日本では膵癌のために年間2万人が死亡しており，癌の死因の第5位を占める．膵癌患者の8割以上は切除不能な進行癌であり，その予後は著しく不良である．切除不能膵癌は，局所進行膵癌と遠隔転移を有する膵癌に分けられる．

表1　進行膵癌に対する単剤療法の治療成績(gemcitabine以外)

抗癌剤	症例数	奏効率(%)	生存期間中央値(月)	報告者
paclitaxel	14	0	7.2	Gebbia(1996)
docetaxel	40	15	7.0	Rougier(2000)
docetaxel	21	0	3.9	Okada(1999)
docetaxel	21	5	5.9	Lenzi(2002)
topotecan	27	0	4.1	O'Relly(1996)
topotecan	35	10	4.4	Scher(1996)
irinotecan	34	9	5.2	Wagener(1995)
irinotecan	37	27	7.3	Funakoshi(2004)
raltitrexed	42	5	NA	Pazdur(1996)
pemetrexed	42	6	6.5	Miller(2000)
capecitabine	42	10	6.1	Cartwright(2002)
S-1	19	21	5.6	Okada(2002)
tipifarnib	20	0	4.6	Cohen(2003)
marimastat	102	3	4.2	Bramhall(2001)
BAY12-9566	138	1	3.7	Moore(2003)

NA：not available

ン酸化されてDNAの合成を阻害する．gemcitabineは30分かけて点滴する方法が一般的であるが，gemcitabineがdeoxycytidine kinaseによって効率よくリン酸化されるための投与方法の検討がなされ，10 mg/m²/minの速度で投与する方法(定速静注法：fixed dose rate infusion)が最適であることが報告された．これを受けて最近，定速静注法(1,500 mg/m²/150 min，週1回，3週投与1週休薬)と30分の投与法(2,200 mg/m²/30 min，2週に1回投与)の無作為化比較第II相試験が行われ，定速静注法の方が生存期間が優れていたことが報告された[2]．現在，この定速静注法がgemcitabineの標準的な投与方法になり得るかについて米国で無作為化比較試験が行われている．

b．新規抗癌剤

最近報告された膵癌に対するgemcitabine以外の抗癌剤の成績を示す(表1)．docetaxelは開発当初比較的良好な奏効率が報告されたが，その後の追試では良い成績は得られなかった．topoisomerase I阻害剤のirinotecanは，最近わが国で行われた遠隔転移例に対する第II相試験で奏効率27%，MST 7.3ヵ月と良好な成績を示したが，膵癌に対する世界的な評価は確立していない．その他，最近では経口のフッ化ピリミジン系抗癌剤であるcapecitabineやS-1が膵癌に対して試みられている．capecitabineは5-FUのプロドラッグで，現在欧米を中心に臨床試験が行われており，最近報告された第II相試験では，10%の奏効率と24%の症状緩和効果が報告されている．S-1はわが国で開発されたtegafurとbiochemical modulatorの配合剤で，進行膵癌を対象とした前期第II相試験では21%の奏効率が示され[3]，現在後期第II相試験がわが国で進行中である．分子標的治療は現在最も注目されている分野であり，細胞外matrixを分解する酵素

遠隔転移を有する膵癌に対する第一選択の抗癌剤は，gemcitabine である．
gemcitabine の膵癌に対する奏効率は5～15%，MST は5～6ヵ月程度である．
定速静注法は，gemcitabine が効率良くリン酸化されるための投与方法である．

(matrix metalloproteinase)を阻害し腫瘍の発育を抑制することを目的に開発された marimastat や BAY 12-9566，膵癌に K-ras の突然変異が高率にみられることから，ras 蛋白の機能発現に必要な farnesyl 化を抑制するために開発された farnesyl transferase 阻害剤(tipifarnib)，上皮成長因子受容体(ECFR)のモノクローナル抗体である cetuximab や選択的 EGFR チロシンキナーゼ阻害剤の erlotinib，などの分子標的薬剤による臨床試験が膵癌に対して積極的に行われている．現時点では膵癌に対する分子標的薬剤の役割は明らかにされていないが，今後の進展が期待される．

c. 多剤併用療法

gemcitabine は単剤で膵癌に対する効果が証明され，毒性も比較的軽度であることから，近年 gemcitabine と他の抗癌剤との併用療法が積極的に試みられており，多くの第 II 相試験(**表 2**)および第 III 相試験(**表 3**)が報告されている．併用される薬剤は，当初は 5-FU や cisplatin など古くから膵癌に対して使用されてきた薬剤が中心であったが，最近では分子標的薬剤を含む新規抗癌剤が試みられている．

5-FU は週1回の静注や持続静注などのさまざまな投与方法で gemcitabine と併用され，安全性と比較的良好な奏効率(20% 前後)が第 II 相試験で報告されてきたが，gemcitabine と週1回の 5-FU の静注を併用した群と gemcitabine 単独群とを比較した第 III 相試験では，生存期間に有意な差を認めなかった(MST：併用群 6.7 ヵ月，gemcitabine 単独群 5.4 ヵ月)[4]．

次に注目されたのは cisplatin で，gemcitabine との併用療法の第 II 相試験では 20% を越える奏効率が報告され期待されたが，これまでに報告された二つの第 III 相試験では，両試験とも併用群の方が gemcitabine 単独群に比べ無増悪生存期間は優れていたものの，生存期間の有意な延長は認めなかった．また，gemcitabine と irinotecan の併用療法と gemcitabine 単独投与とを比較した第 III 相試験も行われたが，併用群で毒性の増強が認められ，生存期間の差は認めなかった．

最近では，新しい白金製剤である oxaliplatin と gemcitabine の併用療法の第 III 相試験が行われ，奏効率と無増悪生存期間は併用群の方が gemcitabine 単独群に比べ有意に優れていたことが中間解析で報告され注目されたが，最終解析では残念ながら生存期間の有意な差を認めなかった．

現時点では gemcitabine 単剤よりも明らかに生存期間を上回る併用療法の報告はされていないが，奏効率や無増悪生存期間が単剤より優れている報告も多く，今後も積極的に併用療法の臨床試験が展開されていくものと思われる．わが国では，現在，S-1 と gemcitabine の併用療法の多施設共同試験が進行中である．

分子標的薬剤では，matrix metalloproteinase 阻害薬や farnesyl transferase 阻害薬と gemcitabine の併用療法の無作為化比較試験が行われたが，良い結果は得られなかった．その他，EGFR 阻害薬の cetuximab，EGFR チロシンキナーゼ阻害薬の erlotinib，HER 2 阻害薬の trastuzumab，血管内皮細胞成長因子(VEGF)阻害剤の bevacizumab などの分子標的薬剤と gemcitabine の併用療法が行われており，報告が待たれている．

放射線療法 ◉

1. 放射線療法の対象

放射線療法は，局所進行膵癌(画像診断上明ら

新規薬剤では経口フッ化ピリミジン系抗癌剤や分子標的薬剤が注目されている.
gemcitabine を中心とした多剤併用療法が現在積極的に試みられている.
gemcitabine 単剤よりも有意に生存期間が優れた治療法はまだみつかっていない.

表 2　進行膵癌に対する多剤併用療法の治療成績(第 II 相試験)

治療法	症例数	奏効率(%)	生存期間中央値(月)	1 年生存率(%)	報告者
GEM＋5-FU(bolus injection)	36	14	4.4	8.6	Berlin(2000)
GEM＋5-FU(continuous infusion)	26	19	10.3	40	Hidalgo(1999)
GEM＋5-FU(high dose infusion)	23	9	8.3	30	Wein(2002)
GEM＋cisplatin	52	31	NA	NA	Colucci(1999)
GEM＋cisplatin	41	11	8.2	27	Heinemann
GEM＋cisplatin	42	26	7.1	19	Philip(2001)
GEM＋docetaxel	18	6	5.4	NA	Cascinu(1999)
GEM＋docetaxel	34	18	8.9	29	Ryan(2002)
GEM＋irinotecan	45	20	5.7	27	Rocha Lima(2002)
GEM＋irinotecan	60	25	7.0	23	Stathopoulos(2003)
GEM＋oxaliplatin	64	31	9.2	36	Louvet(2002)
GEM＋oxaliplatin	47	11	6.2	NA	Alberts(2003)
GEM＋epirubicin	44	25	10.9	23	Neri(2002)
GEM＋capecitabine	27	19	6.4	33	Hess(2003)
GEM＋capecitabine	41	17	9.5	NA	Scheithauer(2003)
GEM＋raltitrexed	25	12	6.2	12	Kralidis(2003)
GEM＋pemetrexed	42	15	6.5	29	Kindler(2002)
GEM＋trastuzumab	21	22	NA	NA	Safran(2001)
GEM＋cetuximab	41	12	7.1	32	Xiong(2004)
GEM＋bevacizumab	21	38	NA	54	Kindler(2003)

NA：not available, GEM：gemcitabine

表 3　進行膵癌に対する多剤併用療法と gemcitabine 単剤療法の比較試験(第 III 相試験)

