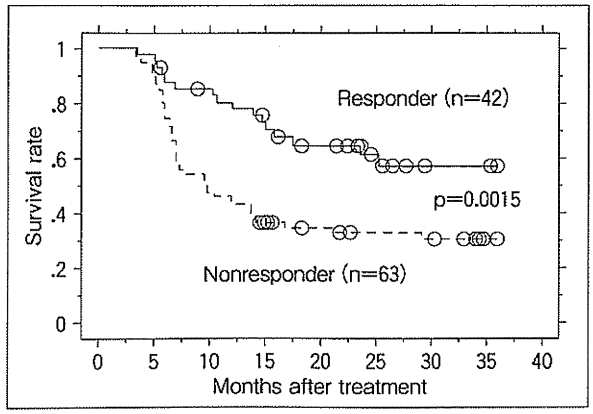

図3 術前化学療法における化学療法効果別の生存曲線
（文献8）より引用）

化学療法群の予後は良好であった。以上の結果より，わが国ではcStage Ⅱ/Ⅲ食道がんに対しては術前化学療法＋手術が標準治療として認められるに至った。

- 一方，欧米では進行食道がんに対しては術前化学放射線療法が広く行われており，community standardとなっている。

期待される効果

- 前述のJCOG9907（術前化学療法 vs 術後化学療法）におけるプロトコール完遂率が，術前化学療法群で85%であるのに対して術後化学療法群では75%と報告されているように，一般に術前化学療法は術後化学療法に比べてプロトコール治療の完遂率が高い。
- 術前化学療法では原発巣を縮小させ，down-stagingによる治癒切除率の向上が期待できる。またリンパ節転移や微小転移（micrometastasis）をコントロールすることで術後再発を減少させ，遠隔成績を向上させることが期待される[5]。
- JCOG9907においてcStageは術前化学療法群と術後化学療法群で差がなかったが，pStageでは術前化学療法群でpStage Ⅱ以下の症例が有意に多く（p＝0.01），術前化学療法によりdown-stagingが可能となったと考えられる。治癒切除（R0）率も術後化学療法群の91%に対して術前化学療法群では96%であり，術前化学療法群で有意に治癒切除率が高かった（p＝0.04）。
- 術前化学療法症例では術後の合併症が増加することが懸念されていた。しかし，JCOG 9907の結果では年齢，性別，腫瘍占拠部位が合併症の発生に影響する因子であったが，術前化学療法は合併症の発生や在院死に影響しなかった[6]。
- 術前化学療法では化学療法の奏効例においては予後の改善が期待できるが，非奏効例の予後は不良と報告されている（図3）[7,8]。
- FDG-PETによる原発巣のSUVmaxの減少率は化学療法効果と相関し，術前化学療法の予後を反映すると報告されている[9]。
- JCOG9907の解析ではcT3症例やcStageⅢ症例では標準的化学療法であるFP療法による予後の上乗せ効果が十分でなく，より進行した症例においてはより強力な補助療法が必要であることが示唆された。
- 現在の標準的化学療法のレジメンは5-FUにシスプラチンを加えたFP療法と考えられているが，同レジメンでの奏効率は35%程度であり，より奏効率の高いレジメンの確立が望まれている。

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高度進行肝細胞癌に対するIFN併用化学療法の作用機序解明と治療効果予測

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特集II　進行肝細胞癌の治療選択

高度進行肝細胞癌に対するIFN併用化学療法の作用機序解明と治療効果予測*

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Key Words: hepatocellular carcinoma, hepatic arterial infusion chemotherapy, interferon, 5-fluorouracil(5-FU), portal vein tumor thrombus

はじめに

門脈の一次分枝から本幹に腫瘍栓(Vp3-4)を伴う高度進行肝細胞癌症例は既存の治療法に抵抗性を示し，有効な治療が施されなければ，ほぼ1年以内に癌死に至り，きわめて予後不良である[1)2)]．このような症例では一般的に化学療法が選択されてきたが，肝細胞癌は抗癌剤の感受性が低く，奏効率は20%以下と抗腫瘍効果は期待しがたい[3)]．また，既存の治療が適応外となる進行肝癌に対しては，分子標的治療薬のソラフェニブの適応であるが，第III相無作為比較試験の結果から，プラセボ群と比較して2.8か月の予後延長効果を示したのみであり十分とは言えない[4)]．最近このような難治性高度進行肝癌に対するインターフェロン(以下IFN)と種々の抗癌剤との併用療法により良好な抗腫瘍効果と生存率の著明な改善が認められることが明らかになってきた[5)~8)]．本稿では，これら抗癌剤の中でIFN-αと5-FUの併用療法(IFN/5-FU併用化学療法)の適応と投与方法，治療成績および抗腫瘍効果の作用機序に関する基礎的検討，治療効果予測について概説する．

肝細胞癌に対するIFN併用化学療法

Laiら[9)]は，肝細胞癌に対するIFN-α単剤投与により31%(11/35例)の奏効率を得たと報告しているが，その後の諸家の追試では奏効率0～7%と高い有効性は確認できず，その抗腫瘍効果は期待できない．一方で，IFN単剤ではなく，5-FUやcisplatin(CDDP)などの薬剤を併用することによって，その効果を確認した報告は少なくない．われわれは，術後肝内多発再発と肺，骨の肝外転移を伴う肝細胞癌に対してIFN-α投与とUFT内服によりcomplete remission(CR)を得られた症例の経験[8)]から，1997年から既存の治療法では十分な治療効果の期待できない門脈内腫瘍栓を伴った高度進行肝細胞癌症例に対して，IFN-αと5-FU持続肝動注化学療法(FAIT)を併用してきわめて良好な結果[10)~14)]を報告してきた．

IFN/5-FU併用化学療法の治療成績についての諸家の報告を表1にまとめた．5-FUの投与方法については，全身投与ではPattらの，肝細胞癌28症例(FLHCCを除く)に対する5-FU持続静脈内投与の報告のみで[15)]，本邦からは，教室からの報告も合わせてすべて動脈内投与であった[10)~14)16)~19)]．

* Molecular mechanism of combined interferon-alpha and 5-fluorouracil treatment for advanced hepatocellular carcinoma.

