治療効果増強のためにわれわれが行ってきた基礎的・臨床的検討に関して報告する．

5-FUによるGEMの効果増強

GEMの抗腫瘍作用は，細胞内に取り込まれたGEMがリン酸化され，それがDNAに取り込まれる際に，正常ヌクレオシドに拮抗的に働く代謝拮抗剤として作用する．GEMは細胞内に取り込まれる場合，正常ヌクレオシドと同様にヌクレオシドトランスポーターを介して取り込まれる．通常，DNA合成に利用されるヌクレオシドは，細胞内で新たにつくられる場合（*de novo* pathway）とヌクレオシドトランスポーターを介して細胞外から取り込まれる場合（salvage pathway）が存在し，5-FUが細胞に作用すると，*de novo* pathwayが阻害され，それに代わりsalvage pathwayが働き，細胞外からのヌクレオシドの取り込みが増強すると考えられている[2]．従って，GEMに先行して5-FUを細胞に作用させると，GEMの細胞内取り込みが増加し，よりGEMの効果が得られることが考えられる（Fig. 1）．実際，ヒト膵癌細胞を用いた実験では，5-FUを作用することにより，GEMの細胞内取り込みは増加し（Fig. 2），5-FUを先行投与した方がGEMの抗腫瘍効果は高かった（Fig. 3）．この効果は，*in vivo*の動物実験でも認められ，経口5-FU系剤であるUFTとGEMを用いた場合，ヌードマウス移植ヒト膵癌に対する抗腫瘍効果は，UFTを先行投与した場合の方が，GEMを先行した場合や同時に投与した場合より高かった（Fig. 4）[3]．この結果を踏まえて，切除不能進行・再発膵癌に対して，UFT先行GEM投与の第I相試験[4]を行い，至適併用投与量（UFT250mg/m²：day1～6, day8～13, GEM 800mg/m²：day7, 14, 休薬：day15～21）を決定した．さらにその第II相試験を行い，奏功率25%，50%生存期間7ヶ月，1年生存率25%（Fig. 5）と言う結果を得た．

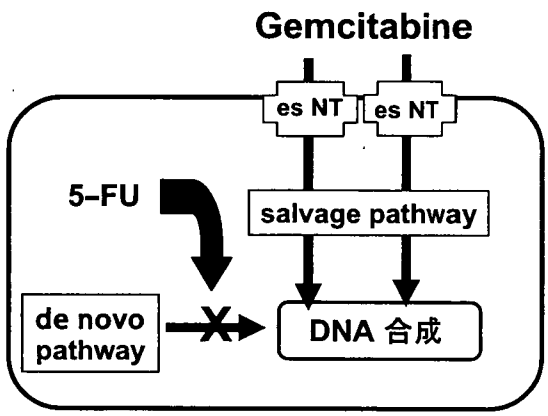

Fig. 1　5-FU先行投与の理論的背景
es NT：ヌクレオシドトランスポーター

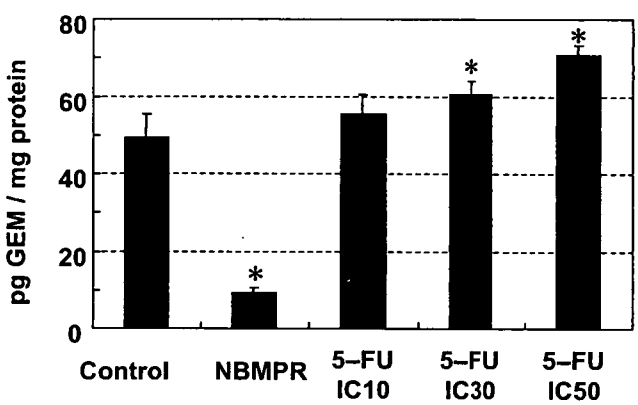

Fig. 2　5-FU投与によるGEM取り込み増強効果
膵癌細胞MiaPaCa-2に対する5-FUのIC10, IC30, IC50で検討した．NBMPR：ヌクレオシドトランスポーター阻害剤．*：$p < 0.05$