治療法	症例数	奏効率(%)	P 値	生存期間中央値(月)	P 値	報告者
GEM＋5-FU	160	7	NS	6.7	0.09	Berlin(2002)
GEM	162	6		5.4		
GEM＋cisplatin	53	26	0.02	7.5	0.43	Colucci(2002)
GEM	44	9		5		
GEM＋cisplatin	98	10	NS	7.6	0.12	Heinemann(2003)
GEM	100	8		6		
GEM＋oxaliplatin	157	27	0.04	9	0.13	Louvet(2004)
GEM	156	17		7.1		
GEM＋irinotecan	173	16	<0.001	6.3	0.79	Rocha Lima(2004)
GEM	169	4		6.6		
GEM＋tipifarnib	341	6	NS	6.4	0.75	Van Cutsem(2004)
GEM	347	8		6.1		
GEM＋marimastat	120	11	NS	5.5	0.95	Bramhall(2002)
GEM	119	16		5.5		

NA：not available, GEM：gemcitabine

明らかな転移は認めないが，局所の切除が困難な膵癌を局所進行膵癌と呼ぶ．
局所進行膵癌に対しては，放射線化学療法が標準治療と考えられている．
放射線化学療法を受けた局所進行膵癌患者の MST は 10～12 ヵ月前後である．

表 4　局所進行膵癌に対する無作為化比較試験

放射線化学療法	コントロール	症例数	生存期間中央値（月）	P 値	報告者
40Gy＋5FU	放射線単独(40Gy)	64	10.4 vs 6.3	＜0.05	Moertel(1969)
40～60Gy＋5FU	放射線単独(60Gy)	194	10.1～10.6 vs 5.7	＜0.01	GITSG(1985)
40Gy＋5FU	化学療法単独(5FU)	91	8.3 vs 8.2	NS	ECOG(1985)
54Gy＋5FU	化学療法単独(SMF)	43	10.5 vs 8.0	0.02	GITSG(1988)

SMF：streptozotocin, mitomicin C, 5-FU, NS：not significant

かな遠隔転移を認めないが，局所への浸潤のために切除が困難な膵癌）を対象として行われている．局所進行膵癌の多くは，腹腔動脈や上腸間膜動脈などの主要な動脈への浸潤のために切除不能と判断された例である．明らかな遠隔転移を有する例では放射線療法を含む局所療法の延命効果は期待できず，化学療法が選択される．

2.　放射線療法の実際

局所進行膵癌に対しては，放射線化学療法と放射線療法，または放射線化学療法と化学療法とを比較した第 III 相試験がこれまでに 4 試験行われており，そのうち 1 試験を除く 3 試験において，放射線化学療法の MST がコントロール群の MST よりも有意に優れていた（表 4）．これらの成績に基づき現在では，放射線化学療法が局所進行膵癌に対する標準治療として位置づけられている．5-FU は膵癌に対して放射線化学療法を施行する際に最も用いられている抗癌剤であり最近は照射期間中持続静注で投与する方法が主流となっている．図 1 に当院で行っている放射線化学療法の方法を示す．5-FU 併用放射線化学療法の主な副作用は，食欲不振，悪心，嘔吐などの消化器症状が中心であり，その他，口内炎や下痢などを認めることがあるが，骨髄抑制は一般に軽度である．消化管潰瘍や穿孔はまれであるが，治療中および治療後は下血や腹痛の増強に注意する必要がある．放射線化学療法を受けた局所進行膵癌患者

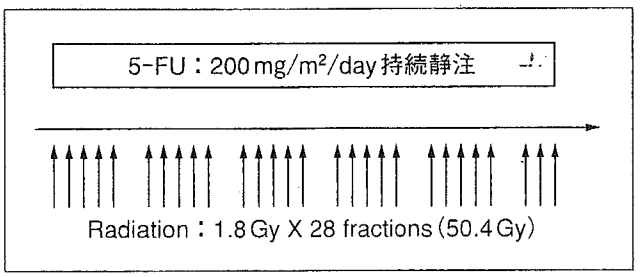

図 1　5-FU 持続静注併用放射線化学療法

の MST は 10～12 ヵ月とする報告が多い．

3.　新しい放射線療法

a.　GEM 併用放射線化学療法

5-FU 以外の抗癌剤としては cisplatin や paclitaxel が検討されているが良好な成績は得られていない．gemcitabine は進行膵癌に対して化学療法を行う際の第一選択薬であり，放射線増感作用をも有するため，放射線療法との併用に期待が集まり，多くの臨床試験が行われてきた．しかし，gemcitabine を併用した放射線化学療法は，従来の方法と比較して消化管毒性や骨髄抑制が強い傾向にあり，現時点では 5-FU 併用放射線化学療法を明らかに上回る評価は得られていない．当院で行った gemcitabine 併用放射線化学療法の MST は 9.5 ヵ月であった[5]．

b.　重粒子線

ブラッグピーク（Bragg peak）を有し，深部の癌組織に線量集中が可能である重粒子線治療は，

膵癌に対する放射線化学療法の際に広く使用されている抗癌剤は5-FUである．gemcitabineと放射線療法の併用は，消化管毒性や骨髄抑制に注意が必要である．日本では多施設共同試験を行うための環境整備が，今後必要である．

従来のX線に比べ相対的生物学的効果比が高く，膵癌のような放射線抵抗性腫瘍に対しても有効性が期待され，現在臨床試験が行われている．

おわりに

化学療法，放射線療法の進歩により，進行膵癌に対しても積極的に非切除療法を試みる機会が増えてきた．しかし，膵癌患者の予後は今なお不良であり，より優れた治療法の開発が求められている．そのためには新しい治療法の開発とともに，効率よく多施設が共同して臨床試験を実施するための環境を整備することがわが国では重要である．

文献

1) Burris, H. A. 3rd, Moore, M. J., Andersen, J. et al.：Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer：a randomized trial. J Clin Oncol **15**：2403-2413, 1997
2) Tempero, M., Plunkett, W., Van Haperen, V. R. et al.：Randomized phase II comparison of dose-intense gemcitabine：Thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol **21**：3402-3408, 2003
3) Ueno, H., Okusaka, T., Ikeda, M. et al.：An early phase II study of S-1 in patients with metastatic pancreatic cancer. Oncology in press
4) Berlin, J. D., Catalano, P., Thomas, J. P. et al.：Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma：Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol **20**：3270-3275, 2002
5) Okusaka, T., Ito, Y., Ueno, H. et al.：Phase II study of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer. Br J Cancer **91**：673-677, 2004

進行膵癌の化学療法—現状と将来*

上野 秀樹[1)] 奥坂 拓志

Key Words：膵癌，化学療法，ゲムシタビン

要旨 画像診断が発達した現在でも多くの膵癌は進行癌の状態で発見され，その予後は極めて不良である．膵癌患者の予後を改善するためには，早期診断技術の進歩とともに化学療法を含む非切除療法の向上が必要である．進行膵癌に対してはゲムシタビン(gemcitabine)が現在広く使用されているが，その効果には限界があり，さらに優れた治療法を求めて新規抗癌剤や多剤併用療法の開発が活発に行われている．本稿ではそれらの新しい化学療法の試みについて，最近の報告を中心に解説する．

消化器画像 2005；7：667-672

はじめに

本邦では年間約2万人が膵癌のために死亡しており，これは癌による死因の第5位を占めている．画像診断が進歩した現在でも大半の膵癌は進行癌の状態で発見されており，膵癌患者全体の5年生存率は5%未満と極めて不良である．したがって，膵癌患者の予後改善のためには，早期診断技術の進歩とともに化学療法を含めた非切除療法の向上が必要である．

膵癌に対しては従来5-fluorouracil(5-FU)を中心とした化学療法が行われてきたが，その治療成績は満足できるものでなかった．Burrisら[1)]は進行膵癌を対象にgemcitabine(GEM)と5-FUの無作為化比較試験(randomized controlled trial：RCT)を行い，GEM群のほうが5-FU群よりも明らかに症状緩和効果，および延命効果が優れていたことを1997年に報告した．この結果を受けて本邦でも進行膵癌に対するGEMの第I相試験が行われ，2001年4月に膵癌に対するGEMの保険適用が承認された．Burrisらの報告以降も，GEMの膵癌に対する効果と安全性は世界中で評価されており，GEMは現在，進行膵癌に対する第一選択の抗癌剤として広く認識されている．しかし，進行膵癌に対するGEMの効果には限界があり(奏効率5～15%，生存期間中央値(median survival time：MST)5～6か月前後)，さらに優れた治療法を求めてGEMを中心とした多剤併用療法や分子標的薬剤を含む新規抗癌剤の開発などが積極的に行われている．本稿ではそれらの新しい化学療法について，最近報告された臨床試験の成績を中心に解説する．

進行膵癌に対する化学療法

GEMの通常投与法よりもさらに優れた治療を開

* Chemotherapy for Advanced Pancreatic Cancer：Present and Future

1) 国立がんセンター中央病院肝胆膵内科(〒104-0045 東京都中央区築地5丁目1-1) Hideki UENO, Takuji OKUSAKA：Hepato-biliary-Pancreatic Oncology Division, National Cancer Center Hospital, *Tokyo*