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表1　IFN/5-FU併用化学療法に関する報告

報告者	奏効例/症例数	奏効率	備考
【全身化学療法】			
Patt YZ, et al(2003)	4/28	14.3%	FLHCCを除くHCC症例
【肝動注化学療法】			
Sakon M, et al(2002)	5/8	62.5%	Vp3-4症例
Ota H, et al(2005)	24/55	43.6%	
Nagano H, et al(2011)	40/102	39.2%	
Obi S, et al(2006)	61/116	52.5%	
Uka K, et al(2007)	9/31	29.0%	
Enjoji, et al(2005)	6/28	21.5%	Vp(−)症例を含む
Uka K, et al(2007)	16/55	29.0%	

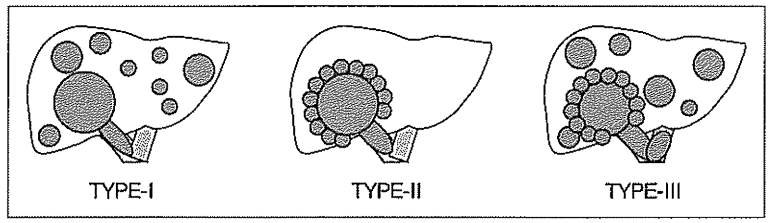

図1　門脈内腫瘍栓を伴う高度進行肝細胞癌症例の病型分類
(文献[13]より引用)

したがって，以降は，IFNを併用した5-FUの肝動注学療法について述べる．

1．適応と投与方法

教室における本療法の対象は，門脈一次分枝または本幹侵襲(Vp3-4)を伴う高度進行肝細胞癌症例であり，図1に示すように3群に分類し切除不能症例のみならず肝機能良好で肝切除可能症例では，肉眼的治癒切除後もしくは減量肝切除後の補助療法として本療法を組み入れている[13]．適応は，副作用や抗癌剤投与による肝障害を考慮して，70歳未満，総ビリルビン値が正常範囲内で，AST, ALTがともに100IU/*l*未満，血小板80,000/mm³以上，血清クレアチニン値が1.5mg/d*l*以下で，外来通院が可能なperformance statusが0, 1としている(表2)．全肝多発病変を伴う症例や耐術が不可能と考えられる切除不能症例では，Seldinger法で肝動注カテーテルを挿入する．肝切除可能例では，術中にカテーテルを留置し，肝切除後の補助療法として本療法を施行している．治療スケジュール(図2)は，皮下埋め込み式動注リザーバーより5-FUを300mg/m²/dayで5日間持続投与を2週間行い，2週間休薬を1クールとする．同時に天然型IFN-αを500万単位/回を週3回，4週間を1クールとして皮下投与する．

表2　IFN-α併用5-FU動注化学療法(FAIT)の適応基準

肝細胞癌	門脈内腫瘍栓	Vp3以上
	肝外転移	なし
肝機能	AST	＜100IU/*l*
	ALT	＜100IU/*l*
	T-Bil	正常(閉塞性黄疸は除く)
血液検査	血小板	8,0000/m*l*以上
腎機能	血清Cr	＜1.5mg/d*l*
PS		0，1

2．治療成績

(1)切除不能症例に対するFAITの治療成績(TYPE-I)

図1に示すTYPE-Iの各施設からの報告249例[14)16)17)]をまとめると，抗腫瘍効果は，CR：31例，PR：79例と，その奏効率は44.2%で，生存期間の中央値は，6.9～9か月あった．また，生存率は，1年生存率が29.0～36.8%，2年生存率が5.6～21.2%であり，これらの治療成績は，対象となる高度進行肝癌は既存の治療法が奏効せず，ほとんどの症例が6か月以内に死亡することと比較すると，きわめて有効な治療法である

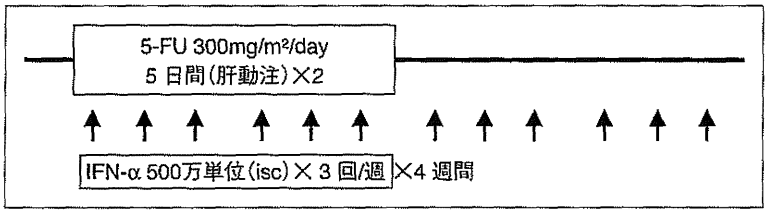

図2 IFN-α併用5-FU肝動注化学療法(FAIT)のプロトコール

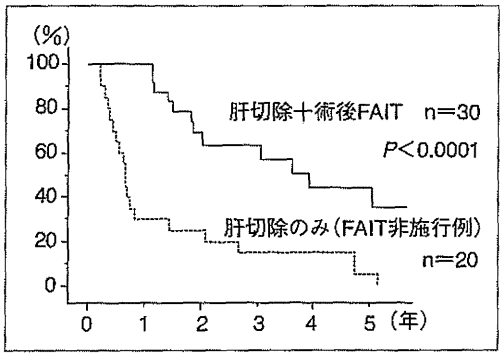

図3 腫瘍遺残のない肝切除十術後補助療法としてFAITの累積生存率(TYPE-II)

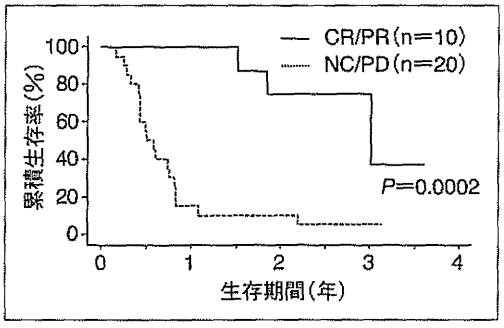

図4 減量肝切除十FAIT施行30例の生存曲線(CR/PR vs. NC/PD)

と考えられる．教室での102例[14]では，治療回数は2クール以上で，効果の得られた症例には繰り返し治療を行った．治療効果は，CR；11例(10.8%)，PR；29例(28.4%)と，その奏効率は39.2%であり，全症例の生存期間の中央値は9か月であり，1, 3, 5年生存率が，それぞれ36.8%，10.8%，7.6%であった．特に，治療が奏効した40例の生存期間の中央値は25か月であり，非奏効62例の6か月と比較して有意に良好であり，奏効例を選別する治療効果予測の確立が重要な課題である．