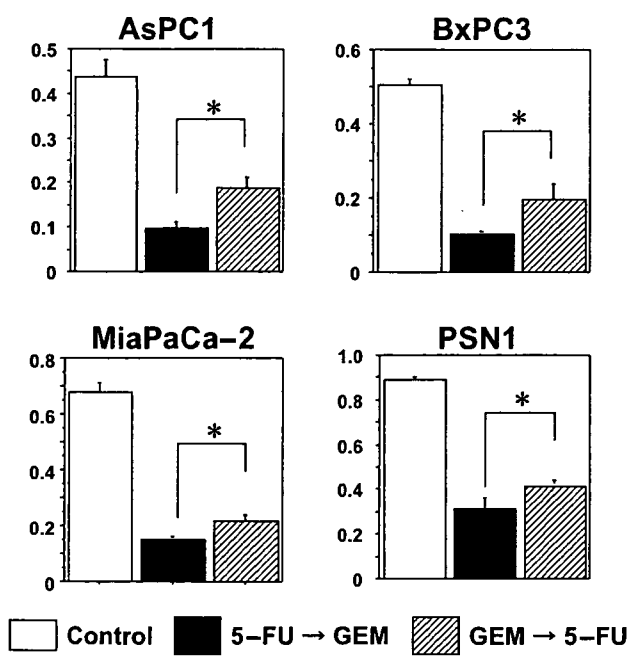

Fig. 3　膵癌細胞株4株における5-FU先行投与によるGEM抗腫瘍効果の増強．*：$p < 0.05$

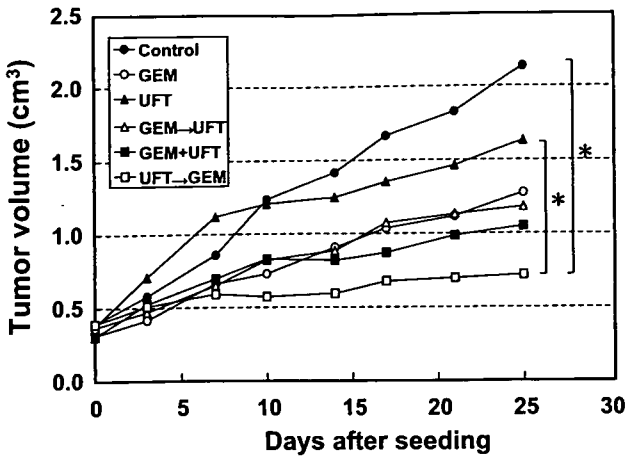

Fig. 4　ヌードマウス移植膵癌に対する5-FUおよびGEMの併用効果．*：$p < 0.05$

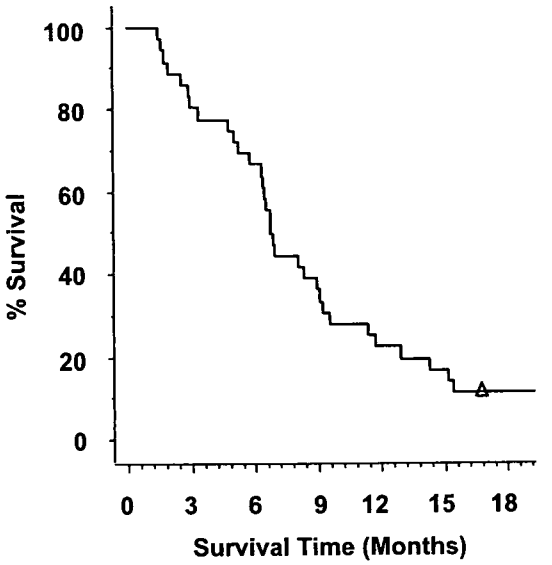

Fig. 5　UFT先行GEM併用療法第Ⅱ相試験における生存率（n = 36）

Table 1　Gem耐性株において発現が亢進していた遺伝子

	発現比	遺伝子名	略名	Accession No.
1	4.46	Ribonucleotide reductase m1 polypeptide	RRM1	NM_001033
2	2.63	Ensembl genscan prediction		AL050329
3	2.29	Kiaa0101 gene product	KIAA0101	NM_014736
4	2.27	Hypothetical protein	ATP5S	NM_015684
5	2.20	Inosine monophosphate dehydrogenase 1	IMPDH1	XM_004627
6	2.19	Hypothetical protein flj20558	FLJ20558	NM_017880
7	2.09	Suppression of tumorigenicity 7	ST7	NM_018412
8	2.07	Hypothetical protein xp_040263	LOC91732	XM_040263
9	2.06	Suppressor of g2 allele of skp1	SUGT1	NM_006704
10	2.02	unknown（protein for image：3456579）	FUBP3	BC001325
11	2.00	Ba196n14.4.1（pro1085 protein, isoform 1）		AL354776
12	2.00	Hypothetical protein xp_039528	LOC91613	XM_039528

従来のGEM単独の投与量より少ないにも拘わらず，良好な治療成績が得られたと考えられた．さらに，2006年夏にUFTよりも有効な5-FU系経口剤としてTS-1が保険適用となり，GEMとの併用療法の有効性が報告されている[5]．この報告でもTS-1先行投与により良好な成績が得られており，作用機序や投与スケジュールを考慮することにより，より有効にGEMを利用できる可能性があるものと考えられる．

GEM耐性機構の解明

現在，GEMは膵癌に対する第1選択薬とされているが，当然のことながら，全ての膵癌にGEMが有効である訳でなく，また，有効であった腫瘍でも，最終的には耐性を獲得し，GEMの効果が得られなくなってくることは事実である．したがって，どのような膵癌がGEMの効果が得られやすいのか，あるいはGEMが効きにくいのかと言ったことや，何故，GEM耐性が獲得されるのかというメカニズムが理解されれば，より有効にGEMを利用できる可能性がある．このような薬剤感受性や耐性獲得には分子レベルでの変化が大きく関与していることが考えられ，GEM耐性ヒト膵癌細胞株を作成し，その母株と耐性株の間で網羅的

遺伝子発現解析を行った[6]．その結果，母株に比べて耐性株で発現が2倍以上ある遺伝子が12個見いだされ(Table 1)，そのうち発現比がもっとも大きな遺伝子は，GEM代謝に関連するRibonucleotide reductase M1 subunit（RRM1）であった．この酵素は，ヌクレオシド代謝の *de novo* pathwayを促進し，salvage pathwayを介したGEMの細胞内での代謝を阻害し，GEMの効果を抑制している可能性がある．実際，RRM1 RNAiを用いた研究により，GEM耐性株においてRRM1発現抑制を行うとGEM感受性が母株と同程度になった(Fig. 6)．さらに，興味あることには，手術後再発に対してGEM投与した18例の手術時に採取した膵癌組織におけるRRM1発現を調べると，RRM1低発現群はGEM治療効果が高発現群に比し良好であった(Fig. 7)．この結果は，必ずしも再発巣が原発巣と同様の遺伝子発現パターンを示しているとは言えないかも知れないが，RRM1の発現は，単に獲得したGEM耐性に関与しているだけでなく，もとの腫瘍の持つGEM感受性にも関与している可能性を示唆しているものと考えられる．

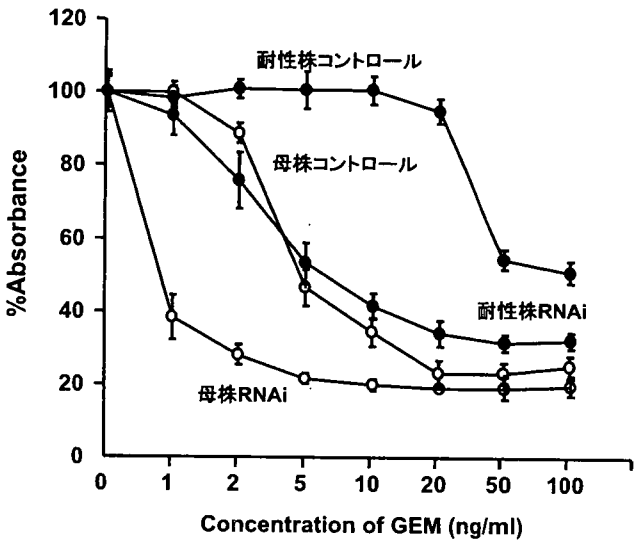

Fig. 6　GEM耐性獲得膵癌細胞株およびその母株に対するRRM1特異的RNAi導入によるGEM感受性の変化

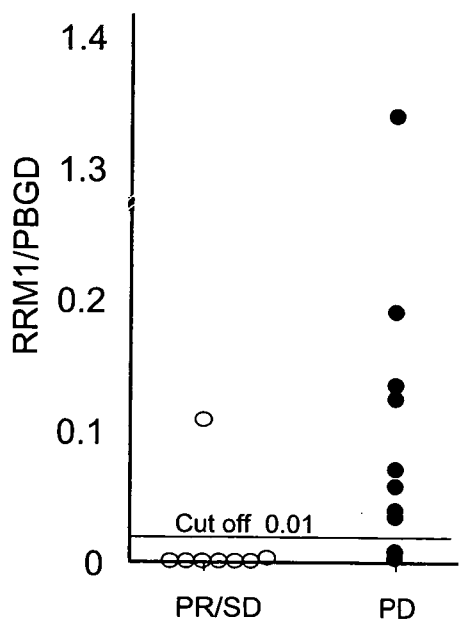

Fig. 7　膵癌組織におけるRRM1発現量とGEMによる抗腫瘍効果
縦軸はRRM1発現量．内因性コントロールのPBGDに対する発現比で示した．PR: partial response, SD: stable disease, PD: progressed disease.

おわりに

現在，GEMは膵癌治療における第1選択薬としての地位を確実に築いていると言える．しかし，その効果には限界があることは確かであり，そのために国内外で，GEMとさまざまな既存の抗癌剤との併用療法や新たな分子標的治療薬との併用療法が臨床試験として検討されてきた．残念ながら，明らかにGEM単独治療による有効性を凌駕するような成績の報告は数少なく，副作用を増加させるのみの報告も多い[7,8]．現在，国内でわれわれが膵癌に対して選択することが可能（保険承認が得られている）な薬剤は数少なく，如何に使用可能な薬剤とGEMを併用し，治療効果を向上させるかや感受性のある腫瘍を如何に選択していくかということが今後の膵癌治療の課題であろう．そのためには，今回報告したようなGEMの作用機序や代謝機序を理解した研究を継続していくことが重要であり，その成果を臨床試験にて検証し，はじめて難治癌の代表である膵癌の治療成績の向上につながるものと思われる．

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Efforts to improve the anti-tumor effect of gemcitabine in human pancreatic cancer

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Key words : Pancreatic cancer, Chemotherapy, GEMcitabine, Drug sensitivity

The systemic administration of gemcitabine has been accepted as the first standard treatment for patients with advanced pancreatic cancer. The survival of patients treated by gemcitabine, however, is still unsatisfactory. To improve the anti-tumor effect of gemcitabine, we investigated molecular changes by gemcitabine in *in vitro* and *in vivo* pancreatic cancer models. The findings suggested that administering gemcitabine after 5-FU may be the optimal combination of gemcitabine/5-FU treatment for pancreatic cancer. Futhermore, a study with gemcitabine resistant pancreatic cancer cells using both *in vitro* and clinical models indicated that ribonucleotide reductase M1 subunit would be a key molecule in gemcitabine resistance in human pancreatic cancer and that RRM1 could have potential as a predictor and modulator of gemcitabine treatment.

