やはり、寄与度は低い結果であった。
表３に示すモデルの妥当性については、診療報酬請求額の予測値と実際額との重相関係数は 0.89 と高かったが、80 例の検証患者群にモデルを適用しても、同様に 0.85 と良好であった。(図２)

D　考察

医療費の正確度の高い推定は、疾患が社会に与える影響の大きさを測る上でも、あるいは、さまざまな治療における費用効果分析などにより医療資源の配分を考える上でも不可欠である。しかし、我が国での疾患別の医療費についての正確な情報は少なく、今後の医療経済における重要な課題となっている。
一方、複数の病態が併存している患者では、それぞれの病態に特異的な検査や治療のみでなく複数の病態に共通の検査や治療がされることからその病態毎に機械的に分けて医療費の算出を行うことは容易ではない。実際の症例を用いた検討でも、さまざまな合併症や併存症をもつ症例が多いことから、その病態の純粋な医療費を推定するには、その中で層別化し、合併症が全くない、あるいは、特定の合併症だけがある症例のみを集めて検討する場合が多い。[5]
そこで、本研究では、それぞれの合併症や治療が医療費の部分的なコンポーネントを構成することを前提として、肝硬変の非代償性の合併症をともなうことが多い肝細胞癌を対象として複合病態における入院患者における医療費の推定モデルを作成し、肝細胞癌治療や合併症の医療費における寄与度、およびモデルの妥当性を検討した。
結果より、それぞれの診療報酬請求額および入院基本料など Hospital fee を除いた診療行為請求額に対する寄与度をみると入院日数＞肝細胞癌治療>合併症(一部)の治療という順であった。また、それぞれの治療が入院日数との相関が強かったことから、有意な治療として上がらなかった合併症治療は、合併症の入院日数の増加による診療報酬請求額の増加にその医療費分が含まれるのに対して、有意であった治療は入院日数の増加による診療報酬請求額の増加に加えて、それぞれの係数分の請求額が加わると理解できることから、図１のような医療費のコンポーネントとしての考え方が妥当であることを肯定するものと考えられた。
今回、従来、行っていた診療録からの合併症、肝細胞癌に対する治療についての情報ではなく、診療請求上の行為明細から判定を行った。これは、レテロスペクティブな診療録の確認では行われた医療行為について十分な情報が得られない場合があり、また、今回のような診療報酬請求の観点からは、実際に請求の対象となった診療行為に注目する方がより正確な推定が可能と考えられたからである。実際、診療行為明細には入っている処置などが診療録からは確認できないケースも多くあり、有用な方法と考えられた。一方、診療行為明細には、患者で異なる様々な行為がなされていることから、医療費の推定の対象となる病態の診療報酬請求に重要と考えられる診療行為を把握する事が重要であり、その如何により推定の正確度が影響されることになる。
医療費の推定方法は医療費を考える立場(perspective)、すなわち、患者、保険支払者、社会などの立場で異なるが、一般的には個々の患者に実際に行われた医療行為に用いられた薬剤や医療材料、医師、看護師など医療提供者の費用、さらには施設や機器利用にともなう費用などをひとつひとつ積み上げる micro-costing の手法がとられる

ことが多い。[2] しかし、今回の医療費の推定は保険支払者の立場で行い、診療報酬請求にともなう保険償還額を医療費とした。我が国では、国民医療費の増大から近年、従来の出来高支払い制に加えて包括評価支払い制度が導入され、DPCに基づく診療報酬額の割り付けが行われているが、この基盤となっているのは、それぞれのDPC別の出来高による診療報酬額の調査であり、今回の検討もそれと同様のアプローチである。そのため、DPCをもとにした包括支払い制度の妥当性を評価する上でも今回の検討は意義あるものと考える。すなわち、DPCそのものが基本的に疾患と手術、処置、副傷病名の有無の組み合わせであり、今回の検討における手術、処置、そして、肝硬変症の合併症の寄与度の相対的な大きさの結果は、それに一致するものと考えられた。特に、肝硬変症の合併症である腹水・浮腫、肝性脳症、食道静脈瘤は、それぞれ治療により医療資源を消費するものであるが、肝細胞癌と複合した病態においては、入院日数と肝細胞癌に対する治療により主に医療費が決定されるといった結果から、例えば、費用効果分析などでは、肝細胞癌がある場合に肝硬変症の合併症別に分ける必要性は少ないものと考えられた。

今回の検討の限界として、次の２点が上げられる。一つは、食道静脈瘤やPEITなどで患者数が少ないことが解析に影響した可能性があり、今後、それらの患者数を増やしての検討が必要と考えられた。二つには、推定モデル作成に線形回帰である重回帰分析を用いたが、有意とされた要因それぞれが入院日数と相関が強く、また、変数の正規化のためにBox-Cox変換を行ったことにより、モデルで有意とされた要因毎に単純なブロック組み立てのように加算できる形にはならなかった。一般的には医療費は分布が正規分布とはならないため、その歪度を考慮に入れる必要があるが、そのため、正規分布を前提としない一般化線形モデルなどのより適切な手法について今後、検討する必要がある。[6]

E 結論

複合病態における医療費(診療報酬請求額・診療行為請求額)の推定の例として肝細胞癌患者を対象として入院日数とともに実施された診療行為に着目した多変量回帰モデルを作成した。モデルは入院日数が最も有意な因子であったが、異なる肝細胞癌治療も有意な因子として挙げられ、それぞれの因子をコンポーネントとして捉えることが妥当と考えられた。今後、適用するモデルの妥当性の検証が必要であるが、従来の病態別、治療別に層別化された患者集団による医療費の変動についての検討およびその組み合わせでの平均的医療費の推定に今回のアプローチは有用と考えられた。

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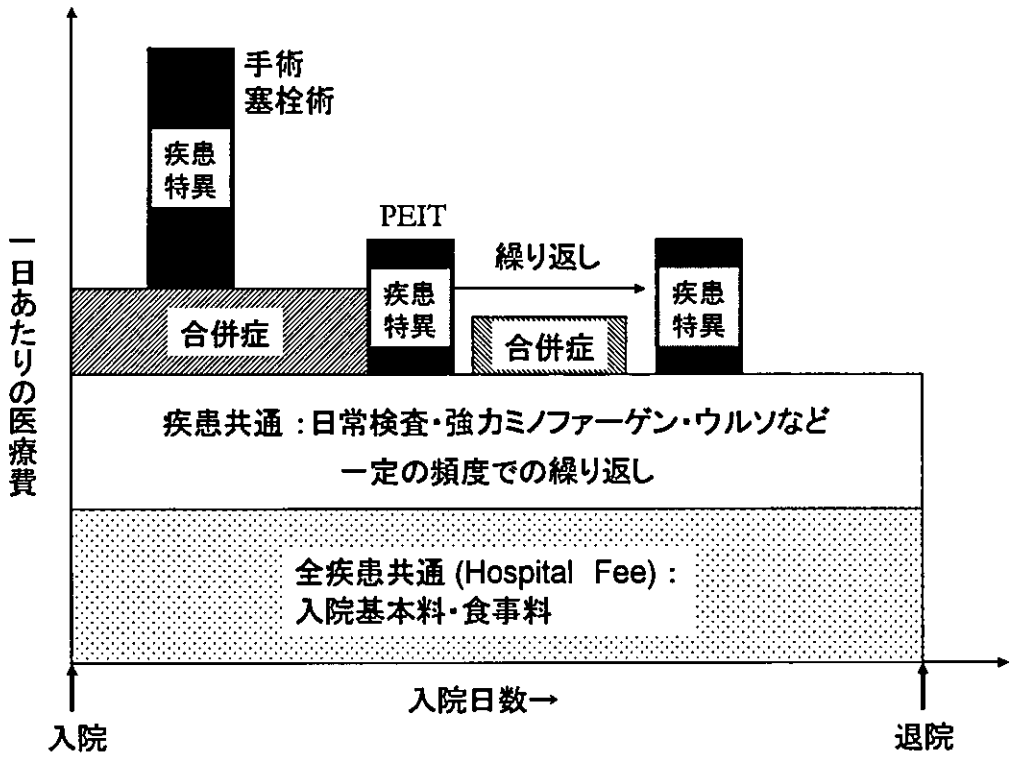