(2)根治肝切除および術後補助療法としてのFAITの治療成績(TYPE-II)

一般的に門脈内腫瘍栓を伴う肝癌症例(Vp3以上)は，仮に腫瘍の完全摘出を施行し得ても高率に発生する残肝再発により，その1年生存率は約40%である[20]．そこで，教室ではこのような進行肝癌30例に対して肉眼的に腫瘍遺残のない肝切除を施行したのちに，術後補助療法としてFAITを3クール施行した．その成績は，1年，3年無再発生存率がそれぞれ70%，39.7%であり，1年，3年生存率は100%，65.9%であった．この成績は，当科において同一ステージの進行肝癌に対して肝切除のみを施行した20例(FAIT非施行例：historical control)と比較して，有意に良好であった($P<0.0001$)(図3)．

(3)減量肝切除および残存腫瘍に対するFAITの治療成績(TYPE-III)

TYPE-IIIにあたる門脈内腫瘍栓に片葉の主腫瘍と全肝多発病巣を伴う30例に対して，減量肝切除と術後にFAITを施行した[13]．肝内病巣に関しては，7例のCRを含む10例に効果を認め，その奏効率は33.3%であった．奏効例(CR/PR)10例の1, 2, 3年生存率は，それぞれ100, 75, 37.5%であり，非奏効例(NC/PD)より有意に良好であった(図4)．しかし，肝内病巣に奏効したものの肺への遠隔転移を3例に認めた．このように，本療法の問題点の一つとして，肝内病巣には有効であるものの，肝外病変の制御は困難であり，今後の検討すべき課題である．

IFN/5-FU併用化学療法の作用機序に関する基礎的検討

IFN-αは単剤でも抗腫瘍効果があるとされ，その機序は癌細胞への直接的な抗腫瘍効果として細胞障害作用，細胞周期遅延作用，癌抗原の発現上昇などが報告されている．しかし，現在ま

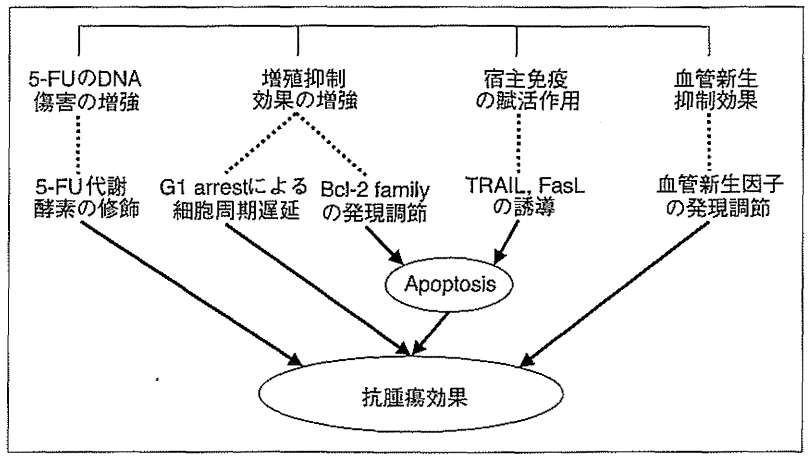

図5　IFN-α/5-FU併用化学療法の作用機序

での肝細胞癌に対する臨床報告の治療成績から考えると，単独での治療効果は乏しく，主にはIFN-αと5-FUの相加・相乗効果による抗腫瘍効果であると考えられる[21]．

その相加・相乗効果について，IFN-αが5-FUの代謝調節に作用し，TP(thymidine phosphorylase)を活性化し中間代謝産物であるFdUMP(5-fluoro-2'-deoxyuridine 5-monophosphate)の細胞内濃度を上昇させる効果やTS(thymidylate synthetase)阻害率の増強効果などにより報告されている[22][23]．さらに，両薬剤併用による作用機序(図3)として，IFN-αによる5-FUのDNA合成阻害作用の増強以外にも，①直接的な増殖抑制効果の増強，②宿主免疫の賦活作用，③血管新生抑制効果が関与しているとの仮説を立てて証明してきた(図5)．

(1)IFNによる直接的な増殖抑制効果

両薬剤併用による細胞周期遅延やapoptosisの誘導による増殖抑制効果について検討を行い，ヒト肝細胞癌株を用いた併用治療により，G0/G1期での細胞集積による細胞増殖遅延と細胞周期関連蛋白であるp27Kip1の発現増強を伴うことを見出した[24]．また，この増殖抑制効果はインタフェロンレセプター(IFNα/βレセプター；IFNAR2)の発現が強い細胞株で顕著に認められ，IFNAR2の発現が，STAT1(signal transducer and activator of transcription)のリン酸化による活性化，apoptosisの頻度およびapoptosis関連蛋白であるBcl-2 familyの発現調節と相関することを確認した[25][26]．この点については，IFNAR2の遺伝子発現が，IFNもしくは併用療法の抗腫瘍効果に重要であることが多施設からも報告されている[27][28]．

(2)宿主免疫賦活作用

IFN-αによる宿主免疫作用として，IFN-α投与により高度進行肝細胞癌患者の末梢血中の単核球にTRAIL(tumor necrosis factor-related apoptosis-induced ligand)mRNAの発現が誘導され，in vitroにおいても同様にIFN-αを添加によってTRAIL mRNAの発現を確認した．さらに末梢血単核球の肝細胞癌株に対する細胞障害活性は，末梢血単核球にIFN-αの前刺激を加えることにより有意に増加し，TRAIL中和抗体によってその活性は阻害されること，肝癌細胞上のTRAILレセプター(TRAILR)発現が5-FUにより増強すること[29]から，その一部はTRAIL-TRAILR系を介していると考えられる．また，Fas/FasL系についても，IFN/5FUの併用によりNK細胞を免疫担当細胞とする間接的抗腫瘍効果が示され，Caspase-3, -8, -9とアポトーシス調節因子としてFLIP, Bcl-xL, Baxの関与が示され，Fas-FasL系を介していることも明らかにした[30]．