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特集 膵癌の診断と治療

膵癌の放射線化学療法

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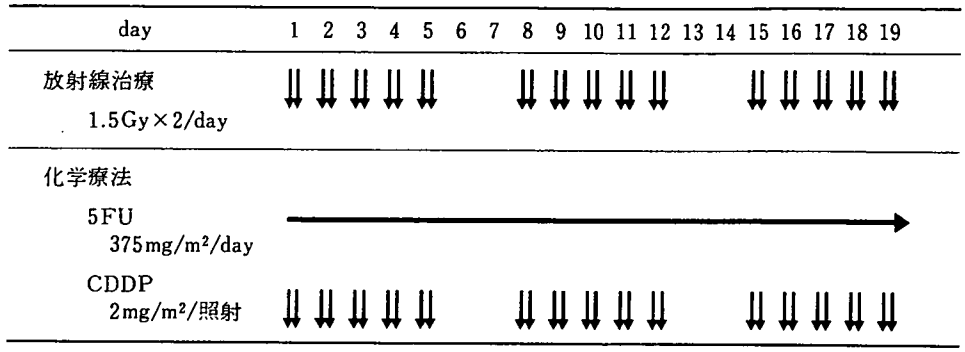

図1 局所進行切除不能膵癌に対する高線量分割照射併用放射線化学療法(第II相試験)

射量の工夫がある．抗がん剤の工夫としては，使用する5FUの投与方法をボーラスに行うか，持続して行う[6]といった投与方法の変更や，併用する抗がん剤として，アドリアマイシン[7]，マイトマイシンC[3]，CDDP[8]などを追加あるいは変更するかということがあげられる．5FU以外の抗がん剤の併用は通常化学療法で使用するのとほぼ同量の抗がん剤を使用し，その直接の抗腫瘍効果を向上させる場合と抗腫瘍効果が得られないような少量投与で放射線増感効果を得ようとするものがある．前者の場合は当然ながら，その副作用の程度や出現頻度高くなる．また，放射線照射の工夫としては，1回照射量や総照射量の増量，照射野の設定，照射方法を多分割高線量とし照射期間の短縮を行うといった工夫が行われてきている．

われわれも切除不能進行膵癌に対する放射線化学療法として，5FU持続投与に加え，放射線増感効果を得るために少量のCDDPを放射線照射前に併用，1.5 Gyの照射を2回/日の多分割高線量照射を全照射量45 Gy行う第I/II相試験(図1)を行った[9]．重篤な副作用はなく，局所進行切除不能膵癌に限れば50%生存期間13ヵ月と比較的良好な成績を得ることができた(図2)．なお，多分割高線量照射では，通常の1回/1日の照射より照射間隔が短いためにより効果的に腫瘍細胞にダメージを与えることができ，分割しない場合の総照射量のほぼ120%程度の照射量と同等の効果が得られると考えられており，治療効果の向上と治療期間の短縮を図ることができる．しかしながら，

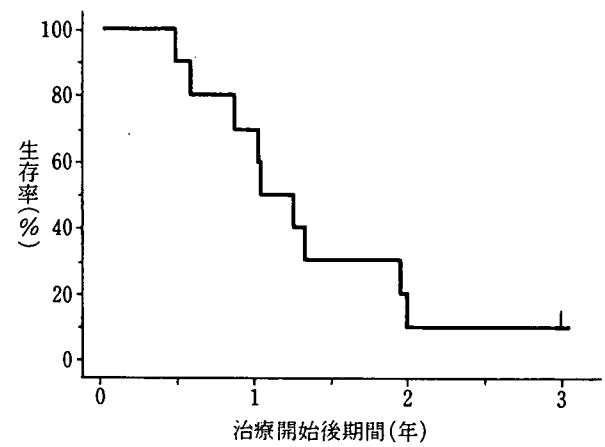

図2 局所進行切除不能膵癌に対する高線量分割照射併用放射線化学療法の第II相臨床試験の治療成績

われわれの報告と同様にこれまでの報告のほとんどが第I相あるいは第II相試験として行われたものであり，安全性や抗腫瘍効果は確認されたが，現在の放射線化学療法の標準的方法となっている5FUを用いた放射線化学療法との無作為比較試験は行われておらず，その評価は定まっていないのが実情である．

3．塩酸ゲムシタビンを併用した放射線化学療法

現在，膵癌に対する化学療法剤の第一選択薬は塩酸ゲムシタビンであり，塩酸ゲムシタビンが放射線増感作用も持つことから，塩酸ゲムシタビンを併用した放射線化学療法[10)-14)]も行われてきている(表3)．塩酸ゲムシタビンの使用量も放射線の増感剤としての低容量からはじめられたが，現在では単独での治療量である1,000 mg/m²という

表3 局所進行膵癌に対する塩酸ゲムシタビン併用放射線化学療法(第II相試験)

報告者	照射量	塩酸ゲムシタビン投与量	症例数	50%生存期間(月)	1年生存率
Epelbaum R, et al[10]	50.4 Gy	400 mg/m²/週× 3	10	<8.	NR
Blackstoch AW, et al[11]	50.4 Gy	40 mg/m²/×1/2週	39	8.2	NR
Moore AM, et al[12]	50.4 Gy	600 mg/m²/週	28	7.9	31%
Okusaka T, et al[13]	50.4 Gy	250 mg/m²/週	43	9.5	28%
Mishra G, et al[14]	50.4 Gy	40 mg/m²/×1/2週	17	8.8	NR

NR : not reported

高容量で設定される場合もある，いまだ第Iあるいは II 相試験の域を出ていない．実臨床ではかなり塩酸ゲムシタビン併用放射線科が行われているようであるが，従来の標準的治療である5FUを主とした放射線化学療法に対する塩酸ゲムシタビンを併用した放射線化学療法の大規模前向き無作為比較試験(第 III 相試験)は行われておらず，その評価はいまだ確実なものではない．さらに，5FU に比べ塩酸ゲムシタビンの膵癌に対する治療効果が高いことから，塩酸ゲムシタビン単独の治療が5FU 併用放射線化学療法に代わって局所進行膵癌に試みられており，ほぼ同等か或いは塩酸ゲムシタビン単独治療のほうが有効な可能性を示唆するような学会レベルでの報告もあるが，エビデンスレベルの高い比較試験はいまだ報告されていない．したがって，米国の NCCN(The National Comprehensive Cancer Network) Clinical Practice Guideline でもわが国における膵癌診療ガイドラインにおいても現在のところ，局所進行切除不能膵癌に対する推奨される治療としては，放射線化学療法が第一であり，その併用抗がん剤は5FU である．塩酸ゲムシタビン以外にパクリタキセルといった新しい抗がん剤を併用した臨床試験も報告[15]されているが，わが国ではいまだ膵癌への適用が認められていない．また，わが国で膵癌に保険適用のあるS-1を併用した第I相試験も報告[16][17]されたが，安全性のみの評価であり，その治療効果は，現在，国立がんセンターを中心に全国規模で第II相試験が行われているところである．

なお，放射線化学療法後の維持化学療法も治療効果を継続させるために重要と考えられるが，そのはっきりした根拠は無い．現在のところ膵癌治療の第一選択薬となった塩酸ゲムシタビンが使用される場合が多いと考えられる．