表1　進行膵癌に対する単剤療法の治療成績(gemcitabine以外)

抗癌剤	報告者	症例数	奏効率(%)	MST(月)	文献
5-FU＋Leucovorin	Rijswijk ら	37	9	4.4	Eur J Cancer 2004
5-FU＋Eniluracil	Rothenberg ら	58	8	3.6	Ann Oncol 2002
Capecitabine	Cartwright ら	42	10	6.1	J Clin Oncol 2002
S-1	Ueno ら	19	21	5.6	Oncology 2005
S-1	Furuse ら	41	37.5	8.8	ASCO 2005
Raltitrexed	Pazdur ら	42	5	NA	Invest New Drug 1996
Pemetrexed	Miller ら	42	6	6.5	Ann Oncol 2000
Oxaliplatin	Ducreux ら	17	0	3.4	Ann Oncol 2004
Paclitaxel	Gebbia ら	14	0	7.2	Eur J Cancer 1996
Docetaxel	Okada ら	21	0	3.9	Br J Cancer 1999
Docetaxel	Rougier ら	40	15	7.0	Eur J Cancer 2000
Topotecan	O'Reilly ら	27	0	4.1	Anti-Cancer Drug 1996
Topotecan	Scher ら	35	10	4.4	Invest New Drug 1996
Irinotecan	Wagener ら	34	9	5.2	Ann Oncol 1995
Irinotecan	Funakoshi ら	37	27	7.3	ASCO 2004
Exatecan	Cheverton ら	169	0.6	5.0	ASCO 2004
Marimastat	Bramhall ら	102	3	4.2	J Clin Oncol 2001
BAY 12-9566	Moore ら	138	1	3.7	J Clin Oncol 2003
Tipifarnib	Cohen ら	20	0	4.6	J Clin Oncol 2003

MST：生存期間中央値，NA：not available　　(作用機序順)

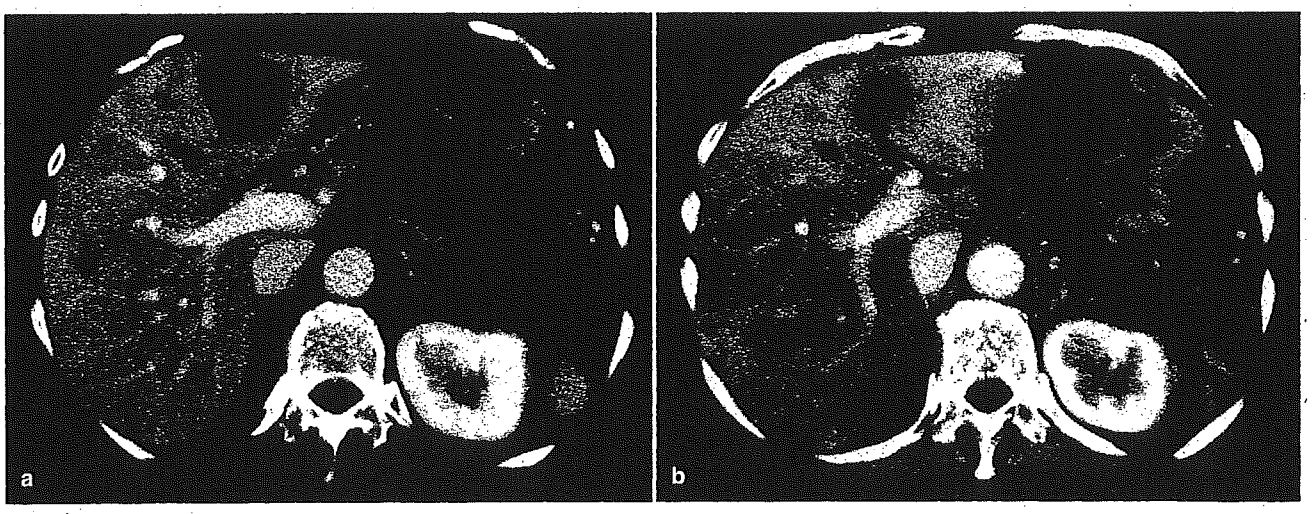

図1　S-1奏効例
a. 治療前，b. 3コース後
S-1　3コース施行後，膵原発，肝転移ともに著明に縮小し，臨床症状の改善を認めた．

発するために，①GEMの投与方法の工夫，②新規抗癌剤の開発，③多剤併用療法の開発，などが進行膵癌に対して試みられている．これらは独立した存在ではなく，オーバーラップした治療法も開発されている．また，GEM不応例に対するセカンドライン治療の開発も最近の重要な課題であり，徐々に報

告が増えている．

1. GEMの投与方法の工夫

静脈内へ投与されたGEMは細胞内でリン酸化され，gemcitabine triphosphateとなって抗腫瘍効果を発揮する．GEMは1,000 mg/m²を30分かけて投与する方法が一般的だが，GEMを10 mg/m²/分の速度で投与する方法(定速静注法：fixed dose rate infusion)では，より効率的にGEMがリン酸化されることが基礎研究で報告された．Temperoら[2]は，定速静注法(1,500 mg/m²/150分，週1回×3週投与後1週休薬)と30分の投与法(2,200 mg/m²/30分，2週に1回投与)との無作為化比較第II相試験を行い，定速静注法の方がMSTおよび1年生存率が優れていたことを報告した．さらに現在，この定速静注法がGEMの標準的な投与法になり得るかについて，米国で第III相試験が行われている(ECOG 6201)．

2. 新規抗癌剤の開発

最近報告された膵癌に対するGEM以外の抗癌剤の成績を示す(表1)．Docetaxelは開発当初比較的良好な奏効率が膵癌に対して報告されたが，その後の追試では効果が確認されなかった．Topoisomerase I阻害剤のirinotecanは，わが国で行われた膵癌遠隔転移例に対する第II相試験で，奏効率27%，生存期間中央値7.3か月の良好な成績を示した[3]が，irinotecanが膵癌患者の延命に寄与するかは明らかになっていない．新しいtopoisomerase I阻害剤であるexatecanに関しては，進行膵癌患者を対象にexatecan vs. GEMのRCTが行われたが，exatecan群のMSTが5.0か月，GEM群のMSTが6.5か月でGEM単剤を上回ることはできなかった[4]．経口のフッ化ピリミジン系抗癌剤のcapecitabineは欧米中心に開発が進められており，進行膵癌に対する第II相試験の奏効率は10%であったが，24%に症状の改善が認められた[5]．また，わが国で開発された経口のフッ化ピリミジン系抗癌剤のS-1に関しては，膵癌遠隔転移例に対する後期第II相試験で37.5% (15/40)の奏効率と8.8か月のMSTが報告され，注目されている[6]．S-1が奏効した膵癌，肝転移症例のCT像を示す(図1)．

分子標的治療は現在最も脚光を浴びている分野であり，様々な作用機序を有する薬剤が膵癌に対して

表2　第III相試験の結果(gemcitabine単剤 vs. gemcitabine併用)

併用薬剤	報告者	症例数		奏効率(%)			MST(月)			文献
		GEM単剤	GEM併用	GEM単剤	GEM併用	P値	GEM単剤	GEM併用	P値	
5-FU	Berlinら[9]	162	160	5.6	6.9	NS	5.4	6.7	0.09	J Clin Oncol 2002
5-FU＋Leucovorin	Riessら[10]	238	235	7.2	4.8	NS	6.2	5.9	0.68	ASCO 2005
Capecitabine	Herrmannら[11]	159	160	7.9	10.1	NS	7.3	8.4	0.31	ASCO 2005
Pemetrexted	Richardsら[14]	282	283	7.1	14.8	0.004	6.3	6.2	0.85	ASCO 2004
Cisplatin	Colucciら[12]	54	53	9.2	26.4	0.02	5.0	7.5	0.43	Cancer 2002
Cisplatin	Heinemannら	100	98	8.0	10.2	NS	6.0	7.6	0.12	ASCO 2003
Oxaliplatin	Louvetら[15]	163	163	17.3	26.8	0.04	7.1	9.0	0.13	J Clin Oncol 2005
Irinotecan	Rocha Limaら[13]	180	180	4.4	16.1	＜0.001	6.6	6.3	0.79	J Clin Oncol 2004
Exatecan	O'Reillyら	174	175	7.1	8.2	NS	6.2	6.7	0.52	ASCO 2004
Marimastat	Bramhallら[16]	119	120	16	11	NS	5.4	5.4	0.95	Br J Cancer 2002
Tipifarnib	Van Cutsemら[17]	347	341	8	6	NS	6.0	6.3	0.75	J Clin Oncol 2004
Erlotinib	Mooreら	284	285	8.0	8.6	NS	5.9	6.4	0.025	ASCO 2005