(3)血管新生抑制効果

IFN/5-FU併用療法が血管内皮細胞に対して，直接的な増殖抑制効果を有し，さらに先の肝細胞癌細胞増殖抑制実験で用いた培養液中の血管新生因子として血管内皮細胞増殖因子(VEGF)，アンジオポイエチン-1, -2(Ang-1, -2)の発現量を測定したところ，IFN-αと5FUの併用によりVEGF, Ang-2の発現が減弱し，Ang-1の発現が増強することを確認した[31](図3)．また，ヌードマ

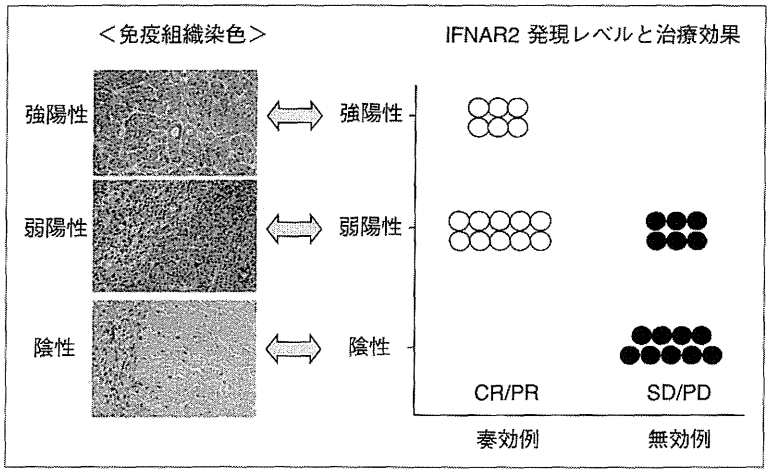

図6　IFNAR2(IFNレセプター)の発現と臨床例での治療効果の関係

ウスを用いたモデルにより，腫瘍内微小血管数の有意な減少とVEGF, Ang-1, Ang-2の各種血管新生因子の発現調節について確認した[32]．

治療効果予測

これまでの臨床治療成績から，IFN併用化学療法は，既存の治療が奏効しない難治性高度進行肝癌に高い奏効率と予後延長効果を有することが確認された．しかし，奏効例では著明に生存期間が延長するのに対して，非奏効例ではほとんどの症例が1年以内に癌死することから，治療効果予測因子を同定することが重要な課題である．

(1)IFNAR2(IFNレセプター)発現による治療効果予測

基礎的検討でも示したように，ヒト肝癌細胞株におけるIFNAR2の発現がIFN/5-FU併用療法の抗腫瘍効果と相関していたことより，切除不能症例の肝腫瘍生検サンプル31例を用いてIFNAR2の発現を免疫組織学的に検討したところ，IFNAR2陽性の22例中16例が奏効例であり，IFNAR2陰性であった9例全例が無効例であり，有意に治療効果との相関を認めた(図6)[11]．そこで，減量肝切除後に残存腫瘍に対するFAITを行った30例についても同様に，IFNAR2の免疫組織染色を行った結果，IFNAR2陰性の10例はいずれも無効例であり，IFNAR2陽性20例では，有意に生存期間が延長することを報告した[13]．

(2)臨床検体を用いた網羅的遺伝子解析よる効果予測因子の同定

IFNAR2の発現がIFN/5-FU併用療法の治療効果予測因子の一つであることがわかったが，IFNAR2発現を認めた症例でも，治療効果が得られない症例が約半数存在する．そこで，先ほどのTYPE-IIIにあたる減量肝切除を施行した後にFAITを行った30症例のうち，IFNAR2発現が陰性であった10例を除く20例を，臨床効果を認めた奏効群(CR/PR)の10例と無効群(NC/PD)の10例の2群にわけて網羅的遺伝子発現解析を行った．

その結果から2群間で有意に発現差が認められた161遺伝子を同定し，さらに遺伝子ネットワーク解析を行ったところ，Wnt/βカテニン経路が治療効果に関与していた．Wnt/βカテニン経路の中で，先ほどの161遺伝の上位に位置していたepithelial cell adhesion molecule(EpCAM)に着目し，EpCAMの発現を免疫組織学的に検討し，治療効果と比較した．EpCAM陽性の6例全例がFAIT無効群であり，EpCAM陽性6例の生存率は，EpCAM陰性の24例と比較して不良であった(図7)[33]．

(3)IFN耐性肝癌細胞株の樹立と耐性化関連遺伝子

ヒト肝癌細胞株：PLC/PRF/5をIFNに持続曝露し，IFNの増殖抑制効果に獲得耐性を示すIFN耐性株(PLC-R)を樹立した．親株と耐性株で，網羅的遺伝子解析を行い獲得耐性にかかわる107遺