II. 切除可能膵癌に対する放射線化学療法

1．術前補助化学療法としての放射線化学療法

これまで切除不能局所進行膵癌に対する標準治療とされてきた5FU 併用放射線化学療法によりdown staging が得られ外科的切除が可能となる割合は10数%以下とされており[18]，それほど高いものではない．このことは，より効果が期待できるであろうとされる最近の塩酸ゲムシタビン併用放射線化学療法であっても同程度である[10]．したがって，局所進行膵癌に対する放射線化学療法は，down staging による切除率向上を目指すというより，現在は切除可能性のある膵癌に対する術前補助療法として放射線化学療法が行われることが多い．その理論的背景として，

①術前に局所を制御することにより，切除断端の癌細胞陰性化ができ根治度の向上が期待できる．

②術後の合併症や回復遅延の影響を受けず，自然な血流を維持したまま治療ができる．

③術前治療効果を評価することで，潜在した遠隔転移の診断が可能となり，不必要な手術をせずにすむ．

などがあげられる．

切除可能な膵癌に対する放射線化学療法の治療成績のこれまでの主な報告を表4に示した[19)-25)]．これらの多くは実地医療として行われたものであり，同一施設からの時期を変えての報告[19][20]で症

表4 切除可能性のある膵癌に対する術前放射線化学療法

報告者	照射量	化学療法	症例数	切除数	切除例 50%生存期間(月)
Staley CA, et al[19]	30 or 50.4 Gy	5 FU(300 mg/m²/5日持続)×5	NR	39	19
Spitz FR, et al[20]	30 or 50.4 Gy	5 FU(300 mg/m²/5日持続)×5	71	41	19.2
Hoffman JP, et al[21]	50.4 Gy	5 FU(1,000 mg/m²/4日持続)×2+MMC(10 mg/m²)×1	53	24	15.7
Pisters PW, et al[22]	30 Gy+10～15 Gy IORT	5 FU(300 mg/m²/5日持続)×5	35	27	25
Pisters PW, et al[23]	30 Gy	パクリタキセル(60 mg/m²/週)	35	25	19
Calvo FA, et al[24]	45～50 Gy	テガフール(1,200 mg/日/経口)	15	9	28
Mornex F, et al[25]	50 Gy	5 FU(300 mg/m²/5日持続)×5+CDDP(200 mg/m²/日/週)×2	41	26	NR

NR：not reported

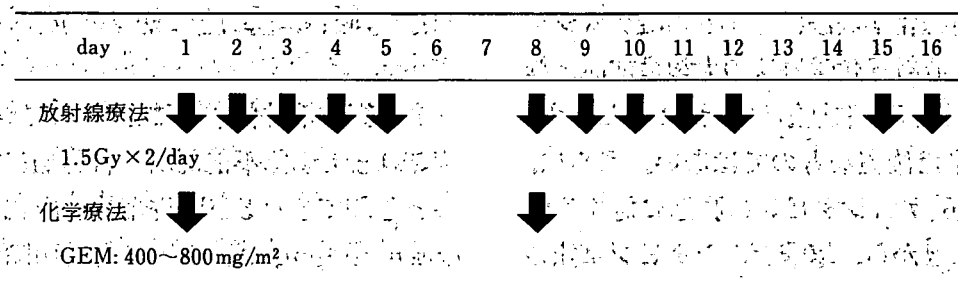

図3 切除可能膵癌に対する塩酸ゲムシタビン併用術前放射線化学療法(第Ⅰ相試験)

例が重複していると考えられるものもある．また，第Ⅱ相や第Ⅲ相の比較臨床試験として行われたものは少なく，抗がん剤の使用量，放射線照射量も切除施行率や手術への影響，術後の合併症を指標として第Ⅰ相試験から決定しているものもほとんどない．多くの報告では，手術は放射線化学療法終了後大体4～6週で手術が行われ，局所再発率が低下し，肝転移再発率が上がったと報告されているが，治療成績や再発形式の違いなど，その有効性に関して，外科的切除のみの場合や術後補助療法単独の場合との大規模の比較試験がないために，現時点ではその有効性に安易に結論を下すことはできない．現在進められている無作為比較試験[26]等の結果を待ちたい．

われわれも画像所見で切除可能のある膵癌に対して，塩酸ゲムシタビン併用多分割高線量照射の臨床試験(図3)を行ってきており，現在第Ⅰ相試験[27]が終了し，第Ⅱ相試験での塩酸ゲムシタビン使用量と照射量を決定し，現在症例の蓄積中である．なお，切除可能膵癌に対する術前照射を行う場合，その照射野の広さや中心が問題となる場合が多い．局所進行切除不能膵癌の場合ように腫瘍を中心としてある程度の均一なマージンを取る場合(図4)と，局所再発予防として主腫瘍よりも

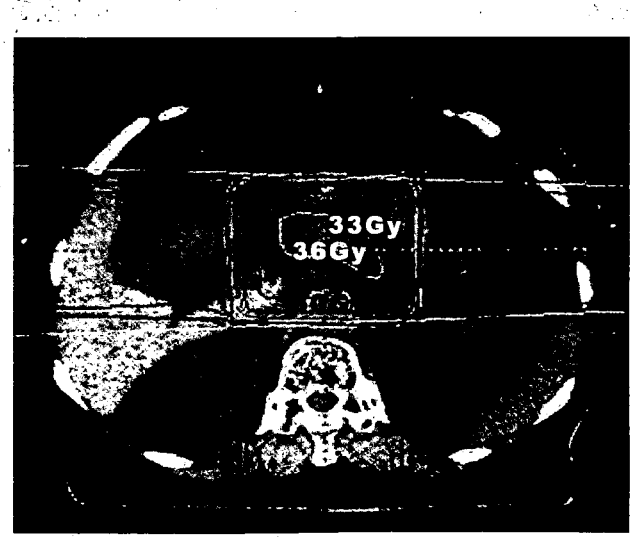

図4 切除可能膵癌に対する塩酸ゲムシタビン併用術前放射線化学療法における線量分布図

表5 術後補助療法としての放射線化学療法

報告グループ	発表年	症例数	照射量	化学療法	50%生存期間(月)	2年生存率	p値
GITSG	1985	22	なし	なし	10.9	18%	
		21	40 Gy	5 FU	20	43%	<0.05
GITSG	1987	22	なし	なし	10.9	18%	
		30	40 Gy	5 FU	18	46%	<0.05

GITSG：Gastrointestinal Tumor Study Group

むしろ上腸間膜動脈根部や大動脈周囲などの後腹膜側を中心として照射する工夫[28]も行われているようである．また，照射野は当然広く取ればとるほど，副作用は出現しやすくなる．

2．術後補助化学療法としての放射線化学療法

膵癌術後補助化学療法は，切除不能局所進行膵癌に対する放射線化学療法と同様にかなり以前から行われており，米国のGITSG(Gastrointestinal Tumor Study Group)の行った古典的な2つの無作為試験[29][30]によって，米国では術後補助療法として標準的治療となった(表5)．しかし，抗がん剤は塩酸ゲムシタビン登場以前の5 FUを用いたものであり，現在では，そのエビデンスレベルは低いものとなっている．また，その後，ヨーロッパのグループが同様の術後放射線化学療法施行群と無治療群との間に有意差を認めなかったと報告[31]し，最近ヨーロッパを中心として行われた大規模比較試験でも，術後無治療群に比べ，術後化学療法は有意に予後を改善するが，術後放射線化学療法は，予後を改善しなかったという報告[32]がある．したがって，現在では，術後補助療法の臨床試験は，化学療法主体に移り，最近，塩酸ゲムシタビンの転移性膵癌に対する標準的投与量である1,000 mg/m^2×1/週×3，1週休薬とする4週1コースの治療を術後6ヵ月行うという後補助化学療法が有意に無再発生存率を向上したという報告[33]が行われ，切除術後の補助療法として標準的治療となりつつある．