MST：生存期間中央値，GEM：gemcitabine，NS：not significant

表3　Gemcitabine不応例に対するセカンドライン治療の成績

治療法	報告者	症例数	奏効率(%)	MST(月)	文献
Irinotecan＋Raltitrexed	Ulrich-Pur ら	19	16	6.5	Br J Cancer 2003
MMC＋Docetaxel＋Irinotecan	Reni ら	15	0	6.1	Cancer Invest 2004
Irinotecan＋Oxaliplatin	Cantore ら	30	10	5.9	Oncology 2004
Oxaliplatin	Androulakis ら	18	0	NA	Cancer Invest 2005
GEM＋Oxaliplatin	Van Laethem ら	33	23	4	ASCO 2004
Raltitrexed＋Oxaliplatin	Reni ら	38	24	NA	ASCO 2005
Capecitabine＋Erlotinib	Blaszkowsky ら	30	11	5.7	ASCO 2005
5-FU＋Leucovorin＋Oxaliplatin	Oettle ら	23	NA	4.8	ASCO 2005

MST：生存期間中央値，NA：not available

試みられている．Marimastat や BAY12-9566 は，細胞外 matrix を分解する酵素である matrix metalloproteinase を阻害し，癌の発育を抑制することが期待されて開発された薬剤である．また，膵癌に K-ras の突然変異が高率にみられることに着目し，ras 蛋白の機能発現に必要な farnesyl 化を抑制する farnesyl transferase 阻害剤(tipifarnib)も試みられている．さらに，上皮成長因子受容体(epidermal growth factor receptor：ECFR)のモノクローナル抗体である cetuximab や選択的 EGFR チロシンキナーゼ阻害剤の erlotinib，血管内皮細胞成長因子(vascular endothelial growth factor：VEGF)阻害剤の bevacizumab などの分子標的薬剤についても臨床試験が進んでいる．これらのうち，marimastat と BAY 12-9566 は，それぞれ GEM 単独との間で第 III 相試験が行われたが，何れの試験においても GEM 単剤を上回る成績は得られなかった[7, 8]．

3. 多剤併用療法の開発

GEM は毒性が比較的軽度であることから他の抗癌剤と併用しやすく，GEM を含めた併用療法は膵癌に対する新しい治療開発の中心的存在となっている．最近では大規模な第 III 相試験も膵癌に対して行われており，結果が相次いで報告されている(表2)：

5-FU は古くから膵癌に対して使用されてきた抗癌剤であり，bolus injection，continuous infusion，leucovorin との併用，など様々な方法を用いて GEM との併用が試みられてきた．しかし，Berlin ら[9]が行った GEM と 5-FU bolus injection との併用療法と GEM 単独療法との RCT では，MST が併用群 6.7 か月，GEM 単独群 5.4 か月で有意差を認めなかった．また，GEM に 5-FU と leucovorin を併用したレジメンの RCT も行われたが，併用群の MST は 5.85 か月，GEM 単独群の MST は 6.2 か月で差を認めなかった[10]．最近では，5-FU のプロドラッグである capecitabine と GEM の併用療法の RCT が行われ，全身状態が良好な(KPS 90-100)群では MST が併用群 10.1 か月，GEM 単独群 7.5 か月と有意差($p = 0.024$)を認めたものの，KPS60-80 の患者も含めた全例での解析では有意差は認めなかった[11]．Cisplatin も GEM と相乗効果を有することから併用の効果が期待されたが，Colucci ら[12]が行った RCT では，GEM + cisplatin 群の方が GEM 単独群よりも奏効率や無増悪生存期間は優れていたものの，生存期間の有意な延長は認めなかった．同様に，irinotecan や pemetrexed に関しても，併用群のほうが GEM 単独よりも優れた奏効率を示したものの，生存期間の延長には寄与しなかった[13, 14]．新しい白金製剤である oxaliplatin と定速静注の GEM を併用した Louvet ら[15]の報告では，併用群のほうが奏効率と無増悪生存期間が有意に優れており期待されたが，生存期間では有意差が認められなかった(MST9.0 か月 vs. 7.1 か月，$p = 0.025$)．GEM と oxaliplatin の併用療法に関しては現在米国でも第 III 相試験が行われており(ECOG 6201)，その報告が待たれている．

分子標的薬剤では，marimastat や tipifarnib と GEM の併用療法の第 III 相試験が行われたが，GEM 単独療法との間に生存期間の差を認めなかった[16, 17]．一方，2005 年の米国腫瘍学会(ASCO)では，EGFR チロシンキナーゼ阻害剤の erlotinib と GEM の併用療法

がGEM単剤療法よりも有意に生存期間を延長したことが報告され注目を集めた．しかし，その差は小さく(MST6.4か月 vs. 5.9か月，$p = 0.025$)，本併用療法に関してはさらなる評価が必要と考えられている．その他，cetuximabやbevacizumabなどの併用療法の臨床試験が現在進行中である．

4. セカンドライン化学療法

GEM登場後，膵癌に対して化学療法が積極的に行われるようになったため，それに伴ってGEM不応例に対する二次治療の重要性が増している．最近報告された臨床試験の結果を表3に示す．CPT-11，raltitrexed，oxaliplatin，capecitabineなどの比較的新しい抗癌剤を組み合わせたレジメンが多く試みられている．2005年のASCOではoxaliplatinと5-FU，leucovorinの併用療法とbest supportive careの比較試験が行われ，二次治療開始からの生存期間は併用群の方が有意に優れていたことが報告された(MST 21週 vs. 10週，$p = 0.0077$)[18]．現時点でGEM不応例に対するセカンドラインの標準治療は確立していないが，今後この分野でも研究が発展することが期待されている．

おわりに

GEMの登場により，膵癌にする化学療法は大きな変貌を遂げており，最近では大規模な試験の結果も相次いで報告されている．2005年には，初めてGEM単独投与よりも有意差をもって生存期間が優れていた治療(GEM + erlotinib)が報告された．分子標的薬剤を含む医学の進歩は目覚しく，今後より優れた治療が開発されることを期待したい．

文　献

1) Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer : a randomized trial. J Clin Oncol 1997 ; 15 : 2403-2413
2) Tempero M, Plunkett W, Van Haperen VR, et al. Randomized phase II comparison of dose-intense gemcitabine : Thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 2003 ; 21 : 3402-3408
3) Funakoshi A, Okusaka T, Ishii H, et al. Phase II study of irinotecan (CPT-11) alone in Patients (pts) with metastatic pancreatic cancer [abstract]. Proc ASCO 2004 ; 23 : # 4102
4) Cheverton P, Friess H, Andras C, et al. Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naïve patients with advanced pancreatic cancer (APC) [abstract]. Proc ASCO 2004 ; 23 : # 4005
5) Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 2002 ; 20 : 160-164
6) Furuse J, Okusaka T, Funakoshi A, et al. A phase II study of S-1 in patients with metastatic pancreatic cancer [abstract]. Proc ASCO 2005 : # 4104
7) Bramhall SR, Rosemurgy A, Brown PD, et al. Marimastat Pancreatic Cancer Study Group. Marimastat as first-line therapy for patients with unresectable pancreatic cancer : a randomized trial. J Clin Oncol 2001 ; 19 : 3447-3455
8) Moore MJ, Hamm J, Dancey J, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas : a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2003 ; 21 : 3296-3302
9) Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma : Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 2002 ; 20 : 3270-3275
10) Riess H, Helm A, Niedergethmann M, et al. A randomized, prospective, multicenter, phase III trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs. gemcitabine alone in patients with advanced pancreatic cancer [abstract]. J Clin Oncol 2005 ; 23 : 2005 ASCO Annual Meeting Proceedings # 4009
11) Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine (G) plus capecitabine (C) versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group. Proc ASCO 2005 : # 4010
12) Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and / or metastatic pancreatic carcinoma : a prospective, randomized phase III study of the Gruppo Oncologia dell' Italia Meridionale. Cancer 2002 ; 94 : 902-910
13) Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004 ; 22 : 3776-3783
14) Richards DA, Kindler HL, Oettle H, et al. A randomized phase III study comparing gemcitabine + pemetrexed versus gemcitabine in patients with locally advanced and metastatic pancreas cancer [abstract]. Proc ASCO 2004 ; 23 : # 4007
15) Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer : results of a GERCOR and GISCAD phase III trial. J Clin Oncol

2005 ; 23 : 3509-3516
16) Bramhall SR, Schulz J, Nemunaitis J, et al. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. Br J Cancer 2002 ; 87 : 161-167
17) Van Cutsem E, Van de Velde H, Karasek P, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol 2004 ; 22 : 1430-1438
18) Oettle H, Pelzer U, Stieler J, et al. Oxaliplatin / folinic acid / 5-fluorouracil [24h] (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine refractory advanced pancreatic cancer (CONKO 003) [abstract]. Proc ASCO 2005 : # 4031

書評

山口幸二　田中雅夫　著
外科臨床と病理よりみた 小膵癌アトラス

白鳥敬子（東京女子医科大学教授 消化器内科）

膵癌で死亡する患者数は年間2万人，男女とも癌死亡率の第5位を占めるようになった．近年，胃癌や大腸癌の死亡率がかなり低下してきているのに比べ，膵癌だけは罹患率と死亡率がいまだに同じであり，膵癌が治癒してないことがわかる．膵癌全国登録調査（日本膵臓学会）によれば膵癌切除例の5年生存率は約13%に過ぎないが，2 cm以内の小膵癌で切除されれば約30%に向上する．しかし，小膵癌の症例数は全膵癌症例の6%（87例）（1999年度全国調査）に過ぎず極めて少ないのが現実である．したがって，膵癌の治療成績をあげる近道は，小膵癌をいかに早く発見するかにかかっているといっても過言ではない．