図１． 入院医療費の構成概念図

表１：肝細胞癌および合併症に対する医療行為の特異的マーカー

合併症・治療		診療行為・薬剤
抗炎症基礎治療		強力ミノファーゲンC・ウルソ・プロヘパール等
合併症	腹水・浮腫	ラシックス・アルダクトンなど利尿剤(＋アルブミン)
	肝性脳症	アミノレバン・モニラック・ラクツロース+アンモニア測定
	食道静脈瘤	食道静脈瘤結紮術・食道静脈瘤硬化療法・オルダミン
肝細胞癌治療	手術	手術術式(肝切除術)
	PEIT療法	エタノール局所注入
	Chemolipiodol療法	抗ガン剤+リピオドール(+スポンゼル)
	化学療法	抗ガン剤-リピオドール(-スポンゼル)
	放射線療法	放射線治療管理料・体外照射

表２：診療行為の有無による在院日数、診療請求額

診療行為		あり	なし	p値*
抗炎症基礎治療	N*	196	42	
	入院日数	24.6(1.4)**	23.1(2.8)	NS
	診療請求額	968,286(71,306)**	752, 114 (93, 847)	NS
合併症				
腹水・浮腫	N	118	120	
	入院日数	27.8(2.1)	20.9(1.3)	p=0.002
	診療請求額	1,163,191(113,388)	700,969(38,258)	p<0.001
肝性脳症	N	60	178	
	入院日数	34.6(3.7)	20.9(1.0)	p<0.001
	診療請求額	1,432,769(209,225)	760,711(33,747)	p<0.001
食道静脈瘤	N	11	227	
	入院日数	38.4(4.1)	23.6(1.3)	p<0.001
	診療請求額	1,422,741(127,768)	906,267(63,447)	p<0.001
肝細胞癌治療				
手術	N	20	218	
	入院日数	34.4(4.4)	23.4(1.3)	p<0.001
	診療請求額	2,034,772(398,626)	828,795(51,216)	p<0.001
PEIT療法	N	28	210	
	入院日数	29.9(2.9)	23.6(1.3)	p=0.005
	診療請求額	923,314(93,981)	931,047(68,249)	NS
Chemolipiodol療法	N	124	114	
	入院日数	20.2(1.2)	28.7(2.2)	p<0.001
	診療請求額	787,001(30,180)	1,085,830(122,057)	NS
化学療法	N	23	215	
	入院日数	41.6(5.4)	22.5(1.2)	p=0.001
	診療請求額	1,371,762(185,545)	882,895(64,046)	p=0.005

* 症例数

** 平均(標準誤差)を示す。

表３：診療行為別の入院日数と診療報酬請求額、診療行為請求額との相関

診療行為	診療報酬請求額	診療行為請求額
抗炎症基礎治療	0.783	0.502
合併症		
腹水・浮腫	0.820	0.626
肝性脳症	0.841	0.622
食道静脈瘤	0.747	0.433
肝細胞癌治療		
手術	0.718	0.612
PEIT療法	0.858	0.602
Chemolipiodol療法	0.897	0.475
化学療法	0.924	0.690

表４：診療報酬請求額に対する多変量解析結果

治療・合併症	回帰係数(SD)	t値	p値
入院日数	58.89 (2.72)	21.65	<0.001
手術	108.00 (12.10)	8.93	<0.001
Chemolipiodol	48.25 (6.82)	7.07	<0.001
化学療法	36.09 (11.31)	3.19	0.002
腹水・浮腫	12.39 (6.75)	1.84	0.068
肝性脳症	11.56 (7.78)	1.49	0.139

R=0.89

表５：診療行為請求額に対する多変量解析結果

治療・合併症	回帰係数(SE)	t値	p値
入院日数	189.53 (20.99)	9.03	<0.001
手術	840.68 (93.82)	8.96	<0.001
Chemolipiodol	431.40 (52.59)	8.20	<0.001
化学療法	354.02 (87.21)	4.06	<0.001
腹水・浮腫	120.78 (48.30)	2.50	0.013
食道静脈瘤	181.01 (112.82)	1.60	0.110

R=0.74

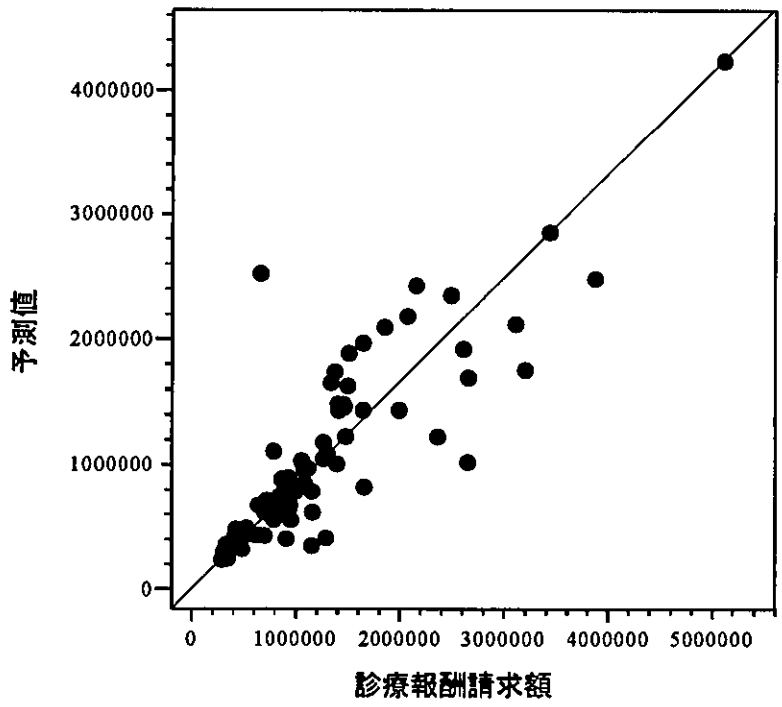

図２．モデルによる予測値と実際の診療報酬請求額との相関

Ⅲ　関連発表論文別刷り

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Interferon therapy as chemoprevention of hepatocarcinogenesis in patients with chronic hepatitis C

Keisuke Hino[1]* and Kiwamu Okita[2]

[1]*Department of Laboratory Sciences, Faculty of Health Sciences, and* [2]*Department of Gastroenterology and Hepatology, Faculty of Medicine, Yamaguchi University, School of Medicine, Ube, Yamaguchi, 755–8505, Japan*

Hepatocellular carcinoma (HCC) is currently a very common malignancy and its incidence is increasing, both in Japan and the USA. Persistent hepatitis C virus (HCV) infection is a major risk factor for the development of HCC. A number of large-scale retrospective cohort studies have demonstrated that interferon therapy reduces the incidence of HCC not only in sustained virological responders but also in transient biochemical responders without the elimination of HCV. We also demonstrated that retreatment with interferon at certain intervals reduced the incidence of HCC in patients with chronic hepatitis C, even if eradication of HCV was not achieved by retreatment. We cannot, however, explain how a transient normalization of serum alanine aminotransferase levels induced by a maximum 6 months of interferon treatment reduces the incidence of HCC during the progression of chronic hepatitis to cirrhosis or HCC, which requires dozens of years. In this article, we discuss how interferon treatment might reduce the incidence of HCC even in transient biochemical responders, especially in view of antiproliferative or antioxidative activity of interferon-α.