さいごに

膵癌に対する放射線化学療法について，その現状を紹介した．塩酸ゲムシタビンが膵癌に対する第一選択薬となった現在，従来の5 FUを主体とした放射線化学療法が局所進行膵癌に対する標準的治療としての位置は低くなったものの，塩酸ゲムシタビンや新たな抗がん剤を併用した放射線化学療法の有効性が確立していないというのが現状と考えられる．今後，その有効性を明らかにし，標準的治療としてのエビデンスを確立していくためには，実地臨床として施設ごとの異なった治療を行い，経験のみを蓄積していくよりも，多施設で共通したプロトコールに基づき大規模な比較試験を行い，膵癌に対する放射線化学療法の有効性の科学的根拠を作り上げていく必要であろう．そのような努力が，わずかずつではあるが，代表的な難治癌の膵癌の治療成績を向上していくことにつながっていくものと考えられる．

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書評

Jürgen Thorwald 著　小川道雄 訳
「外科医の世紀　近代医学のあけぼの」

桑野　博行
群馬大学大学院病態総合外科

本書は1999年から2004年にかけて雑誌『消化器外科』(へるす出版)に連載されたものであり、『消化器外科』が手元に届くと、まず最初に読んだことを記憶している。本書は1966年（昭和41年)に塩月正雄氏訳で『外科の夜明け』として出版されていたが、それを新たに現在の若き医師や看護師を中心として広く読んでほしいとの溢れんばかりの熱意で小川道雄先生（熊本大学名誉教授、現熊本労災病院院長）が全訳された著著である。小川先生は外科学、医学、教育にとどまらず、博識と人間性に溢れた私の最も尊敬する外科医であり、読みすすんでゆくたびに先生の厳格かつ温厚なお顔が浮かんでくる。本書からは、我々が現在、当たり前のように行っている治療が、ここ150年の進歩によって成し遂げられたことがわかる。医学の進歩、とくに外科学の進歩が先駆者の血の滲むような努力によってなされ、また、多くの犠牲者の上に築かれたことを本書は克明に記している。現代に医療を行っている我々は、先人たちの努力や犠牲を無駄にしないように、努力を継続しなければならないと改めて考えさせられる。

外科手術の進歩が、手術器具の改良や麻酔法の発見、消毒法の発見の上に発展してきたことが本書で再認識させられるが、医学は急速な進歩をとげつつも一方で緩徐にすすむものもある。ビルロートが胃切除を1881年に最初に成功させたが、胃切除の術式がほぼ完全に完成された現在でも、胃切除の標準的術式であるビルロートのI法、II法が100年以上にわたって変わっていないことにも驚かされる。

「歴史を鏡とよぶ発想は鏡の発明とともに古いように想像される。歴史の鏡に映る見ず知らずの幾多の人間達に、己れの姿を観ずることが出来なければ、どうして歴史が、私達に親しかろう。(中略)人間は歴史を持つ。社会だけなら蟻でも持つ。」(小林秀雄『考えるヒント』プルターク英雄伝より)

医学、とくに外科の歴史に携わった多くの人々の息づかいを感じつつ、本書を味わっていただくことをお勧めしたい。

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CASE REPORT

Follicular Lymphoma of the Pancreas: A Case Report and Proposed New Strategies for Diagnosis and Surgery of Benign or Low-Grade Malignant Lesions of the Head of the Pancreas

Naohiro Sata, Akira Kurogochi, Kazuhiro Endo, Kunihiko Shimura, Masaru Koizumi, Hideo Nagai

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ABSTRACT

Context Primary pancreatic lymphoma is a rare form of extranodal lymphoma originating in the pancreas. The present report describes a case of follicular lymphoma of the pancreas with unique CT and MRI findings.

Case report A 58-year-old male complained of sudden abdominal pain, and routine ultrasonography detected an 8 cm hypoechoic tumor in the head of the pancreas. The 3D image generated using multi-cholangiography and virtual duodenography provided the information necessary for a laparotomy. The tumor was enucleated for diagnosis. Follicular lymphoma is quite rare in the pancreas and gastrointestinal tract. A considerable number of pancreatic lymphoma subtypes have been reported. The expression "pancreatic lymphoma" has been used to describe both primary lymphoid neoplasms originating in the pancreatic parenchyma and tumors invading from a peri-pancreatic lymphadenopathy. The present case belongs to the latter, which might explain the unique imaging findings and histological type. These subtypes display different imaging findings and different clinical characteristics. In the future, primary pancreatic lymphoma should be discussed separately depending on the subtype.

Conclusion We propose a new subtype of primary pancreatic lymphoma. Multi-cholangiography and virtual duodenography provided the information necessary for a laparotomy in the present case. Enucleation is indicated for benign and low-grade malignant tumors of the pancreas, even if the tumor is located in the head of the pancreas.

Table 1. Behrns *et al.* criteria for primary pancreatic lymphoma [8].

1. No palpable superficial lymphadenopathy
2. No enlargement of mediastinal nodes
3. Normal leukocyte count
4. At celiotomy, the pancreatic mass predominates, with grossly-involved nodes confined to the peri-pancreatic region
5. No hepatic or splenic involvement

INTRODUCTION

Primary pancreatic lymphoma (PPL) is a rare form of extranodal lymphoma originating in the pancreas, and constitutes less than 0.5% of all pancreatic malignancies [1, 2, 3, 4, 5, 6]. Some confusion surrounds the definition of PPL. Dawson *et al.* published the first criteria for the diagnosis of a primary lymphoid tumor of the intestinal tract [7]. As Dawson's criteria did not refer to pancreatic lymphomas, Behrns *et al.* modified Dawson's original criteria and applied it to PPL (Table 1) [8].

Salvatore *et al.* proposed new criteria for PPL and a novel nomenclature system, including primary, secondary and tertiary pancreatic lymphoma definitions [5]. They limited primary pancreatic lymphomas to lymphoid tumors originating in the pancreatic parenchyma, and defined secondary pancreatic lymphomas as peri-pancreatic lymphadenopathy invading the pancreas. In the literature, these two types of pancreatic lymphoma have both been referred to as PPL. Pancreatic lymphomas usually appear as large pancreatic masses, and sometimes mimic pancreatic cancer or other pancreatic neoplasms. PPLs appear as low-density and heterogeneous lesions when viewed using plane CT, show poor yet homogeneous enhancement when viewed using dynamic CT, show low signal-intensity with subtle enhancement after i.v. gadolinium-contrast medium administration when viewed using T1-weighted MR imaging, and show heterogeneous low signal-intensity when viewed using T2-weighted MR imaging [9, 10]. In the latest review, Saif reported two PPL prototypes in image findings, a localized well-circumscribed tumoral form and a diffuse enlargement infiltrating or replacing most of the pancreas [6], and these appear to represent the primary and secondary pancreatic lymphomas proposed by Salvatore *et al.* [5].