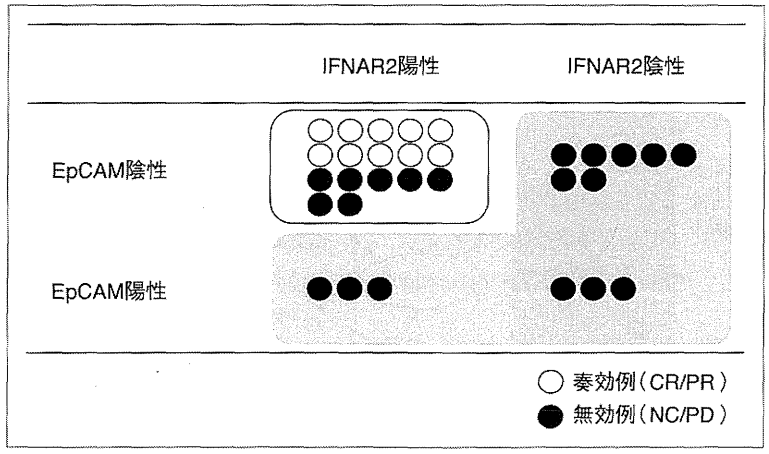

図7　IFNAR2およびEpCAM発現状況と治療効果

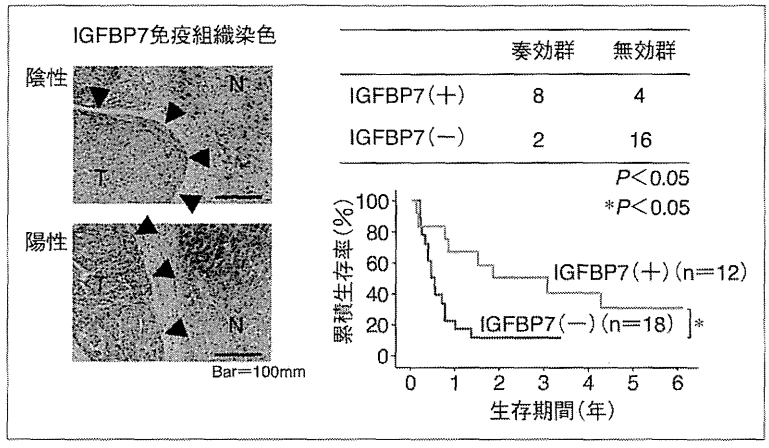

図8　IGFBP7の発現状況とFAIT治療効果

伝子を同定した．この遺伝子群の中で，insulin-like growth factor binding-protein 7(IGFBP7)に着目し，減量肝切除30例におけるIGFBP7の発現とFAITの治療効果を検討したところ，IGFBP7陽性の12例では奏効率が66.7%に対して，IGFBP7陰性の18例の奏効率11.1%であり，IGFBP陽性例は陰性例と比較して有意に予後良好であった(図8)[34]．

基礎的検討および臨床検体を用いた検討によってFAITの治療効果と相関する因子として，IFNAR2, EpCAM, IGFBP7を同定した．それぞれ単一因子としてもFAITの治療効果を予測可能であるが，これら3つの因子を組み合わせることによって，表3に示すように，感度80.0%(8/10)，特異度90.0%(18/20)，正確度86.7%(26/30)でFAITの治療効果を予測することが可能であった．

表3　IFNAR2, EpCAM, IGFBP7の3因子の組み合わせによるFAIT治療効果予測

	奏効群(CR/PR)	無効群(NC/PD)
IFNAR2(+)and EpCAM(−) and IGFBP7(+)	8	2
IFNAR2(−)or EpCAM(+) or IGFBP7(−)	2	18

おわりに

IFN-α/5-FU併用化学療法(FAIT)は難治性高度進行肝癌に対して，きわめて有効な治療法である．そして集学的治療の一選択肢として，IFN/

5-FU併用療法を肝切除と組み合わせることによって，その治療成績の飛躍的な向上が期待できる．しかし，無効例が約半数存在すること，肝外病変の制御は困難であることなどが今後の問題点であり，これらの克服のためには，治療前に有効例，無効例を判別する分子生物学的手法を確立や作用機序の解明により，本療法の効果増強が可能となる分子の同定などが必要である．

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ORIGINAL ARTICLE

Combination chemotherapy with S-1 plus cisplatin for gastric cancer that recurs after adjuvant chemotherapy with S-1: multi-institutional retrospective analysis

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Abstract
Background It is unclear whether S-1 plus cisplatin is effective for patients with recurrent gastric cancer after adjuvant S-1 chemotherapy.
Methods We retrospectively evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant S-1 chemotherapy.
Results In the 52 patients evaluated, the median duration of adjuvant S-1 chemotherapy was 8.1 months, and the median recurrence-free interval (RFI) since the last administration of adjuvant S-1 was 6.4 months. Among the 36 patients with measurable lesions, 7 achieved a complete or partial response, and 13 were evaluated as having stable

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disease, for an overall response rate of 19.4% and a disease control rate of 55.6%. For all patients, the median progression-free survival (PFS) was 4.8 months, and the median overall survival (OS) was 12.2 months. Compared with patients with an RFI of <6 months ($n = 25$), patients with an RFI of ≥6 months ($n = 27$) had a significantly higher response rate (5.0 vs. 37.5%, respectively), longer PFS (2.3 vs. 6.2 months, respectively), and longer overall survival (7.3 vs. 16.6 months, respectively). According to a multivariate Cox model including performance status (PS) and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS and OS.
Conclusions S-1 plus cisplatin is effective for patients with gastric cancer that recurs after adjuvant S-1 chemotherapy, especially for those with an RFI of ≥6 months.

Keywords Adjuvant chemotherapy · Gastric cancer · Recurrence · S-1

Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of total malignancy cases) and the second leading cause of cancer death (737,419 deaths, 9.7% of total) [1]. The prognosis of patients with advanced or recurrent gastric cancer remains poor; chemotherapy confers only a minimal survival advantage, with a median survival of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine [5-fluorouracil (5-FU) or oral fluoropyrimidine] plus a platinum agent with or without docetaxel or anthracyclines [2–6].

S-1 is an oral anticancer drug composed of the 5-FU prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7, 8]. In the Japan Clinical Oncology Group (JCOG) 9912 trial, which compared S-1, cisplatin plus irinotecan, and 5-FU, S-1 demonstrated non-inferiority compared to 5-FU [9]. In another phase III trial that compared S-1 alone to S-1 plus cisplatin (SPIRITS trial), S-1 plus cisplatin showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer overall survival (OS; 13 vs. 11 months) [4]. Also, in a large, non-Japanese, phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial), S-1 plus cisplatin was associated with fewer toxic effects and demonstrated non-inferiority compared with 5-FU plus cisplatin by exploratory analysis [6]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent gastric cancer.