Keywords: cell cycle, hepatocellular carcinoma, MEK/ERK pathway, oxidative stress

Introduction

Hepatocellular carcinoma (HCC) is currently a very common malignancy and its incidence is increasing, both in Japan and the USA. Persistent hepatitis C virus (HCV) infection is a major risk factor for the development of HCC. Approximately 80% of Japanese HCC patients are also diagnosed with HCV-associated cirrhosis or chronic hepatitis C. It has also been shown that the risk of HCC increases with the degree of liver fibrosis.[1] Thus, HCV patients are a high-risk group for the development of HCC, and inhibition of hepatocarcinogenesis remains a crucial issue in treating patients with HCV-related chronic liver disease.

A number of large-scale, retrospective, cohort studies conducted in Japan have demonstrated that interferon therapy reduces the incidence of HCC, not only in sustained virological responders but also in transient biochemical responders, without eliminating HCV (Table 1).[1–6] On the other hand, the incidence of HCC has been shown to increase 5 years or more after interferon therapy in transient biochemical responders, suggesting that, in this population, interferon's effects are time sensitive.[7] In this respect, we demonstrated that re-treatment with interferon at certain intervals reduced the incidence of HCC in patients with chronic hepatitis C, even if eradication of HCV was not achieved by re-treatment.[8] It seems plausible that eradicating HCV would result in a reduced incidence of HCC. We cannot, however, explain how a transient normalization of serum alanine aminotransferase (ALT) levels, induced by a maximum 6 months of interferon treatment, reduces the incidence of HCC during the progression of chronic hepatitis to cirrhosis or HCC, which requires dozens of years. We discuss herein how interferon treatment might reduce the incidence of HCC even in transient biochemical responders.

Hypercarcinogenic condition in HCV-associated chronic hepatitis or liver cirrhosis

We need to find out the molecular mechanism of hepatocarcinogenesis in HCV infection, which remains unclear, to understand how interferon therapy reduces the incidence of HCC in transient biochemical responders. In persistent HCV infection, hepatocarcinogenesis is closely related to the presence of chronic hepatitis with advanced liver fibrosis or liver cirrhosis, which represents a precancerous state accompanied by increased DNA synthesis. In fact, it has been shown in a prospective manner that cirrhotic patients with high liver cell proliferative activity, estimated by proliferating cell nuclear antigen staining, are more likely to develop HCC as compared with those without it.[9] It has been suggested that HCV core protein enhances cell proliferation via activation of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK).[10] Activation of MAPK/ERK has also been reported in human HCC tissues.[11] The mitogen-activated protein kinase kinase (MEK)/ERK signalling pathway is fundamental in controlling cell development, proliferation and the cell cycle.[12,13] There is clear evidence that the MEK/ERK pathway is essential for the activation of the molecular events regulating cell cycle progression, such as degradation of

*Corresponding author. Tel and Fax: +81-836-222824; E-mail: k.hino@yamaguchi-u.ac.jp

Table 1. Reduction in the development of hepatocellular carcinoma in sustained virological responders and transient biochemical responders: characteristics of Japanese selected studies

Reference	Number of patients[a]	Observation period (years)	Estimated cumulative incidence of HCC at the 5th year (%)			Risk ratio[b]	
			SVR	TBR	NR	SVR	TBR
Kasahara *et al.*[2]	1022	3.1 ± 12.9	4.3	4.7	21.4	0.13	NA
Imai *et al.*[3]	563	4.0	0.9[c]	6.1[c]	12.8[c]	0.06	0.51
Ikeda *et al.*[4]	1643	5.1 (0.1–11.3)	1.4	1.9	2.9	0.32[d]	
Yoshida *et al.*[1]	2890	4.4	NA	NA	NA	0.25	0.27[e]
Tanaka *et al.*[5]	738	4.8 ± 1.2	1.2	3.7	10.0	0.16	0.27
Okanoue *et al.*[6]	1370	5.6	NA	NA	NA	0.10	0.55

SVR, sustained virological responders; TBR, transient biochemical responders; NR, non-responders; HCC, hepatocellular carcinoma; NA, not assessed.
[a]These numbers include untreated patients except for references 2 and 6.
[b]Adjusted risk ratios for development of HCC were calculated compared with untreated patients in references 1, 3, 4 and 5, and with non-responders in references 2 and 6.
[c]These figures represent the 4 year incidence of HCC.
[d]This risk ratio was for the groups that responded; these included SVR and TBR.
[e]This risk ratio was for the patients who had normal serum ALT levels and were positive for HCV RNA.

mitotic inhibitors ($p21^{Waf1}$ and $p27^{Kip1}$) and the induction of the cyclin–cyclin dependent kinase (Cdk) complexes.[14,15]

A recent study has revealed that protein levels and kinase activities of cyclin D1, Cdk4, cyclin E, cyclin A and Wee1 are significantly elevated in HCV-associated HCC compared with surrounding cirrhotic tissues.[16] More importantly, these kinases are already activated in cirrhosis before the development of HCC, compared with normal liver tissues, suggesting that this activation is an early event in hepatocarcinogenesis and that HCV-associated cirrhosis is a pre-cancerous condition. Thus, in a chronic hepatitis state, the cell cycle progresses and hepatocytes divide rapidly. As a result, irregular regeneration is bound to happen, accelerating genomic instability. Of course, the MEK/ERK pathway is not the only pathway potentially leading to the development of HCC. For, instance, there is considerable interest in the wnt/β-catenin pathway, specifically in the context of HCV-associated HCC.[17] The complexity of all the biochemical pathways implicated in HCC development is well described in a broad review on the genetics of HCC.[18]

Another scenario for hepatocarcinogenesis in HCV infection is the involvement of oxidative stress, which can produce genetic mutations as well as gross chromosomal alterations. HCV core protein has been shown to produce reactive oxygen species (ROS) derived from mitochondria in inducible cell culture systems.[19] A positive feedback effect of ROS on mitochondrial ROS generation further sensitizes cells to other oxidative insults, which may finally cause both mitochondrial and chromosomal DNA damage. In a transgenic mouse model for HCV-associated hepatocarcinogenesis, it is also demonstrated that HCV core protein causes a state of oxidative stress in the absence of inflammation.[20]

Although these results suggest the direct induction of oxidative stress by HCV proteins, the consequences of impaired mitochondrial function and abnormal ROS generation would be exacerbated by the immune-mediated inflammatory process present in patients with chronic hepatitis C, and the additional oxidant load it would present to the HCV-infected liver. Continuous ROS generation is likely to cause 8-hydroxy-2′-deoxyguanosine (8-OHdG) to accumulate in DNA. Kato *et al.*[21] reported that lowering levels of 8-OHdG by phlebotomy potentially decreased the risk of hepatocarcinogenesis in patients with chronic hepatitis C. According to them, hepatic 8-OHdG levels decreased significantly in the short-term (initial iron reduction phase) and were almost completely normalized by the end of therapy (6 years later) by keeping a state of mild iron deficiency, defined by either <10 μg/L serum ferritin and/or 11 g/dL blood haemoglobin concentration. Thus, oxidative stress appears to be responsible, in part, for the development of HCV-associated HCC.

Clinical evidence suggesting the anti-hepatocarcinogenic effect of interferon in patients with HCV-associated chronic liver disease

As mentioned above, chronic hepatitis C with advanced liver fibrosis or liver cirrhosis is hypercarcinogenic at the molecular level. This is supported clinically in Japan by the high annual incidences of HCC in non-treated chronic hepatitis C patients with F3 staging[22] of liver fibrosis (2%–3%) and those with liver cirrhosis (6%–7%). The rate of recurrence of HCC after complete surgical resection is much higher than these figures, suggesting that the post-operative state is more hypercarcinogenic.[23]

A recent randomized study has shown that interferon-β prevents the recurrence of HCC after complete resection or ablation of the primary tumour in patients with HCV-associated cirrhosis.[24] This inhibitory effect on HCC recurrence by interferon was not associated with biochemical and virological improvement. Therefore, these results clearly suggest that interferon acts as an anti-hepatocarcinogenic agent in patients with HCV-associated chronic liver diseases.