本書は，長年，膵疾患の研究，外科診療に取り組んでこられた九大臨床・腫瘍外科，山口幸二先生と田中雅夫先生が共著で出版された．小膵癌だけに焦点をあてたtextbookは今までになく，本書が初めてと思われる．例数が限られる中，小膵癌35症例を集積されアトラスとして一挙にまとめられたことに心から敬意を表したい．折しも昨年来，日本膵臓学会主導で田中雅夫先生を委員長として「エビデンスに基づいた膵癌診療ガイドライン」が作成されつつある．山口先生も事務局幹事として取りまとめ役をされており，膵癌診療のエキスパートだからこそ書けた小膵癌アトラスであるといえる．また，本書の特徴として英文による写真説明と症例解説が付記され，外国人も読者の対象としている．国際的にも広く活躍されている著者ならではの企画であろう．

本書では，小膵癌の豊富な経験例の中から選ばれた35例について，病歴，検査成績，各種画像，そして切除標本の写真，シェーマ，病理までを簡潔にまとめている．各章のネーミングにも工夫がされており，「糖尿病と小膵癌」，「膵炎と小膵癌」，「背部痛と小膵癌」，「黄疸と小膵癌」などのように，日常診療でみられる疾患や症状が小膵癌の発見につながることを読者に伝えたいという著者の気持ちがよく表れている．提示された症例から，小膵癌発見の最前線に立っているのは高次医療施設の膵臓専門医よりも，むしろ地域医療，プライマリ診療，一般内科に携わる医師たちであることがわかる．その意味で，本書は広く消化器領域以外の先生がたにも推薦したい一冊である．内容は疾患解説→症例提示→問題点の順に構成され，消化器医でなくとも大変わかりやすい．

小膵癌の発見は容易ではないように思われているが，提示された症例を読むと膵癌検出のきっかけの多くが腹部超音波検査であることがわかる．腫瘍マーカーなどはほとんどが正常値である．日常診療で疑わしい患者さんを腹部超音波検査へ早く導くことが，小膵癌の最初の検出になるのかもしれない．小膵癌の知識と認識を少しでも広げることが，早期発見率の上昇と膵癌全体の治療成績を向上させることにつながるのであり，本書の果たす大きな役割に期待したい．

A4・184頁・定価15,750円（本体15,000円＋税5%）
2005年　[ISBN4-260-12267-3]　医学書院刊

Jpn J Clin Oncol 2005;35(12)733–738
doi:10.1093/jjco/hyi190

Phase I Study of Fixed Dose Rate Infusion of Gemcitabine in Patients with Unresectable Pancreatic Cancer

Junji Furuse[1], Hiroshi Ishii[1], Takuji Okusaka[2], Michitaka Nagase[1], Kohei Nakachi[1], Hideki Ueno[2], Masafumi Ikeda[2], Chigusa Morizane[2] and Masahiro Yoshino[1]

[1]Division of Hepatobiliary and Pancreatic Medical Oncology, National Cancer Center Hospital East, Kashiwa, Chiba and [2]Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan

Received July 20, 2005; accepted September 24, 2005; published online November 22, 2005

Objective: The purpose of this study was to determine the feasible dose of gemcitabine when administered as a fixed dose rate infusion (10 mg/m^2/min) on a weekly schedule to Japanese patients with unresectable advanced pancreatic cancer.
Methods: Patients were required to have histologically or cytologically proven locally advanced or metastatic pancreatic cancer for which they had received no previous chemotherapy. Gemcitabine was administered intravenously weekly for three consecutive weeks every 4 weeks. Patients at three dose levels were scheduled to receive escalating doses of gemcitabine: 1000 mg/m^2 over 100 min (Level 1), 1200 mg/m^2 over 120 min (Level 2) and 1500 mg/m^2 over 150 min (Level 3).
Results: A total of 16 patients were enrolled in this study between December 2003 and September 2004. Maximum-tolerated dose was not reached during the first course. Dose-limiting toxicity was Grade 4 neutropenia. Grade 3 or 4 neutropenia was observed at Level 3 in all six patients in the first course, and administration of gemcitabine on Day 8 or 15 was skipped in all six patients. Non-hematologic toxicity was mild and the most common symptoms were anorexia, nausea and vomiting. Partial response was achieved in 1 of the 17 patients (7%). Median overall survival was 7.3 months.
Conclusions: Gemcitabine administered at a rate of 10 mg/m^2/min was tolerated up to 1500 mg/m^2, but 1200 mg/m^2 represented a more appropriate recommended dose in further studies owing to neutropenia in Japanese patients with advanced pancreatic cancer.

Key words: advanced pancreatic cancer – systemic chemotherapy – gemcitabine – fixed dose rate infusion

INTRODUCTION

Pancreatic cancer is the fifth most common cause of cancer death in Japan, with an estimated 19 000 deaths annually (1). Early-stage diagnosis of pancreatic cancer is difficult because of the lack of specific early symptoms, and surgery with curative intent can be performed in only 5–20% of patients (2). The prognosis for unresectable pancreatic cancer remains extremely poor.

Gemcitabine (2′,2′-difluorodeoxycytidine) is a novel pyrimidine antimetabolite with a broad spectrum of antitumor activity against various solid tumors, such as pancreatic and lung cancer (3). This prodrug is initially phosphorylated by deoxycytidine kinase to gemcitabine monophosphate, with subsequent phosphorylation steps yielding gemcitabine di- and triphosphate (4). Gemcitabine triphosphate inhibits DNA synthesis by competing with deoxycytidine triphosphate for incorporation into DNA by DNA polymerase (5). A dose of 790 mg/m^2 gemcitabine weekly for 3 weeks every 28 days was recommended for Phase II studies on the basis of a Phase I study in which gemcitabine was administered as a once-weekly 30 min bolus infusion (6). This dosing schedule was used in subsequent Phases II and III studies, and once-weekly 30 min infusion of the 1000 mg/m^2 dose was subsequently selected as the standard schedule (7,8). In a randomized clinical trial, gemcitabine was confirmed to provide a survival advantage over 5-FU in addition to symptom-relieving benefits in patients with advanced pancreatic cancer (8). Based on these results, gemcitabine has generally been accepted as the standard chemotherapeutic agent for advanced pancreatic cancer. However, the advantages in terms of survival rate are inadequate, and various chemotherapeutic regimens have been investigated in clinical studies in efforts to prolong survival.

For reprints and all correspondence: Junji Furuse, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.
E-mail: jfuruse@east.ncc.go.jp

The cellular pharmacokinetics of the active metabolite, gemcitabine triphosphate, in mononuclear cells have been examined in previous studies, and the rate of gemcitabine triphosphate accumulation and peak intracellular concentration were highest at a dose rate of 350 mg/m^2 over 30 min, during which steady-state gemcitabine levels of 15–20 μmol/l were achieved in plasma (6,9). A dose ~10 mg/m^2/min that achieves plasma gemcitabine concentrations of 15–20 μmol/l would thus maximize the intracellular rate of accumulation for gemcitabine triphosphate. This schedule of gemcitabine administration, with fixed dose rate (FDR) infusion of 10 mg/m^2/min, would enable exposure to higher concentrations of gemcitabine, and should improve clinical efficacy.

Phase I studies of FDR infusion of gemcitabine in the United States recommended a Phase II dose of 1500 mg/m^2 (10,11). A subsequent randomized Phase II trial comparing this FDR gemcitabine infusion schedule and high-dose gemcitabine (2200 mg/m^2) using a standard 30 min infusion showed improved median survival time for the FDR arm (12). The FDR infusion schedule is expected to become the optimal method of gemcitabine administration, but has not previously been assessed in Japan. We, therefore, conducted a Phase I study to determine whether FDR infusion of gemcitabine would be tolerated in Japanese patients with unresectable advanced pancreatic cancer. The primary objectives of this study were to confirm whether the recommended dose in the United States, 1500 mg/m^2 over 150 min, would be feasible in Japanese patients and to determine the relationship between dose and toxicity for gemcitabine administered using the FDR infusion schedule. The secondary objective was to evaluate antitumor activity of the schedule.