In addition, the ACTS-GC trial has demonstrated that S-1 is also effective as adjuvant chemotherapy for Japanese patients who have undergone curative gastrectomy for locally advanced gastric cancer [10]. However, approximately 30% of patients still develop recurrence after curative resection followed by adjuvant S-1 [10]. As few patients who received adjuvant chemotherapy were included in the phase III trials described above [4, 7, 9], it is unclear whether patients who develop recurrence after adjuvant S-1 could achieve efficacy with S-1 plus cisplatin similar to that achieved in patients without adjuvant chemotherapy. To address this issue, we conducted the following multi-institutional retrospective analysis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy of first-line chemotherapy with S-1 plus cisplatin for recurrence in patients with gastric cancer who had undergone curative gastrectomy followed by adjuvant S-1 chemotherapy. Patients with histopathologically proven recurrent gastric adenocarcinoma after gastrectomy and lymph node dissection with no residual tumor were eligible for analysis. Additional eligibility criteria were: (1) previous adjuvant S-1 chemotherapy at a planned standard dose and schedule (80 mg/m^2 for 28 consecutive days followed by a 14-day rest; 42-day cycles to be repeated for 1 year); (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) adequate bone marrow, hepatic, and renal function to be treated with S-1 plus cisplatin; (4) evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1); and (5) treated with a standard regimen of S-1 plus cisplatin (S-1 80 mg/m^2 for 21 consecutive days followed by a 14-day rest; cisplatin 60 mg/m^2 intravenous infusion on day 8; 35-day cycles to be repeated) [4]. Written informed consent for treatment was obtained from each patient prior to treatment initiation. The Institutional Review Board of each participating center approved the study.

Evaluation of treatment and statistical analysis

The tumor response was assessed objectively according to RECIST ver. 1.1, and the best overall response was recorded as the antitumor effect for that patient. The disease control rate (DCR) represented the percentage of patients with a complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the date of initiation of S-1 plus cisplatin to the date of progressive disease or death from any cause. Time to treatment failure

(TTF) was measured from the date of initiation of S-1 plus cisplatin to the date of last administration of S-1. OS was estimated from the date of initiation of S-1 plus cisplatin to the date of death or last follow-up visit, using the Kaplan–Meier method. The interval from the last administration of adjuvant S-1 to recurrence was defined as the recurrence-free interval (RFI).

The Cox proportional hazards model was used to estimate the impact of the RFI on TTF, PFS, and OS, with adjustment for other factors that were shown to be significant with a univariate log-rank test. *P* values for testing differences between proportions and response rates were calculated with χ^2 tests for homogeneity or for trend, or with Fisher's exact test. Results were considered to be statistically significant when the *P* value was <0.05. All reported *P* values are two-sided. In particular, we compared the response rate, DCR, time to progression (TTP), PFS, and OS between patients with RFIs of ≥6 and <6 months, because several clinical trials in the first-line setting set this interval of ≥6 months as an inclusion criterion [5, 9, 11].

Results

Patient characteristics

A total of 406 patients with recurrent gastric cancer after adjuvant S-1 chemotherapy had received chemotherapy at 18 institutions until October 2010. Among them, 57 patients (14.0%) had received S-1 plus cisplatin as first-line chemotherapy for recurrence. After the exclusion of 5 patients (1 patient with a non-evaluable lesion and 4 patients with insufficient data), 52 patients were included in the final

Table 1 Patient characteristics

Characteristic	All ($n = 52$)	RFI <6 months ($n = 25$)	RFI ≥6 months ($n = 27$)	*P* value
Age, years				
Median (range)	61 (32–77)	59 (32–77)	62 (32–77)	
Gender, *n* (%)				
Male	30 (58)	15 (60)	15 (56)	0.75
Female	22 (42)	10 (40)	12 (44)	
ECOG PS at recurrence, *n* (%)				
0	32 (62)	11 (44)	21 (78)	*0.012*
1	20 (38)	14 (56)	6 (22)	
Histological type[a], *n* (%)				
wel or mod	27 (52)	10 (40)	17 (63)	0.1
por or sig	24 (46)	15 (60)	9 (33)	
Other	1 (2)	–	1 (4)	
Pathological stage[a], *n* (%)				
Stage I or II	8 (15)	4 (16)	4 (15)	0.57
Stage IIIA	17 (33)	6 (24)	11 (41)	
Stage IIIB	15 (29)	8 (32)	7 (26)	
Stage IV	12 (23)	7 (28)	5 (19)	
Site of recurrence, *n* (%)				
Peritoneum	21 (40)	7 (28)	14 (52)	0.08
Lymph node	25 (48)	13 (52)	12 (44)	0.59
Liver	14 (27)	10 (40)	4 (15)	*0.041*
Lung	4 (8)	3 (12)	1 (4)	0.262
Bone	6 (12)	1 (4)	5 (19)	0.102
Local	2 (4)	1 (4)	1 (4)	0.96
Number of recurrence sites, *n* (%)				
1	38 (73)	18 (72)	20 (74)	0.87
2 or more	14 (27)	7 (28)	7 (26)	

P values shown in italics indicate significant differences

RFI Recurrence-free interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *wel* well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring-cell-like carcinoma

[a] According to the Japanese classification

analysis (Table 1). The median duration of adjuvant S-1 chemotherapy was 8.1 months (range 0.7–37.4 months), and the median RFI since the last administration of adjuvant S-1 was 6.4 months (range 0–81.3 months). Thirty of the 52 patients (57.7%) completed the planned duration of adjuvant S-1 therapy. In contrast, 14 patients discontinued S-1 due to disease recurrence, and 8 patients stopped therapy due to toxicity or patient refusal. Other than PS and liver metastasis, characteristics did not differ significantly between patients with an RFI of ≥6 months ($n = 27$) and those with an RFI of <6 months ($n = 25$) (Table 1).

Treatment results and efficacy

The median TTF was 4.1 months (95% confidence interval [CI] 2.5–5.1 months), with a median duration of follow-up of 32 months. Forty-four patients discontinued S-1 plus cisplatin due to disease progression ($n = 40$, 90.9%) or toxicity ($n = 4$, 9.1%). Of the 36 patients with measurable lesions, 7 achieved a CR ($n = 3$) or a PR ($n = 4$), and 13 were evaluated as having SD, for an overall response rate of 19.4% (95% CI 7.0–37.0%) and a DCR of 55.6% (95% CI 38.1–72.1%). The median PFS was 4.8 months (95% CI 3.9–6.2 months), and the median OS of all patients was 12.2 months (95% CI 10.2–16.6 months) (Fig. 1). Of the 44 patients who had discontinued S-1 plus cisplatin, 31 (70.4%) received second-line or third-line chemotherapy, including taxanes ($n = 25$) or irinotecan ($n = 17$).