Molecular mechanism by which interferon prevents hepatocarcinogenesis in patients with chronic hepatitis C

Taking into account the molecular mechanisms underlying the hypercarcinogenic condition in HCV infection, we focused on the mechanism responsible for the antiproliferative or antioxidative activity of interferon-α. The regulatory signals triggered by interferon-α are transduced to the nucleus through the Janus tyrosine kinase/signal

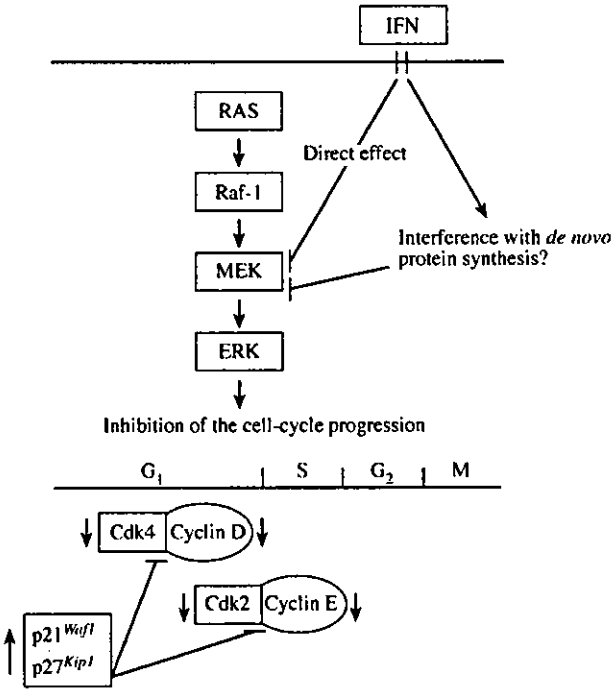

Figure 1. A schematic diagram illustrating the proposed mechanisms of action by which interferon might inhibit carcinogensis through the regulation of the MEK/ERK pathway. Interferon has been shown to inhibit MEK/ERK function without affecting Ras and Raf-1 activity. Mechanisms by which interferon regulates MEK phosphorylation may involve interference with *de novo* protein synthesis and/or regulation of a specifc gene(s). Analysis of downstream events controlled by the MEK/ERK pathway showed reduced activity of Cdk2 and Cdk4, high levels of mitogenic inhibitors ($p21^{Waf1}$ and $p27^{Kip1}$), and decreased cyclin D and E expression. Cdk4 and Cdk2 are activated by binding to cyclin D and cyclin E, respectively. Cyclin D–Cdk4 complexes are required for G1 phase progression. Cyclin E–Cdk2 complexes are required for the G1/S transition. Cdk activity is curtailed by $p21^{Waf1}$ and $p27^{Kip1}$.

transducers of activation and transcription (Jak/STAT) pathway, whereby ligand-activated Jak kinases phosphorylate STAT proteins, which subsequently dimerize and migrate to the nucleus to regulate gene expression. Interferon-α was initially described as an antiviral cytokine able to inhibit viral replication, and thereafter additional properties of this multifunctional cytokine that can affect the growth, differentiation and function of many cell types were discovered. The cross-talk between the Jak/STAT and the MEK/ERK pathways was demonstrated by the observation that interferon-β can directly activate ERK, which associates with STAT1.[25] Romerio & Zella[26] demonstrated that treatment with interferon-α hindered the transition from G0/G1 to the S phase in purified primary CD4 cells stimulated with anti-CD3 and interleukin 2. This inhibitory effect of interferon-α was linked to the impairment of the MEK/ERK function without affecting Ras and Raf-1 activity. Their analysis of downstream events controlled by the MEK/ERK pathway showed reduced activity of Cdk2 and Cdk4, high levels of mitogenic inhibitors ($p21^{Waf1}$ and $p27^{Kip1}$), and decreased cyclin D and E expression (Figure 1). Interestingly, these downstream events inhibited by interferon-α have been shown to be activated in HCV-associated HCC or cirrhotic tissues as compared with normal liver tissues by another group.[16] In a number of different cellular systems it has been shown that inhibition of mitogenic induction of MEK and ERK results in impairment of cell-cycle progression and proliferation. Therefore, the inhibitory effect on MEK/ERK function by interferon may be one of the important mechanisms involved in anti-hepatocarcinogenic actions.

Another cell cycle analysis of G1-synchronized, interferon-α-treated HCC cell lines revealed a substantial delay in S-phase progression, but no alteration of G1/S-phase transition.[27] Reflecting the time course of S-phase accumulation, cell cycle-dependent induction of cyclin A and cyclin B was demonstrated to be impaired. The ability of interferon-α to interfere with cyclin A expression in HCC is noteworthy in view of the reported overexpression of cyclin A in ~40% of tumour tissues from HCC patients.[28] The mechanism by which interferon-α inhibits cell-cycle progression and proliferation may be influenced by the cell line systems analysed, but its variation, alternatively, reflects differences in the available spectrum of interferon-α-susceptible growth-relevant effector molecules because of specific oncogenic alterations present in the target cell.

Interferon-α has been shown to reduce intrarenal oxidative stress in rats with carbon tetrachloride-induced nephrotoxicity.[29] Another study revealed that interferon-α dose-dependently increased the protein levels of copper-, zinc- and manganese-dependent superoxide dismutase, as well as the enzyme activities of glutathione peroxidase, and decreased the lipid peroxidation product levels in oxidative-stressed rat hepatocytes.[30] As HCV RNA levels are usually decreased or undetectable, even though uncommonly unchanged, during interferon therapy in transient biochemical responders, such antioxidative actions of interferon may be amplified in a condition where oxidative stress is attenuated due to decreased HCV load. In fact, 2 months interferon therapy has been shown to decrease the serum lipid peroxidation products (thiobarbituric acid reactive substances) of hepatitis C patients, whose serum ALT levels fall to the normal range.[31]

Conclusions

Needless to say, eradication of HCV and normalization of the serum ALT level by interferon are the most important issues for chemoprevention of hepatocarcinogenesis in patients with chronic hepatitis C. However, the antiproliferative activity of interferon-α also seems to play a critical role in preventing chronic hepatitis C patients from developing HCC. Furthermore, interferon may have a direct antitumour effect on clinically undetectable HCC, since combination therapy with interferon-α and intraarterial 5-fluorouracil has been shown to be effective in reducing tumours in patients with HCC.[32] With respect to this issue, a very recent study demonstrated the integration of interferon-α/β signalling to p53 responses in tumour suppression, which resulted in enhancement of cancer cell apoptosis by interferon.[33] We need to ascertain whether the anti-proliferative action of interferon is actually elicited in transient biochemical responders, not in non-responders, and induces a normo- or hypocarcinogenic condition in those patients.

There is no strong clinical evidence linking the antioxidative action of interferon to the inhibition of HCC development in patients with chronic hepatitis C. Thus, further studies are required to determine how the antioxidative activity of interferon is involved in reducing the HCC incidence in HCV infection.

Acknowledgements

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Cost-effectiveness of ribavirin plus interferon alpha-2b for either interferon relapsers or non-responders in chronic hepatitis C: a Japanese trial

Haku Ishida[a,*], Yuji Inoue[a], John B. Wong[b], Kiwamu Okita[c]

[a] *Department of Medical Informatics and Decision Sciences, Yamaguchi University School of Medicine, Ube, Japan*
[b] *Tufts–New England Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[c] *Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, Ube, Japan*

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Abstract

The aim of this study was to examine the cost-effectiveness of combination therapy with ribavirin plus interferon alpha-2b compared with interferon monotherapy for hepatitis C-infected Japanese patients who had either temporarily responded or not responded to initial interferon treatment. Data from a recent randomized clinical trial among relapsed or non-responding patients comparing combination therapy to interferon alone were applied to a computer cohort simulation Markov process model to project lifelong clinical and economic outcomes. Combination therapy for 24 weeks should increase life expectancy by 1.6 quality-adjusted life years and should reduce discounted (3% per year) lifetime costs by ¥121,000 when compared to retreatment with interferon alone. For the subgroup of patients with genotype 1b and high viral load, combination therapy should be cost-effective (¥187,000 per QALY gained with a 3% annual discount rate) by well-accepted international standards. These results were robust with combination therapy remaining cost-effective or cost saving in sensitivity analysis involving reasonable variation in all parameters.