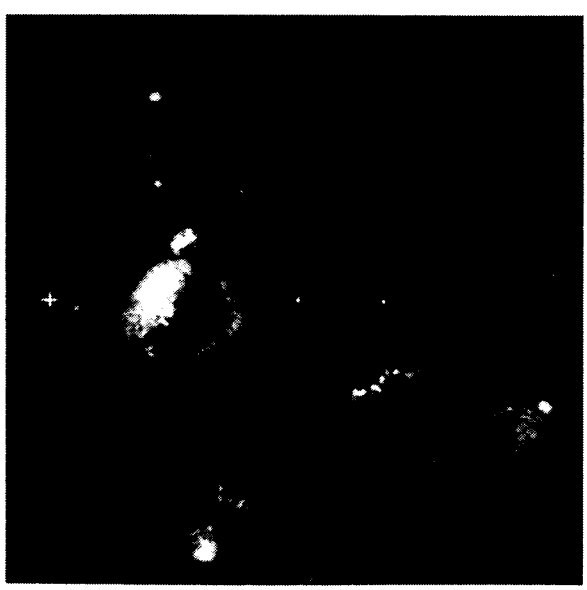

Figure 1. MRCP showing encasement of the common bile duct and main pancreatic duct.

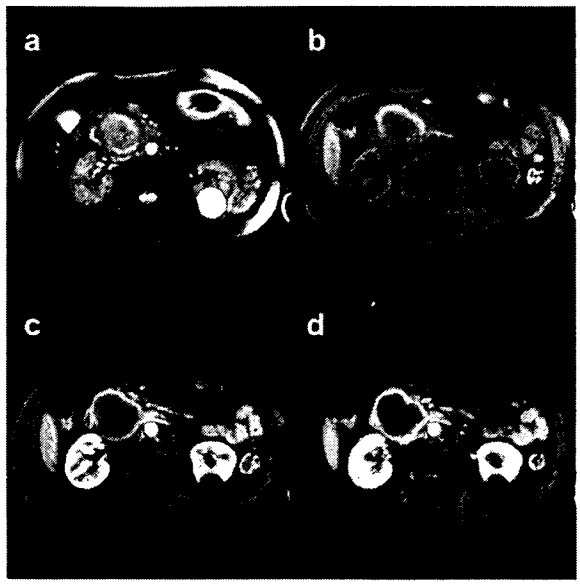

Figure 2. The tumor showed heterogeneous iso- or low signal-intensity on T2-weighted images, and low signal-intensity with marginal enhancement on T1-weighted images after i.v. administration of gadolinium-contrast medium. **a.** T2-weighted MR image. **b.** T1-weighted MR image. **c-d.** Postcontrast T1-weighted MR image.

The present report describes a unique case of PPL. In this case, a novel method of multi-detector raw CT (MD-CT) examination and post-processing was used in the preoperative diagnosis and enucleation of the tumor, and contributed to the histological diagnosis.

CASE REPORT

A 58-year-old male complained of sudden abdominal pain, and routine ultrasonography detected an 8 cm hypoechoic tumor in the head of the pancreas. The tumor was carefully examined using MRI and MD-CT. MRCP showed encasement of both the common bile duct and the main pancreatic duct (Figure 1). The tumor showed heterogeneous iso- or low signal-intensity on T2-weighted images, and low signal-intensity with marginal enhancement on T1-weighted images after i.v. administration of gadolinium-contrast medium (Figure 2). Ordinary CT demonstrated a low density tumor with marginal enhancement in a dynamic study of the head of the pancreas (Figure 3). There appeared to be neither hepatic nor splenic involvement. A 2 cm lymph node was detected in the retro-

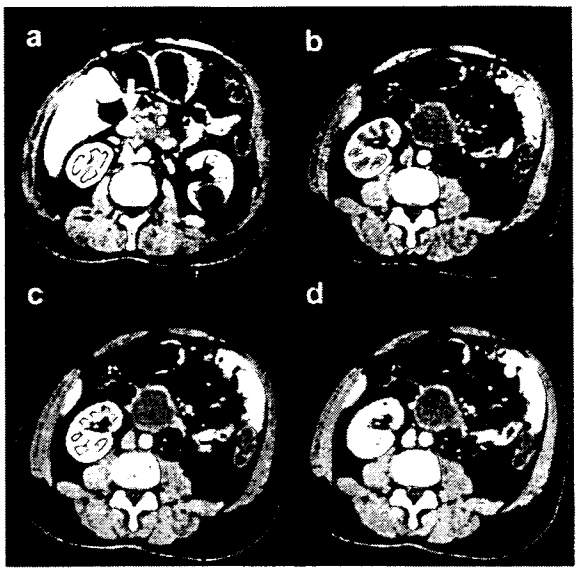

Figure 3. a. Enhanced CT of the retro-pancreatic lymph node (white arrows). **b-c-d.** Dynamic CT image study of the tumor in the head of the pancreas showing weak marginal enhancement of the tumor.

pancreatic region (Figure 3a white arrows). The patient then underwent a distinct diagnostic procedure involving MD-CT scanning and post-processing, multi-cholangiography and virtual duodenography [11]. This process allowed the tumor (which appeared as dark purple according to the window level) to be clearly observed in a 3D manner (Figure 4), and allowed interaction with the adjacent organs and vessels to be viewed. The tumor was shown to be in the parenchyma of the head and the uncus of the pancreas, and there appeared to be no portal vein or artery involvement.

No peripheral lymph nodes were palpable and no lymphadenopathy in the pleural and abdominal cavity was detected other than the retro-pancreatic lymph node described above. Biochemical analysis and peripheral blood cell counts on entry showed normal results. Pancreatic hormones, enzymes and tumor markers (including soluble IL-2 receptor) were at normal levels.

A preoperative diagnosis of a benign or low-grade malignant lesion of the pancreas, such as an endocrine tumor or neurogenic tumor provided the information necessary for a laparotomy. The tumor, located in the head of the pancreas, was elastic, hard, covered with pancreatic tissue, and clearly bordered the pancreatic parenchyma according to intraoperative ultrasonography findings. The first procedure involved the removal of a 2 cm retro-pancreatic lymph node. While intraoperative histological examination indicated that the tumor was a lymphoid proliferative mass, a definitive diagnosis could not be made. The border between the tumor and the pancreas was clear. The tumor was then enucleated, a procedure which was

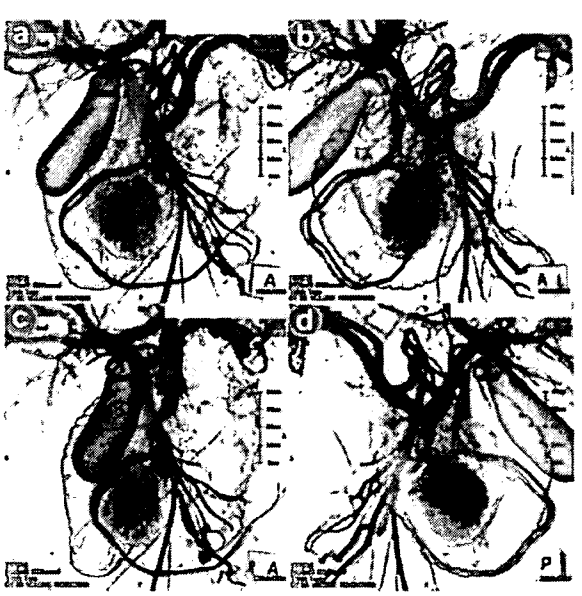

Figure 4. A multi-cholangiography and virtual duodenography image. The tumor appears as dark purple (according to the window level) in the 3D image. **a.** Anterior view. **b.** Left oblique view. **c.** Right oblique view. **d.** Posterior view.