PATIENTS AND METHODS

Patients Eligibility

Eligibility criteria for enrollment in the study were as follows: (i) histologically confirmed pancreatic ductal adenocarcinoma; (ii) unresectable locally advanced or metastatic disease; (iii) no previous treatment for pancreatic cancer except surgery; (iv) age ≥20 and ≤74 years old; (v) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (vi) adequate bone marrow (leukocyte count ≥4000 cells/mm^3, platelet count ≥100 000 cells/mm^3 and hemoglobin ≥9.0 g/dl), renal function (serum creatinine concentration ≤upper limit of normal) and hepatic function (serum bilirubin level ≤2.0 mg/dl, serum albumin level ≥3.0 g/dl, serum aspartate and alanine transaminase (AST and ALT) levels ≤2.5 times upper limit of normal); (vii) life expectancy ≥8 weeks; and (viii) written informed consent from the patient. Percutaneous biliary drainage was performed in patients with obstructive jaundice, and these patients were required to have serum bilirubin levels of ≤2.0 mg/dl and serum AST and ALT levels ≤5 times the upper limit of normal before enrollment. Exclusion criteria comprised serious complications such as active infection, active gastrointestinal ulcer, cardiac disease or renal disease; central nervous system metastasis; marked pleural effusion or ascites; symptomatic interstitial pneumonitis; and pregnancy or lactation for women. This protocol was approved by the National Cancer Center's institutional review board for clinical investigation.

Treatment Methods

Gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) was administrated intravenously at 10 mg/m^2/min, weekly, for three consecutive weeks, followed by a week of rest. This cycle was continued until disease progression or serious adverse effects developed or until the patient requested discontinuation. When patients developed leukopenia of <2000/mm^3, neutropenia of <1000/mm^3, thrombocytopenia of <70 000/mm^3, total bilirubin >2.0 mg/dl or AST and ALT levels >5 times the upper limit of normal, gemcitabine administration was suspended until the patient recovered. If a rest period of >4 weeks was required owing to toxicity, the patient was withdrawn from the study.

Study Designs

Patients at three dose levels were scheduled to receive escalating dose of gemcitabine. At the first dose level (Level 1), gemcitabine was administered at a dose of 1000 mg/m^2. The dose level was increased to 1200 mg/m^2 for Level 2 and 1500 mg/m^2 for Level 3. Patient cohorts had a minimum of three patients at each level. If no dose-limiting toxicity (DLT) was observed in the initial three patients during the first cycle of treatment, the dose was advanced to the next level. If DLT occurred in the initial three patients, three additional patients were studied at the same dose level. If two or more of these six patients experienced DLT at that level, the dose was escalated to the next level. The maximum-tolerated dose (MTD) was defined as the highest dose level at which more than two of the six patients experienced DLT during the first cycle of treatment. If DLT occurred in three patients at Level 1, the dose was reduced to 800 mg/m^2 (Level 0). DLT was defined as follows: (i) Grade 4 leukopenia or neutropenia; (ii) febrile neutropenia; (iii) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring transfusion; (iv) ≥Grade e 3 non-hematological toxicity with the exception of nausea, vomiting, anorexia, fatigue and constipation; and (v) any toxicity requiring two consecutive skips of administration or a >4 week delay in treatment. Toxicity was graded according to the National Cancer Institute common toxicity criteria version 2.0.

Clinical Assessments

Physical examination, complete blood cell counts, serum chemistries and urinalysis were performed at baseline and at least once weekly after initiating treatment. Patients underwent dynamic computed tomography (CT) to evaluate response at 4–8 week intervals after start of treatment. CT was performed by obtaining contiguous transverse sections using the helical scanning method at a section thickness of 5 mm. Tumor response was assessed according to the World Health Organization criteria (13). Serum carbohydrate antigen (CA)19-9

levels were measured monthly by immunoradiometric assay. Progression-free survival was calculated from the first day of treatment until evidence of tumor progression, clinical progression or death owing to any cause. Overall survival was calculated from the first day of treatment until death owing to any cause. Survival data were analysed using the Kaplan–Meier method.

RESULTS

PATIENT CHARACTERISTICS

Between December 2003 and September 2004, a total of 16 patients were enrolled in this study. Dose escalation schedule and the number of patients at each level are shown in Table 1. The first administration of 1200 mg/m^2 of gemcitabine in one patient receiving Level 2 was later found to have been infused over 90 min, departing from the FDR of 10 mg/m^2/min. As a result, an additional patient was added to Level 2 and ultimately seven patients were treated at Level 2. Patient characteristics are shown in Table 2. The 16 patients received 60 courses of gemcitabine. Median number of courses administered per patient was 3 (range 1–9 courses). All 16 patients were evaluable for toxicity, but the Level 2 patient not infused with gemcitabine at a rate of 10 mg/m^2/min was excluded from the evaluation of DLT.

TOXICITY

Toxicities of the 15 patients evaluated for DLT during the first course are shown in Table 3. The first three patients enrolled on Levels 1 and 2 did not experience any DLT, but one of the six patients at Level 3 experienced DLT. MTD was not reached in this study. However, since all six patients at Level 3 (1500 mg/m^2 over 150 min) experienced Grade 3 or 4 neutropenia after Day 1 or 8 of the first course and did not receive the second or third dose of gemcitabine, an additional three patients were entered at Level 2 to accurately determine the recommended FDR for gemcitabine. Finally, no Grade 4 hematological toxicity was observed in any of the six patients at Level 2, and Grade 3 neutropenia developed in three of these patients. While five of the six patients received the full three doses of gemcitabine in the first course, the remaining patient did not receive the third dose owing to Grade 3 neutropenia. Level 2 (1200 mg/m^2) was therefore selected as the recommended dose for further studies of this FDR gemcitabine regimen in Japan.

Table 1. Dose escalation scheme

Dose levels	Gemcitabine (mg/m^2/wk)	Infusion time (min)	*n*
1	1000	100	3
2	1200	120	7
3	1500	150	6

Table 2. Patient characteristics

Variable	No. of patients (n = 16)
Gender	
Male	7
Female	9
Median age (range)	62 (47–74) years
ECOG performance status	
0	11
1	4
2	1
Disease stage	
Locally advanced	3
Metastatic	13
Site of metastatic disease	
Liver	10
Lung	3
Distant lymph nodes	2
CA19-9 before treatment (U/ml)	
≤37	4
>37, ≤1000	6
>1000	6

ECOG, Eastern Cooperative Oncology Group; CA19-9, carbohydrate antigen 19–9.

Table 3. Toxicities across first course by patient

	Dose levels											
	Level 1 (n = 3)				Level 2 (n = 6)				Level 3 (n = 6)			
	Grades				Grades				Grades			
	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	0	0	2	0	3	1	2	0	0	2	4	0
Neutropenia	0	0	2	0	1	2	3	0	0	0	5	1
Anemia	1	1	2	0	2	3	0	0	4	2	0	0
Thrombocytopenia	1	2	0	0	2	0	1	0	0	2	1	0
Anorexia	1	1	0	0	2	0	1	0	2	2	0	0
Nausea	1	1	0	0	1	0	1	0	4	1	0	0
Vomiting	0	1	0	0	0	0	1	0	1	1	0	0
Rash	0	0	0	0	2	2	0	0	1	3	0	0
Fatigue	2	0	0	0	2	0	0	0	0	1	0	0
Fever	0	1	0	0	0	0	0	0	1	0	0	0
Mucositis	0	1	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	1	0	0	0
AST, ALT elevation	0	1	0	0	1	1	0	0	0	1	0	0

AST, serum aspartate transaminase; ALT, serum alanine transaminase.

Toxicities throughout the entire period of this protocol were assessed in all 16 patients enrolled in this study (Table 4). The most common toxicity was leukopenia, particularly neutropenia, with 13 of the 16 patients (81%) developing Grade 3 or 4

Table 4. Toxicities during entire course by patient

	Dose levels											
	Level 1 (n = 3)				Level 2 (n = 7)				Level 3 (n = 6)			
	Grades				Grades				Grades			
	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	0	0	2	0	2	2	3	0	0	1	4	1
Neutropenia	0	0	2	0	1	1	5	0	0	0	3	3
Anemia	1	0	2	0	1	5	1	0	3	2	1	0
Thrombocytopenia	1	2	0	0	2	1	1	0	0	2	2	0
Anorexia	1	0	1	0	4	0	1	0	4	2	0	0
Nausea	1	0	1	0	4	0	1	0	5	1	0	0
Vomiting	0	0	1	0	2	0	1	0	1	1	0	0
Constipation	0	0	0	0	0	1	0	0	1	0	0	0
Diarrhea	0	0	0	0	1	0	0	0	0	0	0	0
Rash	0	0	0	0	3	2	0	0	1	2	0	0
Fatigue	1	1	0	0	2	0	0	0	0	1	0	0
Fever	0	1	0	0	0	0	0	0	2	0	0	0
Mucositis	0	1	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	1	1	0	0	3	0	0	0
AST, ALT elevation	0	1	0	0	1	1	0	0	0	1	0	0

AST, serum aspartate transaminase; ALT, serum alanine transaminase.

neutropenia during treatment. Non-hematological toxicities were generally mild at all levels, and one patient developed Grade 3 nausea, vomiting, and anorexia at Level 1 and Level 2, respectively. Skin rashes were mild, but tended to occur in a larger number of patients as the dose was escalated.

Tumor Response and Survival

Partial response was achieved in 1 of the 16 patients (6.3%), but no complete responses were observed. Overall response rate was thus 6.3% (95% confidence interval = 0.2–30.2%). No change was noted in 12 patients (75.0%), and progressive disease was in two patients (12.5%). The patient with DLT was not evaluated for tumor response because she received standard gemcitabine chemotherapy as second-line chemotherapy before the evaluation. Serum CA19-9 levels were reduced to >50% in 2 of the 12 patients (16.7%) in whom pretreatment level was elevated to above the upper limit of normal.