For patients similar to those enrolled in the interferon alpha-2b and ribavirin trials in Japan, combination therapy should be considered cost-effective with the higher drug treatment costs nearly completely offset by future savings through reductions in future liver complications from hepatitis C.

Keywords: Chronic hepatitis C; Interferon; Ribavirin; Cost-effective analysis

1. Introduction

Hepatitis C virus (HCV) affects 170 million individuals worldwide and more than 2 million in Japan. Hepatitis C can lead to cirrhosis and hepatocellular carcinoma (HCC). In Japan, it results in more than 30,000 deaths annually [1], and 84% of Japanese HCC patients were reported to be seropositive for anti-HCV antibody [2]. Interferon treatment of hepatitis C-infected patients has been found to reduce substantially the incidence of HCC in those who respond completely or partially to interferon [3–7].

Interferon monotherapy for chronic hepatitis C infection in Japan leads to complete remission with viral eradication in 30–40% and to normalization of liver tests without eradication in 10–20%. The majority of patients however relapse once treatment is stopped with only 15–20% of interferon treated patients demonstrating a durable effect 6–12 months after therapy. More than one-half of patients are non-responders or relapsers and usually receive another course of interferon with a higher dose or for a longer duration [8,9].

Because the Japanese Ministry of Health, Labor and Welfare has recently launched an HCV screening program in the general population, many previously unidentified individuals and their physicians will be facing antiviral treatment decisions in the near future. It will be critical to determine how such HCV-infected patients should be treated clinically and to assess the social and monetary implications for Japan.

* Corresponding author. Present address: 1-1-1 Minami-kogushi Ube, Yamaguchi 755-8505, Japan. Tel.: +81-836-22-2120; fax: +81-836-22-2718.
E-mail address: hishida@hmi.yamaguchi-u.ac.jp (H. Ishida).

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A randomized controlled study to determine the effectiveness of the combination of interferon alpha-2b plus ribavirin, an oral nucleoside analogue, was conducted in Japan recently. Combination therapy was found to significantly increase sustained response rates compared with interferon monotherapy in patients in whom prior interferon monotherapy had failed to eradicate HCV [10].

A prior study has shown that treating Japanese patients who have hepatitis C with interferon is "cost-effective" with an incremental or marginal cost-effectiveness ratio that is within the range of other well-accepted medical interventions. Combination therapy, however, is more expensive than interferon alone, raising questions about its economic value or cost efficiency.

The aim of this study was to estimate the incremental cost-effectiveness of the combination of ribavirin plus interferon compared with interferon alone for patients with hepatitis C who have relapsed (relapsers) or who did not respond to interferon at all (non-responders). We used data from a randomized clinical trial to estimate short-term events such as viral eradication and then projected long-term outcomes using a published Markov model that simulates the natural history of chronic hepatitis C.

2. Methods

We performed a cost-effectiveness analysis for the clinical trial of ribavirin and interferon alpha-2b in treating chronic hepatitis C patients who have relapsed or who were non-responders to prior interferon monotherapy in Japan. Summary data (age, gender, initial histology, genotype and virological response) from the clinical trial were then applied to a previously published and validated computer cohort simulation. The model was originally adapted to reflect the natural history and the clinical management of hepatitis C in Japan [11,12] and was further updated to reflect more recent studies [13].

We used actual data for 126 patients (mean age 49.5 years and 31% women) from a clinical trial in Japan [10]. Briefly, the study was a double-blind randomized placebo-controlled trial, comparing 24 weeks of interferon alpha-2b plus a placebo with the combination of ribavirin and interferon alpha-2b. Our analysis used the following data from the trial: age, gender, pretreatment histology, viral response after 24 weeks of treatment, viral response 24 weeks after treatment discontinuation, and treatment discontinuation as occurred in the trial whether due to an adverse event or other cause (Table 1).

We modified a previously published computer simulation model using current data regarding the natural history of chronic hepatitis C in Japan to estimate the long-term outcomes for each treatment arm. The original model has been previously validated by showing that predicted estimates match closely results found in natural history studies [11,12].

Table 1
Japanese randomized controlled trial of combination therapy vs. interferon[a]

Patient characteristics (n = 126)		
Mean age (years)	49.6	
Female	31 (39)	
Body weight > 60 kg	50 (63)	
Genotype 1b	68 (86)	
High viral load	77 (96)	
Histology		
Mild hepatitis	41 (51)	
Moderate hepatitis	54 (67)	
Cirrhosis	4 (5)	
	Response rates	
	Interferon alone	Combination therapy
Overall	(n = 64)	(n = 62)
Sustained viral negative[b]	9.4 (6)	35.5 (22)
Remission–relapse[c]	46.9 (30)	48.4 (30)
Withdrawal	9.4 (6)	8.1 (5)
Genotype 1b and high viral load	(n = 36)	(n = 37)
Sustained viral negative[b]	0 (0)	10.8 (4)
Remission–relapse[c]	47.2 (17)	67.6 (25)
Withdrawal	8.3 (3)	8.1 (3)

[a] Values are percentage (number) unless otherwise indicated.
[b] 24 weeks after treatment discontinuation.
[c] Temporarily viral negative but viral positive again 24 weeks after treatment.

In the base-case, we performed analyses for two cohorts: (1) patients similar to all those enrolled in the trial and (2) the subgroup of patients with genotype 1b and a high viral load. High viral load was defined as a viral titer exceeding 100k copies/ml by the RT-PCR assay and 1 Meq/ml by the branched DNA assay. The subgroup of patients with genotype 1b and high viral load comprised 34% of the study population.

3. Decision analytic model

Our updated Markov simulation model consisted of 13 health states: viral positive and negative mild chronic hepatitis, viral positive and negative moderate chronic hepatitis, viral positive and negative compensated cirrhosis, decompensated cirrhosis (ascites, first year or subsequent years following hepatic encephalopathy, first year or subsequent years following variceal hemorrhage), hepatocellular carcinoma, and the dead state.

For cohorts of hypothetically identical patients that matched the mean age and the initial distribution of liver histology of the clinical trial population, we applied the viral responses observed in the trial to our model to estimate the subsequent long-term prognosis. The Markov model simulated the prognosis of each treatment group by tracking each cohort as they moved through alternative states of disease defined by clinical and histological descriptors.

Table 2
Health states and annual probability of disease progression

Initial health state	Subsequent health state	
Mild hepatitis	Spontaneous remission	0.002[a]
	Moderate hepatitis	0.041[a]
Moderate hepatitis	Cirrhosis	0.073[a]
	Heptocellular carcinoma	0.030[b]
Cirrhosis	Ascites	0.025[a]
	Variceal hemorrhage	0.011[a]
	Hepatic encephalopathy	0.004[a]
	Heptocellular carcinoma	0.079[b]
Ascites	Death	0.110[a]
	Heptocellular carcinoma	0.079[b]
Variceal hemorrhage	Death, first year	0.400[a]
	Death, subsequent year	0.130[a]
	Heptocellular carcinoma	0.079[b]
Hepatic encephalopathy	Death, first year	0.680[a]
	Death, subsequent year	0.400[a]
	Heptocellular carcinoma	0.079[b]
Heptocellular carcinoma	Death	0.300[c]

[a] Bennett et al. [11].
[b] Yoshida et al. [7].
[c] Oka et al. [64].

Table 3
Health-related quality of life adjustments health state QOL weight[a]

Health state	QOL weight[a]
Mild hepatitis	
Viral positive	0.87
Viral negative	0.92
Moderate hepatitis	
Viral positive	0.80
Viral negative	0.84
Cirrhosis	
Viral positive or negative	0.65
Ascites	0.52
Hepatic encephalopathy	0.40
Variceal hemorrhage	0.33
Hepatocellular carcinoma	0.38
Interferon therapy	0.97
Combination therapy	0.94
Abortion	−1 week

[a] QOL: quality of life.