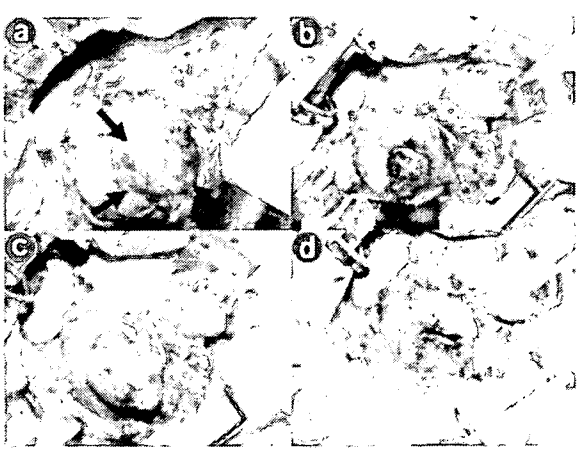

Figure 5. Intraoperative findings. **a.** The tumor was located in the head of the pancreas and was covered with pancreatic tissue (black arrows). **b-c.** The enucleation procedure for the tumor. **d.** The view after tumor enucleation.

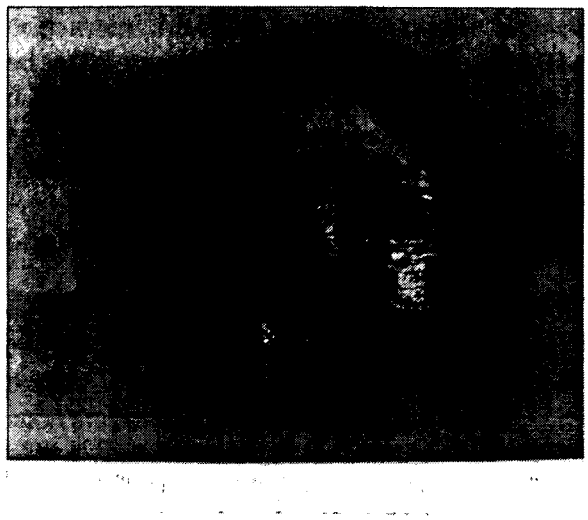

Figure 6. Macroscopic findings of the tumor.

relatively easy and took approximately thirty minutes (Figures 5 and 6). The histology of the tumor was almost the same as the peripancreatic lymph node.

The patient was discharged on the 12th post-operative day without any significant postoperative events. The final histologic diagnosis was a B-cell type follicular lymphoma of the pancreas. The tumor had a fibrous capsule and displayed diffuse central necrosis. Most of the non-necrotic tissue in the peripheral region consisted of proliferating follicles, and immunohisto-chemical analysis found it to be stained positive for BCL2 gene, L26 protein and CD10 antigen (Figure 7). As the lymphadenopathy was located beside the pancreas, this case was categorized as Stage II using the Ann Arbor Staging system [12]. The patient received additional radiation and showed no signs of recurrence over the following 6 months.

DISCUSSION

The present report describes a unique case of PPL. The tumor was located in the head of the pancreas, was a peri-pancreatic lesion as indicated by the lymphadenopathy, was compatible with all the criteria of Behrns, and was hence diagnosed as PPL [8]. Most reported cases of PPL in the English-language literature are intermediate or high-grade non-Hodgkin lymphomas (NHL) with diffuse large cells of the B type [6]. Follicular lymphomas are quite rare in the pancreas and gastrointestinal tract. Shia *et al.* reported 26 cases of primary follicular lymphoma of the gastrointestinal tract, none of which involved the pancreas [13]. Misdraji *et al.* [14] reported a case of follicular lymphoma of the papilla of Vater, and Salvatore *et al.* [5] summarized three cases of follicular lymphoma of the pancreas out of 60 cases in the literature.

In the present case, the tumor showed unique findings according to CT and MRI. Saif summarized PPL imaging findings and concluded that neither calcifications nor necrosis within the tumor mass had been described in any case of untreated PPL [6]. However, the present tumor showed diffuse central necrosis, which explained the unique CT and MRI findings. No particular findings of follicular lymphoma have been reported in the literature. Central necrosis is possibly linked to the rare histoloic findings. The 3D multi-cholangiography image provided the information necessary for the laparotomy in the present case. A safe and successful laparotomy procedure requires knowledge of the precise location of the tumor and any interactions with vessels and adjacent organs. The present method provided such information, and we believe it is applicable to

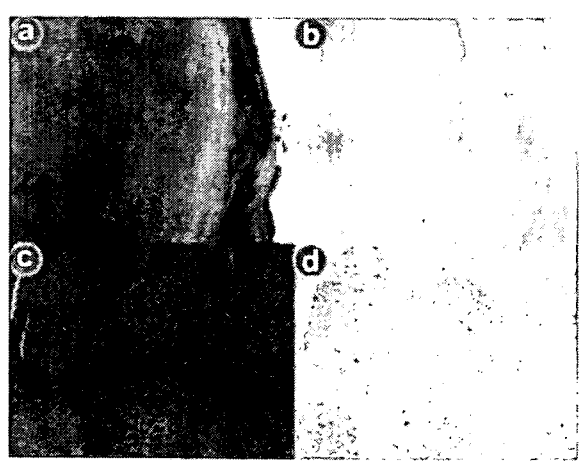

Figure 7. Microscopic examination following hematoxylin-eosin staining (**a.** x10, **c.** x200) and L26 immunostaining (**b.** x10, **d.** x200). The tumor showed central necrosis and L26-positive proliferating follicles in the peripheral region.

all pancreatic tumors including pancreatic cancers and neoplasm of any etiology.

The initial treatment of a PPL depends on the method by which the diagnosis is made. If the diagnosis is made using a relatively mild invasive technique, chemotherapy and/or radiation is initiated soon after diagnosis. Recently, fine needle aspiration or biopsy has become the "gold standard" for PPL diagnosis as it is highly accurate [6, 9]. Recent reports recommend US- and CT-guided biopsy as the first choice diagnostic tool for PPL [9, 15, 16, 17, 18]. The present patient underwent a laparotomy mainly because the unique CT and MRI findings did not indicate a PPL. Even if a tumor is located deep within the head of the pancreas, it is worthwhile attempting enucleation for benign and low-grade malignant pancreatic tumors. Since such tumors usually display expansive growth and low interaction with the pancreatic parenchyma, careful observation and resection can avoid bleeding and leakage of pancreatic juice during enucleation. Enucleation can also be applied to other types of pancreatic tumors, such as solid, pseudopapillary, neurogenic and endocrine tumors.

There has been considerable variation in the reporting of lymphomas involving the pancreas. The expression "pancreatic lymphoma" has been used for both primary lymphoid neoplasms originating in the pancreatic parenchyma and for tumors invading from peri-pancreatic lymphadenopathies [5]. The present case belongs to the latter category. These subtypes display different image findings and different clinical characteristics. In the future, PPL should be discussed separately depending on the subtype.

In conclusion, the present report describes a rare follicular lymphoma of the pancreas. Multi-cholangiography and virtual duodenography provided the information necessary for a laparotomy. Enucleation is indicated for benign and low-grade malignant tumors of the pancreas, even if the tumor is located in the head of the pancreas.