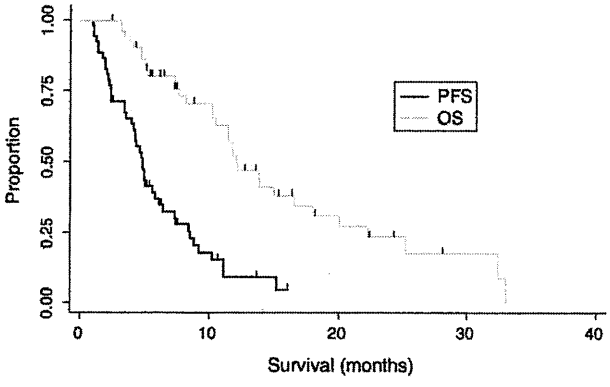

Fig. 1 Progression-free survival (*PFS*) and overall survival (*OS*) in all patients. The median PFS was 4.8 months (95% confidence interval [CI] 3.9–6.2 months), and the median OS was 12.2 months (95% CI 10.2–16.6 months). *PFS* progression-free survival, *OS* overall survival

Significance of the RFI

The response rate was significantly better in patients with an RFI of ≥6 months (37.5%; 95% CI 14–61%) than that in patients with an RFI of <6 months (5.0%; 95% CI 0–15%, $P = 0.014$, Table 2). In addition, compared with patients with an RFI of <6 months, patients with an RFI of ≥6 months had a significantly longer TTF (2.5 vs. 5.1 months, respectively, $P = 0.025$), longer PFS (2.3 vs. 6.2 months, respectively, $P < 0.001$, Fig. 2), and longer OS (7.3 vs. 16.6 months, respectively, $P = 0.003$, Fig. 2). According to a multivariate Cox model including PS and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS (hazard ratio [HR] 0.35, 95% CI 0.16–0.77, $P = 0.009$) and OS (HR 0.21, 95% CI 0.08–0.54, $P = 0.001$), although the association with TTF was not significant (HR 0.55, 95% CI 0.27–1.12, $P = 0.1$). When we divided the patients into two groups based on an RFI of 12 months, no significant difference between the groups was found in response rate, TTP, PFS, or OS.

Discussion

In the ACTS-GC study, adjuvant S-1 chemotherapy significantly improved the survival of patients who had undergone curative gastrectomy for locally advanced gastric cancer [10]. On the other hand, several small studies have suggested that patients with recurrence after adjuvant S-1 were refractory to S-1-containing regimens or had a worse prognosis compared with that of patients without adjuvant chemotherapy [12–14]. Although these reports never precluded the use of adjuvant S-1 chemotherapy, they raised the issue of how to treat recurrent disease after adjuvant S-1.

In the present retrospective study, we evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant chemotherapy with S-1. The response rate of 19.4% and PFS of 4.8 months were

Table 2 Objective response rates in patients with measurable lesions

	n	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)
All	36	3	4	13	14	2	18.8	7–32
RFI <6 months	20	0	1	6	13	0	5.0	0–15
RFI ≥6 months	16	3	3	7	1	2	37.5	14–61

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

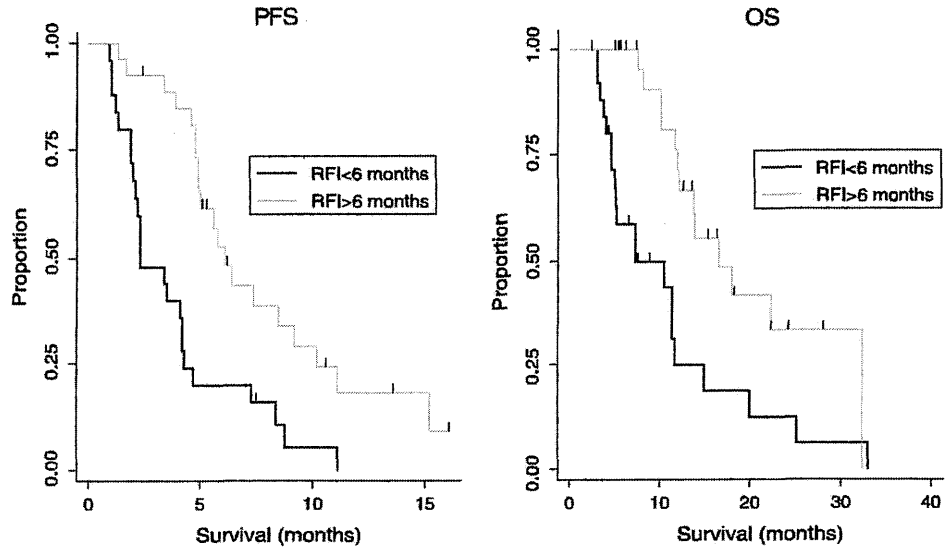

Fig. 2 Progression-free survival (*PFS*) and overall survival (*OS*) according to the length of the recurrence-free interval (*RFI*). Patients with an RFI of ≥6 months had a significantly longer median PFS (6.2 vs. 2.3 months, $P < 0.001$) and OS (16.6 vs. 7.3 months, $P = 0.003$) than patients with an RFI of <6 months. *RFI* recurrence-free interval, PFS progression-free survival, OS overall survival

relatively worse compared with those in the SPIRITS study [4]. However, our results also suggested that patients with an RFI of ≥6 months who received S-1 plus cisplatin had a significantly better response rate, longer PFS, and longer OS compared to patients with an RFI of <6 months. The efficacy of S-1 plus cisplatin for patients with an RFI of ≥6 months in this study was almost compatible with that of patients in the SPIRITS trial in terms of PFS and OS, although these results should be interpreted cautiously due to the heterogeneity of the characteristics of the patients in the two studies. Although no prospective study has evaluated any chemotherapy specifically for patients who have failed adjuvant S-1, Kang and colleagues [15] conducted a phase II study of capecitabine plus cisplatin for 32 patients with gastric cancer that recurred after adjuvant chemotherapy with doxifluridine or 5-FU-containing regimens. They reported a response rate of 28% and a median TTP of 5.8 months, and concluded that capecitabine plus cisplatin was effective as first-line treatment in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy. In their report, the response rates (21 vs. 39%, $P = 0.427$), TTF (8.3 vs. 5.4 months, $P = 0.072$), and OS (14.1 vs. 9.3 months, $P = 0.075$) tended to be better in patients with an RFI of >6 months ($n = 13$) than in patients with an RFI of ≤6 months ($n = 19$), although the differences did not reach statistical significance [15]. These results were also consistent with those of previous studies in patients with other types of cancer, which suggested the importance of the RFI or treatment-free interval as a predictive marker of responsiveness to similar types of chemotherapy after recurrence [16–18]. Additionally, in the present study, the RFI cut-off value of 6 months was better than that of 12 months for predicting better outcomes and this finding may support the use of the conventional exclusion criteria in clinical trials in the first-line setting, which excluded patients who experienced disease recurrence within 6 months after the last adjuvant chemotherapy [5, 9, 11]. Therefore, selected patients with an RFI of ≥6 months with sufficient organ function may be adequately treated as chemo-naïve patients with standard chemotherapies such as S-1 plus cisplatin.