Time was represented by annual cycles during which patients remained in the same histological or clinical state, died from liver disease, or died from other causes based on gender and attained age (Table 2). The computer simulation continued until all patients died.

As would likely occur in clinical practice in Japan, we continued treatment in patients who remained viral positive after 12 weeks of interferon alone or combination therapy, as opposed to practice in the US where treatment would be discontinued. By recording the proportion of the cohort remaining alive and their medical costs for each year, the simulation estimated the average life expectancy and lifetime cost associated with each treatment. Simulations and analyses were performed with Decision Maker 7.0 (Pratt Medical Group, Boston).

To reflect the morbidity associated with some states of disease, we also adjusted life expectancy for quality of life on a scale from 0 (death) to 1 (perfect health), based on assessments by family practice doctors in Japan using a modified Delphi technique. These physicians received a description of the Markov model health states and an explanation of the time-trade off and standard reference gamble techniques. They were then asked to assess the utilities for each health state. Patients who were alive but in less desirable states of health were not given full credit for each year lived and instead received only partial credit (e.g. 0.65 quality-adjusted year or 7.8 quality-adjusted months for living 1 year with cirrhosis) (Table 3).

Because ribavirin has been shown to be teratogenic in animal studies, we decreased quality of life by 1 week for patients undergoing an elective abortion for an unplanned pregnancy during ribavirin treatment. For antiviral treatment, combination therapy was assumed to have twice the negative impact on quality of life as interferon alone.

4. Data sources

4.1. Likelihood of events

The annual likelihood of transition from one health state to another was estimated from published studies that we judged to be the best currently available (Table 2).

4.2. Cost

Because of differences in the health insurance system in Japan compared with other countries, direct resource consumption in Japan is difficult to estimate. We applied reimbursement from health insurance data to estimate the annual cost of each health state (Table 4). For outpatient care costs associated with mild chronic hepatitis, moderate chronic hepatitis and compensated cirrhosis, we estimated resource utilization for office visits and treatment according to expert opinion and guidelines from the Japan Society of Hepatology.

For the decompensated cirrhosis and hepatocellular carcinoma states of health, we surveyed actual reimbursement data for patients at Yamaguchi University Hospital and obtained average annual costs including hospital admissions and subsequent office visits. These estimated costs included periodic screening tests for hepatocellular carcinoma with tumor markers, abdominal ultrasonography and computer tomography as performed widely in Japan because of the effectiveness of screening for high risk patients.

We assumed that patients treated with either combination therapy or interferon alone would be admitted to the hospital for a month and would visit the hospital three times a week

Table 4
Cost data

	Total	Admission	Outpatient
Cost of antiviral treatment (Japanese yen)			
Mild chronic hepatitis			
Interferon only	1,626,000	978,000	648,000
Combination therapy	2,228,000	1,122,000	1,107,000
Moderate chronic hepatitis			
Interferon only	1,710,000	978,0007	732,000
Combination therapy	2,305,000	1,121,000	1,183,000
Annual cost of care for health states (Japanese yen)			
Mild hepatitis			
Viral positive	16,500		16,500
Viral negative	6,980		6,980
Moderate hepatitis			
Viral positive	183,000		183,000
Viral negative	76,000		76,000
Cirrhosis			
Viral positive or negative	267,000		267,000
Decompensated cirrhosis			
With ascites	1,156,000	730,000	426,000
With hepatic encephalopathy	1,050,000	624,000	426,000
With variceal hemorrhage	1,557,000	1,131,000	426,000
Hepatocellular carcinoma	1,326,000	1,009,000	317,000

Interferon: interferon alpha-2b and costs ¥1784 per mega unit; Combination therapy: interferon alpha-2b and ribavirin with ribavirin costs: ¥937 per capsule and includes costs for contraception and accidental pregnancy.

after discharge until the end of treatment. Drug dosage was as received during the trial and included discontinuation for adverse events. Ribavirin was recently approved by the Ministry of Health, Labor and Welfare in Japan and assigned a cost of ¥937 for one 200 mg pill based on insurance reimbursement.

As in the US study, we assumed that women younger than 50 years of age had a qualitative pregnancy test before beginning treatment and every month thereafter. We further assumed that ribavirin-treated women and men would use contraception with condoms (¥100 each based on the mid-range cost at local pharmacies) which would be used three times a week and would continue for 6 months after discontinuation of ribavirin. We assumed a 1.2% likelihood of pregnancy with condom contraception and assumed patients and their partners would elect to have an abortion at a cost of ¥30,000 including initial and follow-up office visits should they or their partner become pregnant [14]. Finally, the analysis took the insurance system perspective and excluded indirect or time costs (e.g. time lost from work or nonmedical costs).

4.3. Outcome measures and threshold for "cost-effectiveness"

Summing all of the costs, annual survival, quality-adjusted survival for each treatment strategy yielded the average expected lifetime costs, life expectancy, and quality-adjusted life expectancy associated with that treatment. As recommended, survival and costs were discounted at an annual 3% rate, but a discount rate of 5% was also applied to permit comparison to previously published studies.

The incremental cost-effectiveness ratio of combination therapy was calculated as the additional cost divided by the increase in life expectancy compared with interferon alone.

Most well-accepted medical interventions have incremental cost-effectiveness ratio falling below ¥6.0 million per discounted quality-adjusted life year gained (US$ 50,000 at ¥120 for a US dollar). For incremental cost-effectiveness ratios falling below this specific threshold amount, we considered the intervention to be "cost-effective."

4.4. Treatment response

Because viral negativity correlates better with long-term response than normalization of alanine aminotransferase (ALT), we used a viral negative response 24 weeks after treatment discontinuation as the primary endpoint. The results of the trial are shown in Table 1.

4.5. Histology data

To match the histological states defined by our model, cirrhosis required an International Classification System fibrosis score of 4, same as the Knodell score [15,16]. In the absence of cirrhosis, we defined mild chronic hepatitis as a fibrosis score of 0–1 (no fibrosis to fibrous portal expansion), moderate chronic hepatitis as a fibrosis score of 2–3 (bridging fibrosis: portal–portal or portal–central linkage), respectively. Bridging fibrosis could not be considered a distinct state of health because of insufficient data to estimate the likelihood of progression. However, patients with bridging fibrosis would have a poorer prognosis than those with moderate hepatitis [17,18], and because our model included patients with bridging fibrosis among those with moderate hepatitis, we thus assumed a better prognosis for these patients than most likely occurs. This assumption biased our analysis against antiviral therapy by underestimating disease progression, and because those treated with interferon alone are less likely to respond and more likely to progress, this assumption affects combination therapy more than interferon alone.

4.6. Assumptions of the model

1. We assumed that patients who did not have a sustained viral response after treatment would be managed with regular office visits and the periodic screening program as recommended by the guidelines of the Japan Society of Hepatology.
2. We assumed that patients who did not have a sustained viral response after treatment and whose disease was felt to be highly active received Strong Neo Minophagen C® (glycyrrizin) and ursodeoxychoric acid. As long-term

efficacy of glycyrrizin in preventing liver carcinogenesis in chronic hepatitis has been reported by Arase et al. [19] and these medications have for years been quite commonly administered in Japan to patients with highly active chronic hepatitis, we assumed that their effect would be reflected in the baseline rate of occurrence of hepatocellular carcinoma. Therefore, only the costs of these medications were added to the model.