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Keywords Lymphoma, Follicular; Pancreatic Diseases

Abbreviations BCL2: B-cell CLL/lymphoma 2 [*Homo sapiens*]; MD-CT: multi-detector raw computed tomography; PPL: primary pancreatic lymphoma

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Phase II Study of Combination Chemotherapy with Gemcitabine and Cisplatin for Patients with Metastatic Pancreatic Cancer

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Objective: The objectives of this study were to evaluate the efficacy and toxicity of combination chemotherapy with gemcitabine and cisplatin in patients with metastatic pancreatic cancer.
Methods: Patients naïve to chemotherapy who had histologically or cytologically confirmed metastatic pancreatic adenocarcinoma were entered. Gemcitabine was given at a dose of 1000 mg/m^2 over 30 min on days 1, 8 and 15, and cisplatin was given at a dose of 80 mg/m^2 over 150 min on day 1, in 28-day cycles.
Results: A total of 38 patients were enrolled in this study between August 2001 and December 2003. There were no complete responses and 10 partial responses, resulting in an overall response rate of 26% (95% CI: 13.4–43.1%]. Twenty-one patients (55%) had stable disease, whereas 7 (18%) had progressive disease. The median time to progression was 4.2 months and the median overall survival was 7.5 months with a 1-year survival rate of 24%. Grade 3–4 toxicities included neutropenia in 26 patients (68%), thrombocytopenia in 19 (50%), anorexia in 15 (39%) and nausea in nine (24%). There was only one episode of neutropenic fever and there were no significant bleeding episodes or treatment-related deaths.
Conclusion: The combination of gemcitabine and cisplatin administered by this schedule produced a good response rate associated with moderate but manageable toxicities in patients with metastatic pancreatic cancer.

Key words: gemcitabine – cisplatin – phase II study – chemotherapy – pancreatic cancer

INTRODUCTION

Pancreatic cancer currently represents the fifth leading cause of cancer-related mortality in Japan, with an estimated 22 260 deaths attributable to the disease in 2004 (1). Most patients with pancreatic cancer have advanced, unresectable disease at the time of diagnosis and their prognosis is extremely poor. Since a randomized study by Burris et al. in 1997 demonstrated that gemcitabine had a survival benefit versus fluorouracil (2), gemcitabine has been accepted as the standard treatment for advanced pancreatic cancer. However, the median survival of patients with advanced pancreatic cancer treated with single-agent gemcitabine has been only about 6 months (2–4), indicating the pressing need for development of novel treatment strategies.

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Combination of gemcitabine with other agents would be one promising avenue for improving the effect of treatment for advanced pancreatic cancer. In fact, a few recent randomized phase III studies of combinations such as gemcitabine/erlotinib (5) and gemcitabine/capecitabine (6) have demonstrated statistically significant survival benefit in comparison with gemcitabine alone in patients with advanced pancreatic cancer, although there is still no worldwide consensus about the results. As well as these combinations, gemcitabine plus cisplatin has been considered an attractive regimen for pancreatic cancer for several reasons: (i) single-agent cisplatin shows modest activity against pancreatic cancer (7), (ii) preclinical *in vitro* and *in vivo* studies have demonstrated synergistic effects between gemcitabine and cisplatin (8), (iii) the two drugs have non-overlapping, dose-limiting toxicities, and (iv) this combination has demonstrated activity against various malignancies, and is accepted as one of the standard therapies for non-small-cell

lung cancer and urothelial cancer based on large randomized studies (9,10). Several phase II studies of gemcitabine plus cisplatin for advanced pancreatic cancer have been published to date, most of which have shown that this combination seems to be effective, with response rates of 9–31%, and median overall survivals of 5.6–9.6 months (11–16). However, because there have been few studies of Asians receiving gemcitabine and cisplatin for treatment of pancreatic cancer, we conducted the present phase II study to evaluate the efficacy and toxicity of this combination therapy in Japanese patients with metastatic pancreatic cancer. Although various schedules for the combination of gemcitabine and cisplatin have been reported in previous studies, we administered gemcitabine at a dose of 1000 mg/m^2 on days 1, 8 and 15 and cisplatin at a dose of 80 mg/m^2 on day 1 of a 28-day cycle, based on the results of a phase I study conducted in Japanese patients with non-small-cell lung cancer (17).

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically proven pancreatic adenocarcinoma with at least one bidimensionally measurable metastatic lesion were eligible for the study. Other eligibility criteria included: no previous treatment for pancreatic cancer except surgery; age $\geq$20 and $\leq$74 years, Karnofsky performance status (KPS) $\geq$50, life expectancy $\geq$8 weeks, adequate bone marrow function (white blood cell count $\geq$4000/mm^3, neutrophil count $\geq$2000/mm^3, platelet count $\geq$100 000/mm^3 and hemoglobin level $\geq$10.0 g/dl), adequate renal function (serum creatinine concentration $\leq$ upper limit of normal and creatinine clearance $\geq$60 ml/min), adequate hepatic function (serum bilirubin level $\leq$2.0 mg/ml, serum aspartate and alanine transaminase (AST and ALT) levels $\leq$2.5 times upper normal limit or $\leq$5 times upper normal limit if liver metastases or biliary drainage were present) and adequate pulmonary function (PaO_2 $\geq$70 mmHg). Exclusion criteria were as follows: symptomatic pulmonary fibrosis or interstitial pneumonia, marked pleural effusion or ascites, central nervous system metastasis, active concomitant malignancy, severe mental disorder, serious complications such as active infection, active gastrointestinal ulcer, or cardiac disease and pregnant or lactating women. Written informed consent was obtained from all patients. This study was approved by the institutional review board at the National Cancer Center and conducted in accordance with the Declaration of Helsinki.

Treatment Plan

This was an open-label, single-center, single-arm phase II study. The patients received gemcitabine at a dose of 1000 mg/m^2 intravenously over 30 min on days 1, 8 and 15, and cisplatin at a dose of 80 mg/m^2 just after gemcitabine administration over 150 min on day 1. The treatment cycles were repeated every 4 weeks for a maximum of six cycles unless disease progression or unacceptable toxicity occurred. If patients completed the planned six cycles of treatment without disease progression, then they received gemcitabine monotherapy until disease progression. If patients developed leukopenia of <2000/mm^3, neutropenia of <1000/mm^3, or thrombocytopenia of <75 000/mm^3 during the cycle, gemcitabine administration was skipped. If patients developed leukopenia of <3000/mm^3, neutropenia of <1500/mm^3, thrombocytopenia of <100 000/mm^3, total bilirubin of >2.0 mg/dl, or creatinine clearance of <50 mil/min, initiation of the next cycle was prolonged until recovery. Dose reduction of gemcitabine from 1000 to 800 mg/m^2 was allowed when patients experienced (i) grade 4 leukopenia or neutropenia, (ii) febrile neutropenia, (iii) grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring blood transfusion, or (iv) grade 3 or greater non-hematological toxicities other than nausea, vomiting, anorexia and hyperglycemia. Patients were dropped from the study if they required more than two dose reductions, or if they were unable to start the next cycle within 4 weeks from the scheduled day.

Clinical Assessments

Physical examination, complete blood cell counts, serum chemistry and urinalysis were performed at the baseline and at least once weekly after the start of treatment. All patients who received at least one dose of gemcitabine were evaluable for safety. Toxicities were graded according to the National Cancer Institute common toxicity criteria version 2.0. Tumor assessment with computed tomographic scan or magnetic resonance imaging and measurement of the tumor marker CA 19-9 was performed every 4 weeks, and tumor response was evaluated using the criteria of the Japan Society for Cancer Therapy (18), which are similar to those of the World Health Organization. Briefly, a complete response (CR) was defined as the disappearance of all clinical evidence of the tumor for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions for 4 weeks or longer without any evidence of new lesions. No change (NC) was defined as a reduction of less than 50% or a less than 25% increase in the sum of the products of two perpendicular diameters of all lesions for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase of 25% or more in the sum of the products of two perpendicular diameters of all lesions, the appearance of any new lesion, or deterioration of clinical status that was consistent with disease progression. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately. Time to tumor progression (TTP) was calculated from the date of the start of therapy until