In contrast to the results for patients with an RFI of ≥6 months, the response rate in patients with an RFI of <6 months in the present study seemed to be worse than that of commonly used second-line chemotherapy regimens such as irinotecan and taxane combinations, which have a reported response rate of approximately 20% for patients with gastric cancer who received prior chemotherapy with fluoropyrimidines alone [18–23]. Based on these results, it may be suggested that the evaluation of chemotherapy regimens other than S-1 plus cisplatin might be warranted for the initial treatment of gastric cancer recurrence after adjuvant S-1. The response rate of 5.0% in our subset of patients with an RFI of <6 months was also lower than that reported previously by Kang et al. for capecitabine plus cisplatin after adjuvant chemotherapy (21%) [15]. The exact reasons for this difference are unknown. One possible reason is that Kang and colleagues did not use the same fluoropyrimidine (capecitabine after doxifluridine or 5-FU), and this choice might have contributed to a higher response in regard to early recurrence, although rechallenge with different types of fluoropyrimidine after the failure of another drug is still controversial in several types of cancer [24–28]. Second, the planned dose intensity of cisplatin as another key drug for gastric cancer was higher in their capecitabine plus cisplatin regimen (60 mg/m^2 every 3 weeks) [15] than that in the S-1 plus cisplatin regimen (60 mg/m^2 every 5 weeks). The efficacy of capecitabine plus cisplatin compared with other

chemotherapy (irinotecan, taxane or irinotecan plus cisplatin) for recurrence after adjuvant S-1 should be evaluated in future clinical trials.

It is important to note the limitations of the present study. First, it was retrospective, and treatment after recurrence was selected by each physician individually. Considering the low proportion of patients who received S-1 plus cisplatin after recurrence (14.0%), the selected population may have been biased toward patients with good performance status (PS) and low tumor burden. Second, toxicity was not evaluated in this study, although the proportion of patients who discontinued S-1 plus cisplatin due to toxicity was low. Third, human epidermal growth factor receptor 2 (HER2) status was not evaluated. Trastuzumab, a humanized monoclonal antibody against HER2, has recently been shown to improve the prognosis of HER2-positive advanced gastric cancer [29], and the HER2 status of all gastric cancer types should be evaluated, even in this setting of recurrent disease. Fourth, the moderate sample size in a single-country study is another limitation; therefore, it would be better to validate the significance of the RFI after adjuvant failure on the PFS in other cohorts as well.

In conclusion, this is the first report to have evaluated the efficacy of chemotherapy with S-1 plus cisplatin in patients with gastric cancer that recurred after adjuvant chemotherapy with S-1. S-1 plus cisplatin was effective in such patients, especially in those with an RFI of $\geq$6 months. Further well-defined, prospective trials in this important patient population are required to identify optimal treatment regimens.

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Conflict of interest None of the authors have financial or personal conflicts of interest to disclose.

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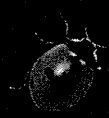

南山堂

② がん治療を支える漢方薬のエビデンス

1 高まる漢方薬のエビデンス

現在，わが国では毎年10万人以上の大腸がん患者が発見されている．世界でもっとも内視鏡が普及し技術的レベルがきわめて高いわが国においても早期がんとして発見される割合は25％程度であり，75％は進行した大腸がんで発見され，その半分近くは肝転移や肺転移などで化学療法を受けることが必要となる[1]．ここ10年間で大腸がんの化学療法は飛躍的に進歩し，以前なら余命6ヵ月と告げられた切除不能大腸がんでも実に5倍に相当する3年程度まで延命が可能となってきている．

その推進力となっているのがオキサリプラチンとイリノテカンというがん細胞を殺すことができる抗がん薬である．最近，注目を集めている分子標的薬はがん細胞の増殖に関連する因子（腫瘍血管や上皮成長因子受容体など）に対する抑制効果を目的とした薬であり，直接的な殺作用はない．今後10年間は新たな殺作用を有する抗がん薬は登場しないとも言われている．

オキサリプラチンはわが国で発見されたものであるが，残念なことに仏国や米国で臨床開発が行われ世界に広まった．イリノテカンは米国で中国原産の喜樹（camptotheca acuminate）から抽出，単離された植物アルカロイドの誘導体だが，第Ⅱ相臨床試験において，出血性膀胱炎と骨髄抑制などの副作用が発現することから開発中止となった．その後，わが国で毒性を軽減した誘導体の開発に成功し，世界に先んじて臨床開発された抗がん薬である．植物をベースにした医療が古代から世界中で盛んに行われてきたが，このように成分を特定し，薬効を明らかにすることで世界的に使用される薬として成功した1例である．わが国伝統の植物薬である漢方薬がイリノテカンと同じように世界的に使用される薬となる可能性が出てきたことを示唆している．

米国では医療費削減と合成薬剤の限界から植物をベースにしたハーバルメディシンに対して門戸を開こうとしている．また自ら年間1億ドル以上の巨額の研究費を拠出し，全米トップの大学や研究所を中心にしたエビデンス構築が行われつつある．しかし，残念ながら西洋医学的発想の原点である単一成分による効果検証を行うというスタイルではポジティブなデータを得ることができないでいた．その結果，議会でこれ