3. We assumed that the subsequent prognosis of patients who did not respond (non-responders) or who only temporarily responded (relapsers) to initial treatment would be identical to those who had never had any antiviral treatment at all except for those who responded temporarily and relapsed after antiviral treatment. These patients were assumed to have a prognosis between that of patients with complete remission and that of non-responders. For example, the annual transitional probability from chronic moderate hepatitis to compensated cirrhosis equaled 0.073 for non-responders and 0.065 (=0.073 × 0.890) for relapsers [20].
4. We assumed that the risk of occurrence of hepatocellular carcinoma would be reduced among patients in whom sustained or temporary viral eradication had been achieved by interferon therapy or combination therapy. From the results of a national surveillance program conducted in Japan (the Inhibition of Hepatocarcinogenesis by Interferon Therapy [IHIT] Study) [7], the relative risk was assigned a value of 0.197 among sustained virological responders and 0.631 among temporary responders. Our model did not consider biochemical responders without virological response.
5. We assumed that patients who lose HCV either spontaneously or from treatment would have a greatly reduced but non-zero likelihood of developing progressive liver disease compared with those who were not treated. For example, the annual likelihood of the progression from mild chronic hepatitis with sustained viral response to moderate chronic hepatitis was 0.0002.
6. We did not consider liver transplantation for hepatocellular carcinoma or decompensated liver cirrhosis, because it is not possible or appropriate for most patients in Japan.
7. Although the model incorporated quality of life decrements for possible adverse reactions from antiviral therapies, it did not consider any additional quality of life decrements for treatment discontinuation. The frequency of withdrawal, however, from combination therapy and from interferon monotherapy was nearly equal.

Table 5
Results

	Interferon alone	Combination therapy	
(a) Base-case analysis[a]: all patients			
Progression			
Developed cirrhosis	40%	26%	33%[a]
Developed HCC	48%	34%	28%[a]
Died from liver disease	56%	40%	28%[a]
Lifetime costs			
Annual discount rate			
0%	6,734,000	6,325,000	−409,000[b]
3%	4,992,000	4,871,000	−121,000[b]
5%	4,296,000	4,301,000	5,000[c]
Quality-adjusted life years			
Annual discount rate			
0%	17.10	20.20	3.10[c]
3%	11.73	13.37	1.64[c]
5%	9.57	10.71	1.14[c]
Incremental cost-effectiveness ratio of combination therapy vs. interferon alone			
Annual discount rate			
0%		D	
3%		D	
5%		4,530	
(b) Subgroup analysis: subgroup with genotype 1b and high viral load			
Progression			
Developed cirrhosis	43%	36%	18%[b]
Developed HCC	52%	44%	16%[b]
Died from liver disease	61%	51%	16%[b]
Lifetime costs			
Annual discount rate			
0%	7,075,000	7,095,000	21,000[c]
3%	5,210,000	5,390,000	181,000[c]
5%	4,465,000	4,717,000	252,000[c]
Quality-adjusted life years			
Annual discount rate			
0%	16.17	18.02	1.85[c]
3%	11.26	12.22	0.97[c]
5%	9.25	9.91	0.67[c]
Incremental cost-effectiveness ratio of combination therapy vs. interferon alone			
Annual discount rate			
0%		11,000	
3%		187,000	
5%		377,000	

D: combination therapy dominated interferon therapy alone by extending survival and reducing costs.
[a] Relative risk reduction.
[b] Incremental cost.
[c] Incremental effectiveness.

5. Results

5.1. Base-case analysis

Model projections suggested that retreatment for initial interferon relapsers or non-responders with combination therapy decreased the lifetime risk of cirrhosis, hepatocellular carcinoma, or liver-related death by 28–33% compared with interferon alone (Table 5a). The cost of combination therapy using actual dosages administered in the trial would be ¥0.6 million more than interferon alone (Table 4). However, when considering only the undiscounted cost of future liver disease complications, combination therapy would

reduce lifetime undiscounted hepatitis C complication costs by ¥1.0 million because of its higher efficacy. These future savings completely offset the higher initial drug costs when compared with interferon alone. Therefore, over a lifetime time horizon, combination treatment was cost saving and would increase life expectancy by 3.1 quality-adjusted life years. Although discounting at a 3% per year rate reduced the benefit of future economic savings and of improved survival, combination therapy still improved prognosis by 1.65 discounted quality-adjusted years and still cost less than interferon alone. For an annual discount rate of 5%, the incremental cost-effectiveness ratio of combination therapy became ¥4 thousand per quality-adjusted year gained.

For the subgroup of patients with genotype 1b and high viral load who also had either relapsed or not responded, 24 weeks of combination therapy reduced the lifetime incidence of cirrhosis, hepatocellular carcinoma or mortality from liver disease by 16–18% compared to interferon alone (Table 5b). Without discounting, combination therapy increased lifetime costs by ¥20 thousand and increased life expectancy by 1.8 quality-adjusted life years compared with interferon alone, for an incremental cost-effectiveness ratio of ¥11 thousand per quality-adjusted life year gained. With annual discounting rates of 3 and 5%, the incremental cost-effectiveness ratio of combination therapy rose to ¥0.19 and 0.38 million per quality-adjusted life year gained, respectively, but still fell well within the cost-effectiveness range of other widely accepted medical interventions. Thus, these analyses suggest that combination therapy should be considered to be cost saving or cost-effective for a ribavirin cost of ¥973 per capsule.

To examine the robustness of these results, we performed additional incremental cost-effectiveness analyses for subgroups defined by gender, histology, genotype and viral load using the observed sustained virological responses for these subgroups (Table 6). Combination treatment for individuals with moderate hepatitis provided more benefit (in quality-adjusted life years) and was also more cost-effective than treatment for individuals with mild hepatitis because patients with moderate hepatitis are more likely to develop hepatic complications sooner. Also as expected, the effectiveness and cost-effectiveness of combination therapy for the subgroups with genotype other than 1b or with low viral load were superior to those for genotype 1b or for high viral load, respectively.

5.2. Sensitivity analysis

The results of the analysis changed little when the values of each model parameter were varied over a wide range. The exceptions included the annual probability of liver disease progression, the probability of sustained response, the cost of ribavirin and age at treatment. Even, however, in the worst case scenario where the progression rate and sustained viral negative response were assumed to be one-third of the baseline rates, the incremental cost-effectiveness ratio of combination therapy still fell well within the cost-effectiveness range of other widely accepted medical interventions. This was also true for the subgroup with genotype 1b and high viral load (Table 7).

Fig. 1 shows the sensitivity analysis of varying the cost of ribavirin. For an annual 3% discount rate, combination therapy for all patients (including some with genotype 1b and high viral load) was cost saving for ribavirin costs below ¥1144. Even for ribavirin costs up to ¥17,900 (19 times the baseline cost), the incremental cost-effectiveness ratio of combination therapy still fell below ¥6.0 million and would be considered "cost-effective." For the subgroup of patients with genotype 1b and high viral load, ribavirin costs below ¥10,540 yielded incremental cost-effectiveness ratio for combination therapy that fell within the range considered to be "cost-effective."

As expected, the survival benefit and cost-effectiveness of combination therapy for chronic hepatitis C decreased

Table 6
Subgroup analyses

Subgroup	Probability of sustained viral negative		Discounted (3%) increase in QALYs	Discounted incremental C/E
	Interferon only	Combination therapy		
Male	0.13	0.36	1.42	D
Female	0.00	0.35	2.34	D
Histology				
Mild hepatitis	0.13	0.33	0.60	564,000
Moderate hepatitis	0.07	0.35	2.36	D
Genotype				
1b	0.02	0.19	1.33	25,000
Other than 1b	0.24	0.74	1.75	D
Viral load[a]				
High	0.06	0.23	1.28	26,000
Low	0.21	0.73	2.18	D

C/E: cost-effectiveness ratio; D: combination therapy is dominates interferon therapy alone: lifetime cost saving.

[a] Patients with a viral titer exceeding 100k copies/ml by the RT-PCR assay or 1 Meq/ml by b-DNA assay were classified as having a high viral load.