Disease progression was finally observed in all patients and 12 of the 16 patients died of disease progression. Median progression-free survival was 3.2 months, and overall median survival time (MST) was 7.3 months (Figs 1 and 2).

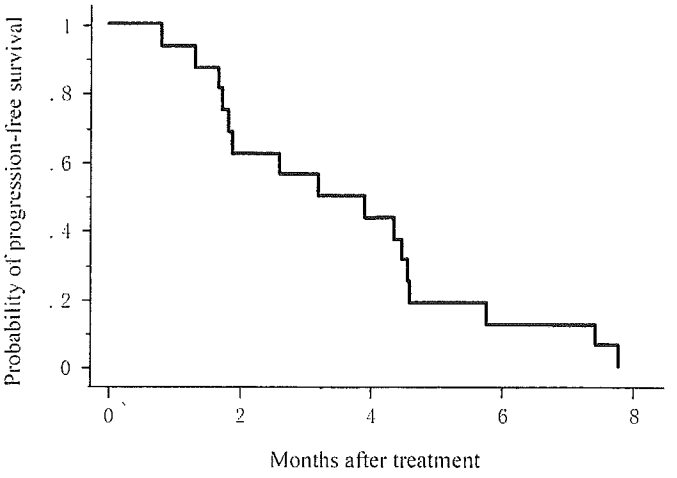

Figure 1. Progression-free survival of all 16 patients.

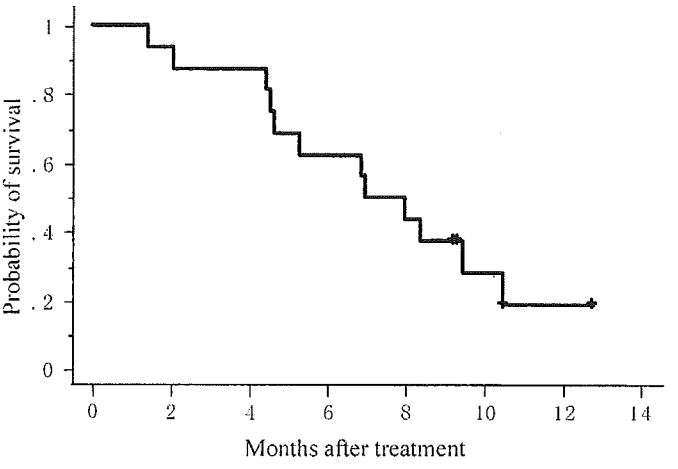

Figure 2. Overall survival of all 16 patients.

DISCUSSION

Gemcitabine is a prodrug that requires initial intracellular phosphorylation by deoxycytidine kinase, ultimately undergoing phosphorylation to the active gemcitabine triphosphate, a cytotoxic agent that inhibits DNA synthesis. Tempero et al. (12) reported on intracellular concentrations of gemcitabine triphosphate in peripheral blood mononuclear cells in a randomized trial comparing FDR infusion over 150 min and high-dose gemcitabine (2200 mg/m^2) using a standard 30 min infusion. The rate of gemcitabine triphosphate accumulation in patients who received conventional infusion decreased markedly after the end of infusion (30 min), whereas patients who received gemcitabine as FDR infusion exhibited linear accumulation of the triphosphate throughout the infusion. Intracellular gemcitabine triphosphate concentration in the FDR arm was 2-fold higher than that in the conventional infusion arm.

In the United States, two Phase I studies have been performed to determine the recommended dose for FDR infusion of gemcitabine (10,11). Brand et al. (11) conducted a Phase I study at dose levels of 1200 mg/m^2, 1500 mg/m^2 and 1800 mg/m^2, administered on Days 1, 8 and 15 of a 28 day cycle. MTD was defined as 1500 mg/m^2, with granulocytopenia and thrombocytopenia representing the DLTs. Brand et al. concluded that myelosuppression was more severe than

anticipated based on previous reports regarding standard gemcitabine administration. Touroutoglou et al. (10) conducted the other Phase I study of FDR infusion of gemcitabine in which the weekly dose was escalated from 1200 to 2800 mg/m^2 for 3 weeks every 4 weeks. They reported that MTD was 1800 mg/m^2, and recommended a Phase II starting dose of 1500 mg/m^2 owing to myelosuppressive effects.

The present study evaluated the safety of FDR infusion of gemcitabine and identified the feasible dose for Japanese patients with unresectable advanced pancreatic cancer. This Phase I study was conducted using dose levels of 1000, 1200 and 1500 mg/m^2, administered on Days 1, 8 and 15 of the 28 day cycle. DLT was observed in only one patient at Level 3, and MTD was not reached in this study. However, all six patients displayed Grade 3 or 4 neutropenia during the first course at Level 3, and no patient received all three doses of gemcitabine during the first course. In contrast, three patients at Level 2 experienced Grade 3 neutropenia, and only one patient had to skip the dose of gemcitabine on Day 15. Based on these results, the recommended dose should be 1200 mg/m^2 in further studies of FDR infusion of gemcitabine in Japan from the perspective of dose intensity for gemcitabine.

Preclinical data, using primary human tumor cell lines including pancreatic carcinoma, have suggested a possible dose–response relationship, and exposure to high concentrations of gemcitabine, independent of infusion duration, might correlate with improved cytoxicity and enhanced clinical effectiveness (12). Thus, a randomized trial of gemcitabine comparing high-dose gemcitabine (2200 mg/m^2) administered using a standard 30 min infusion to FDR infusion of 1500 mg/m^2 over 150 min was conducted in patients with locally advanced or metastatic pancreatic cancer according to the results of two Phase I studies in the United States (10–12). Although no difference in tumor response was noted between the 30 min infusion and FDR arms, MST was reported as 5.0 months in the 30 min infusion arm and 8.0 months in the FDR arm (P = 0.013), and 1 and 2 year survival rates were 9.0 and 2.2%, respectively, in the 30 min infusion arm, and 28.8 and 18.3%, respectively, in the FDR arm. In the study conducted by Burris et al. (8), MST for gemcitabine using the standard 30 min infusion of 1000 mg/m^2 was 5.7 months, and 1 and 2 year survival rates were 18 and 0%, respectively. A retrospective analysis reported that the MST of patients in Japan treated with gemcitabine by standard infusion of 1000 mg/m^2 was 5.7 months (14). In comparison, survival outcomes of patients treated using the standard 30 min infusion are similar, and MST is <6 months. In contrast, in a study with a limited number of patients using FDR infusion, MST was 7.3 months and similar to MST in the FDR arm of the randomized trial in the United States (12).

The most common toxicity for FDR infusion was myelosuppression, particularly neutropenia, as noted in a randomized trial by Tempero et al. (12). In our study, Grade 3 or 4 neutropenia developed in 81.3% of patients, and Grade 3 or 4 leukopenia and thrombocytopenia were observed in 62.5 and 18.8%, respectively. By contrast, a Phase I study for the standard infusion of gemcitabine in Japan reported rates of Grade 3 or 4 neutropenia, leukopenia and thrombocytopenia of 36.4, 27.3 and 0%, respectively (15). The FDR infusion schedule thus seems more hematologically toxic. Conversely, the non-hematological toxicity of FDR infusion was relatively mild. Grade 3 nausea and vomiting that occurred in 12.5% of patients on FDR infusion resembled the results obtained with standard infusion in the Japanese Phase I study, in which 9.1% of patients developed Grade 3 nausea and vomiting. Skin rashes were more frequent with FDR infusion, with 50% of patients developing Grade 1 or 2 skin rashes, than with standard infusion, in which 27.3% of patients developed Grade 1 or 2 skin rashes.

Various regimens of gemcitabine in combination with potentially synergistic drugs have been trialed to improve prognosis in patients with unresectable pancreatic cancer (16–22), and FDR infusion of gemcitabine has also been applied to combination chemotherapy with other anticancer drugs (20–22). A Phase III study comparing standard infusion of gemcitabine, FDR infusion of gemcitabine and combined FDR infusion of gemcitabine and oxaliplatin is under way as an ECOG study in the United States. The results of that study should be awaited before deciding whether FDR infusion of gemcitabine alone can be used as the standard treatment for unresectable pancreatic cancer. However, data from the present study confirm that FDR infusion of gemcitabine is tolerated by Japanese patients, and continued evaluation of FDR infusion, alone or in combination with other agents, is warranted in Japan.