Table 7
Effects of varying baseline assumptions

Assumption	Increase of QALYs with combination therapy	Incremental cost-effectiveness ratio of combination therapy (yen per QALYs gained)		
		Not discounted	Discounted (3%)	Discounted (5%)
For all patients				
Progression rate[a]				
1/2 baseline	2.05	D*	D	118,000
1/3 baseline	1.55	D	3,800	236,000
Sustained viral negative response rate				
1/2 baseline	1.68	27,000	224,000	434,000
1/3 baseline	1.20	164,000	482,000	810,000
Progression rate and sustained viral negative response rate				
1/2 baseline	1.11	48,000	414,000	792,000
1/3 baseline	0.60	370,000	1,150,000	1,940,000
For subgroup with genotype 1b high virus load				
Progression rate				
1/2 baseline	1.20	38,000	377,000	729,000
1/3 baseline	0.90	95,000	578,000	1,067,000
Sustained viral negative response rate				
1/2 baseline	1.08	250,000	624,000	1,006,000
1/3 baseline	0.83	428,000	951,000	1,481,000
Progression rate and sustained viral negative response rate				
1/2 baseline	0.71	395,000	1,063,000	1,747,000
1/3 baseline	0.40	936,000	2,246,000	3,598,000

D*: Combination therapy dominated interferon therapy alone by extending survival and reducing lifetime costs.
[a] Simultaneously reducing the annual probabilities of histologic progression from mild to moderate hepatitis and from moderate hepatitis to compensated cirrhosis, developing hepatocellular carcinoma from moderate hepatitis or from cirrhosis and cirrhotic decompensation.

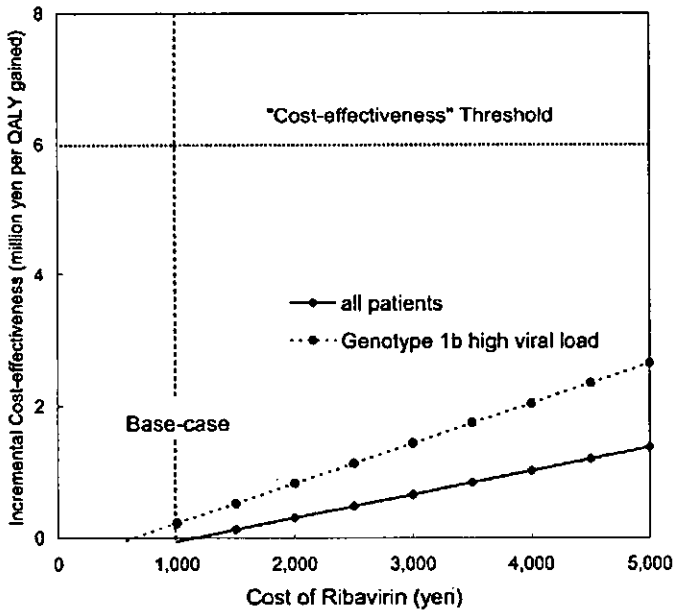

Fig. 1. Sensitivity analysis of the effects of varying the cost of ribavirin with a 3% annual discount rate. Each of the lines represents the incremental cost-effectiveness of combination therapy compared to interferon. The vertical line indicates the base-case cost of ribavirin. The horizontal line at ¥6 million indicates the threshold incremental cost-effectiveness ratio. Values falling below this line can be considered to be "cost-effective" when compared to the incremental cost-effectiveness of widely accepted medical interventions. Even if the cost of ribavirin were five times more than the base-case, the incremental cost-effectiveness ratio of combination therapy still fell well within the range of other widely accepted medical intervention and thus could be considered to be "cost-effective".

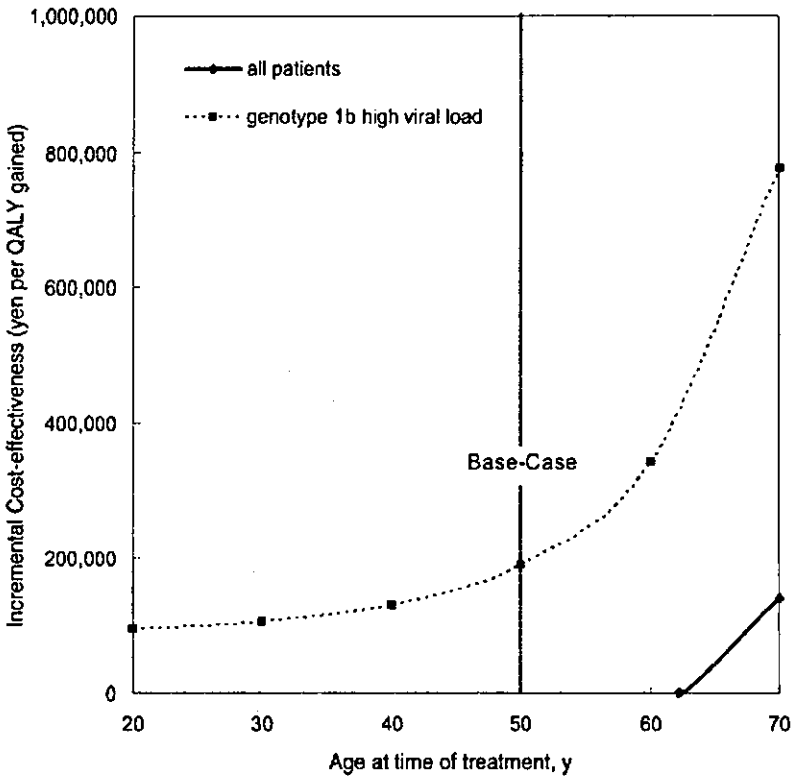

Fig. 2. Sensitivity analysis of the effects of age at start of treatment for chronic hepatitis C on the discounted (3%) incremental cost-effectiveness ratio. The vertical line indicates the base-case age of treatment. The incremental cost-effectiveness of combination therapy for all patient groups was superior to that of interferon monotherapy and the incremental cost-effectiveness ratio was less than 0 until age 63 years.

with age at start of treatment and the incremental cost-effectiveness ratio thus also increased (Fig. 2). At an annual 3% discount rate, combination therapy for all patients up to 63 years old was cost saving and even in the subgroup of patients with genotype 1b and high viral load aged up to 70 years, the incremental cost-effectiveness ratio fell below ¥0.8 million per quality-adjusted life year and therapy was considered "cost-effective".

6. Discussion

Chronic hepatitis C infection rarely resolves spontaneously [21]. Persistent infection with hepatitis C virus can lead to liver cirrhosis after 20–30 years and to hepatocellular carcinoma after 30–40 years [22]. Interferon therapy has been broadly accepted since 1992 in Japan, and although some patients have a sustained viral response, most have either a transient response (relapsers) or no response (non-responders). For patients with genotype 1b, which comprises about 70% of hepatitis C patients in Japan, sustained viral response occurs at best in 15% [23–25].

Recent studies in the US and Europe have found that combination therapy with interferon alpha-2b and ribavirin for relapsers and non-responders was more effective than interferon therapy alone, so it has become the standard therapy in those countries. From 1998 to 2000, an analogous randomized trial was conducted in Japan and found clinical results similar to those observed outside of Japan [26].

Interferon has been shown to be "cost-effective," but drug costs for ribavirin with interferon alpha-2b exceed those for interferon therapy alone by about ¥0.6 million. Moreover, despite the remarkable recent expansion of knowledge of the consequences of chronic hepatitis C virus infection and of the short and intermediate-term benefits of successful treatment, many uncertainties remain. These include an accurate understanding of the natural history of untreated patients and of the long-term benefit of treatment. These uncertainties raise questions about the cost-effectiveness of combination treatment. Therefore, we conducted a cost-effectiveness analysis to estimate lifelong costs and clinical outcomes using the results of the recent study in Japan.

While a randomized controlled study targeting endpoints such as long-term survival and decreases in liver disease complications would be ideal, such a trial is not available. Nonetheless, antiviral treatment for chronic hepatitis C infection has been shown to decrease the risk for development of hepatocellular carcinoma and to improve viral eradication, hepatic histology, and survival in clinical studies. In the absence of a long-term randomized trial, computer simulation analyses such as the one presented here can help estimate lifelong outcomes resulting from antiviral treatment.