Acknowledgment

This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

References

1. National Cancer Center. Cancer statistics in Japan 2003. http://www.ncc.go.jp/en/statistics/index.html. (accessed 30 June 2005).
2. Warshaw AL, Fernandez-del Castillo C. Pancreatic carcinoma. *N Engl J Med* 1992;326:455–65.
3. Noble S, Goa KL. Gemcitabine. A review of its pharmacology and clinical potential in non-small cell lung cancer and pancreatic cancer. *Drugs* 1997;54:447–72.
4. Heinemann V, Hertel LW, Grindey GB, Plunkett W. Comparison of the cellular pharmacokinetics and toxicity of 2′,2′-difluorodeoxycytidine and 1-beta-D-arabinofuranosylcytosine. *Cancer Res* 1988;48:4024–31.
5. Huang P, Chubb S, Hertel LW, Grindey GB, Plunkett W. Action of 2′,2′-difluorodeoxycytidine on DNA synthesis. *Cancer Res* 1991;51:6110–7.
6. Abbruzzese JL, Grunewald R, Weeks EA, Gravel D, Adams T, Nowak B, et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol* 1991;9:491–8.
7. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, et al. Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs* 1994;12:29–34.
8. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with

gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
9. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2′,2′-difluorodeoxycytidine 5′-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. *Cancer Chemother Pharmacol* 1991;27:258–62.
10. Touroutoglou N, Gravel D, Raber MN, Plunkett W, Abbruzzese JL. Clinical results of a pharmacodynamically-based strategy for higher dosing of gemcitabine in patients with solid tumors. *Ann Oncol* 1998;9:1003–8.
11. Brand R, Capadano M, Tempero M. A phase I trial of weekly gemcitabine administered as a prolonged infusion in patients with pancreatic cancer and other solid tumors. *Invest New Drugs* 1997;15:331–41.
12. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2003;24:3402–8.
13. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment, Vol. 48. WHO Offset publication, Geneva: World Health Organization 1979.
14. Ishii H, Furuse J, Nagase M, Yoshino M. Impact of gemcitabine on the treatment of metastatic pancreatic cancer. *J Gastroenterol Hepatol* 2005;20:62–6.
15. Okada S, Ueno H, Okusaka T, Ikeda M, Furuse J, Maru-Y. Phase I trial of gemcitabine in patients with advanced pancreatic cancer. *Jpn J Clin Oncol* 2001;31:7–12.
16. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002;20:3270–5.
17. Philip PA, Zalupski MM, Vaitkevicius VK, Arlauskas P, Chaplen R, Heilbrun LK, et al. Phase II study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. *Cancer* 2001;92:569–77.
18. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schonekas H, Rost A, et al. A phase III trial comparing gemcitabine plus cisplatin vs. gemcitabine alone in advanced pancreatic carcinoma. *Proc Am Soc Clin Oncol* 2003;22:250 (abstract no. 1003).
19. Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004;22:3776–83.
20. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;23:3509–16.
21. Cascinu S, Frontini L, Labianca R, Catalano V, Barni S, Graiff C, et al. A combination of a fixed dose rate infusion of gemcitabine associated to a bolus 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). *Ann Oncol* 2000;11:1309–11.
22. Feliu J, Mel JR, Camps C, Escudero P, Aparicio J, Menendez D, et al. Phase II study of a fixed dose-rate infusion of gemcitabine associated with uracil/tegafur in advanced carcinoma of the pancreas. *Ann Oncol* 2002;13:1756–62.

In: Focus on Pancreatic Cancer Research
Editor: Maxwell A. Loft, pp. 33-47

ISBN 1-59454-270-8

Chapter II

CHEMORADIATION THERAPY FOR LOCALLY ADVANCED PANCREATIC CARCINOMA: INTRAOPERATIVE AND CONFORMAL EXTERNAL BEAM RADIATION THERAPY WITH OR WITHOUT PROTRACTED 5-FLUOROURACIL INFUSION

Junji Furuse[1,*], *Hiroshi Ishii*[1], *Mitsuhiko Kawashima*[2], *Taira Kinoshita*[3], *Takashi Ogino*[2] *and Masahiro Yoshino*[1]

[1]Division of Hepatobiliary and Pancreatic Medical Oncology, National Cancer Center Hospital East, Chiba, Japan
[2]Department of Radiology, National Cancer Center Hospital East, Chiba, Japan
[3]Division of Upper Abdominal Surgery, National Cancer Center Hospital East, Chiba, Japan

ABSTRACT

Purpose: We reviewed retrospectively two studies which we conducted before to clarify the efficacy and feasibility of chemoradiation therapy with a combination of intraoperative radiation therapy (IORT) and conformal external beam radiation therapy (EBRT) alone in one study and with protracted therapy 5-fluorouracil (5-FU) in another study in patients with locally advanced pancreatic carcinoma.
Methods: Fifty-four patients with unresectable locally advanced pancreatic carcinoma diagnosed on the basis of the dynamic computed tomography findings and who satisfied the criteria for our clinical studies were reviewed. There were 24 patients in the radiation therapy alone study (Group A) and 30 in the chemoradiation therapy study (Group B).

* Correspondence concerning this article should be addressed to Junji Furuse, MD, National Cancer Center Hospital East 6-5-1, Kashiwanoha, Kashiwa Chiba 277-8577, Japan. Tel. +81-4-7133-1111, Fax. +81-4-7131-4724; E-mail address: jfuruse@east.ncc.go.jp.

The radiation therapy in both studies consisted of IORT (25 Gy) followed by EBRT (40 Gy in 20 fractions, 5 times/week) beginning 2 to 4 weeks after IORT. In group B, protracted 5-FU infusion (200 mg/m^2) was concurrently combined with EBRT. We compared efficacy and adverse effects on these regimens.

Results: At laparotomy cancer spread in the abdomen was detected in 20 of the 54 patients: 9 of the 24 patients in group A and 11 of the 30 patients in group B. It had spread to the liver in 10 patients, to the peritoneum in 5 patients, to both the liver and peritoneum in 4. patients, and to a distant lymph node in one patient. The overall response rate for the primary pancreatic tumor was 25% in group A and 23% in group B. Grade 3 or 4 toxicity was observed in 50% of the patients in group A and 54% of the patients in group B. The most common toxicities were anorexia and nausea. The overall median survival time (MST) of the 54 patients was 7.7 months, and the 1- and 2-year survival rates were 29.6% and 9.3%, respectively. The MST of the 34 patients without cancer spread in the abdomen was 11.9 months, as opposed to 5.4 months in the 20 patients with cancer spread in the abdomen ($P<0.0001$). However, there was no significant difference in survival between group A and group B.

Conclusions: Approximately one-third of patients clinically diagnosed with locally advanced pancreatic carcinoma already had metastatic disease at the time of diagnosis. The chemoradiation regimen consisting of IORT plus EBRT and continuous infusion 5-FU was no better than radiation therapy alone. Systemic chemotherapy should be developed as part of chemoradiation therapy for locally advanced pancreatic carcinoma.

Key words: pancreatic carcinoma, intraoperative radiation therapy, conformal external-beam radiation therapy, chemoradiation therapy, 5-fluorouracil.

INTRODUCTION

Unresectable pancreatic carcinoma without distant metastasis is classified as "locally advanced," and patients with locally advanced cancer have a particularly poor prognosis. Based on the results of three randomized trials chemoradiation therapy or chemotherapy alone has been thought to be a reasonable approach to the treatment of locally advanced disease.[1-3] In previous reports on the treatment of locally advanced pancreatic carcinoma the external-beam radiation therapy (EBRT) doses ranged from 40 Gy to 55 Gy, and various chemotherapy regimens using 5-fluorouracil (5-FU) were combined with radiation therapy in an effort to improve the efficacy of radiation therapy.[4-6] In other studies, high radiation doses have been administered by using combinations of intraoperative radiation therapy (IORT) and EBRT or high-dose conformal radiation therapy.[7-11] IORT or conformal irradiation using a three-dimensional irradiation system enables the radiation dose to tissues surrounding the pancreas to be reduced.

Between January 1993 and May 2001, we conducted two consecutive prospective studies of intensive chemoradiation therapy consisting of a fixed radiation dose delivered by IORT followed by conformal EBRT with or without protracted infusion of 5-FU for locally advanced pancreatic carcinoma.[12,13] In the first study, we used combined radiotherapy consisting of IORT plus EBRT to evaluate the efficacy and feasibility of intensive radiotherapy alone. In the second study we combined the same radiotherapy with concurrent

infusion of 5-FU. We then retrospectively compared the results in the patients treated by radiotherapy alone and chomeradiotherapy in these two clinical studies and assessed the efficacy and feasibility of intensive radiotherapy and chemoradiation therapy in patients with locally advanced pancreatic carcinoma.

Table 1. Patient Characteristics

	No. of patients in each study	
Variable	IORT±EBRT (n=24)	IORT+EBRT with 5-FU (n=30)
Gender		
Male	11	19
Female	13	11
Median age (range)	61 (45-83) years	58 (32-75) years
ECOG performance status		
0	13	19
1	10	9
2	1	2
Primary site		
Head	13	10
Body and tail	11	20
Tumor size (cm)		
$> 2.0, \leq 4.0$	11	15
$> 4.0, \leq 6.0$	13	15
Metastasis not detected by CT		
Absent	15	19
Present	9	11
CA19-9 before treatment (U/mL)		
≤ 37	7	10
$> 37, < 500$	10	11
> 500	7	9

ECOG, Eastern Cooperative Oncology Group; IORT, intraoperative radiation therapy; EBRT, external beam radiation therapy; 5-FU, 5-fluorouracil.