CASE REPORT

A Case of Gastrointestinal Stromal Tumor of the Small Intestine with Peritoneal Metastasis Successfully Treated with Imatinib Mesylate

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A 46-year-old man was admitted with dizziness and abdominal pain. Laboratory tests showed severe anemia. Computed tomography (CT) scan showed a large heterogeneous mass and fluid collection in the abdominal cavity. Under a diagnosis of intra-abdominal hemorrhage from the intra-abdominal mass, we performed an emergency operation. Laparotomy revealed a 12×10×6 cm solid tumor of the ileum with bleeding at about 150 cm distant from the ligament of Treitz, accompanied by peritoneal metastases. Partial resection of the ileum and coagulation of peritoneal metastases by electric knife were performed. Pathological examination showed interlaced bundles of large bizarre spindle-like tumor cells, high cellularity and 12 mitoses per 50 high-power fields. Immunohistochemical staining showed positive responses for c-kit and CD34, but negative responses for α-smooth muscle actin (SMA) and S-100 protein. Based on the above findings, the tumor was diagnosed as a high risk malignant gastrointestinal stromal tumor (GIST) of the small intestine. C-kit mutation analysis showed tumor had mutation at exon 11 of the c-kit gene. His postoperative course was uneventful. On the 14th postoperative day, oral administration of imatinib mesylate at 400 mg/day was started. The patient has been followed up for 5 years with no evidence of recurrence.

Key Words: small intestinal GIST, peritoneal metastasis, imatinib mesylate

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大腸癌におけるオキサリプラチンの末梢神経障害に対する漢方薬：

牛車腎気丸の有用性に関する多施設共同二重盲検ランダム化

比較検証試験（臨床第Ⅲ相試験）

平成24年度　総括研究報告書（2/2冊）

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Hyperthermic Intra-Peritoneal Chemotherapy, HIPEC for peritoneal dissemination from gastric and colorectal cancer

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Summary

腹膜転移に対する腹腔内温熱化学療法（HIPEC）は，腹膜切除を含めた可及的腫瘍減量手術と併用することで，延命効果を示す。PO スキルス胃癌では，HIPEC 非施行症例で 5 年生存率 12.5%に対し施行群では 50%と有意に腹膜再発予防効果と延命を認めた。胃癌治療的 HIPEC では 2 年生存率は 44%，5 年生存率は 11%であり，非施行群より延命効果を示した。大腸癌 P1 施行例の生存期間中央値（MST）は 25 カ月と有意に予後の延長を認めた。5 年生存率 35%，3 例の 10 年生存を得た。非施行例では 8 カ月だった。腹膜偽粘液腫でも HIPEC により予後の改善が得られた。開腹法の開発により，閉腹法よりも効果的かつ安全に行えた。術後は広範熱傷に準じた集中管理と大量輸液により合併症を減らすことができる。今後は温熱治療の精度管理を行いながらの他施設共同研究によるエビデンス確立が必要である。

Surgery Frontier 19(2)：27-33，2012

Key Words　HIPEC，CHPP，腹膜播種性転移，腹腔内温熱化学療法，腫瘍減量手術

はじめに

腹膜転移は腹腔内を転移経路とする癌の転移形式であり，腹腔内の転移形式としてリンパ節転移に次いで多く，胃癌では非治癒因子，再発形式のなかで最も多い。また，漿膜浸潤を有する低分化胃癌では，肉眼的に腹膜播種がなくても，高率に腹腔内遊離癌細胞が証明され，多くは腹膜転移再発をきたし，予後は不良である。大腸癌では結腸癌で約 6%，直腸癌でも 3%に腹膜播種が認められ，生存期間中央値（median survival time：MST）は 5～9 カ月と不良であり，確立した化学療法はない。

われわれは，1985 年から胃癌の腹膜転移の治療と予防，大腸癌や腹膜偽粘液腫に対しては治療的に腹腔内温熱化学療法（hyperthermic intra-peritoneal chemotherapy：HIPEC）を施行している。最近では，高度な胃癌腹膜播種性転移に対してはタキサン系薬剤の腹腔内化学療法を含む術前化学療法も行っている。ここでは HIPEC を安全かつ効果的に行うために開発した方法の詳細を述べるとともに，その成績について報告する。なお，以前は HIPEC を持続温熱腹膜灌流療法（continuous hyperthermic peritoneal perfusion：CHPP）と称していた。

◆メモランダム◆

HIPEC + CRS の普及

世界で腹膜播種に HIPEC + CRS を行っているセンターはいくつあるでしょうか？ ヨーロッパでは 2009 年に 135 カ所，2011 年には 200 カ所を超えました。フランス，オランダなどいくつかの国では保険診療となっています。北米では，2009 年で 50 施設，2011 年には 120 施設と激増しています。アジア・オセアニアでは，日本 8，韓国 3，中国 2，台湾，シンガポール，オーストラリア各 1 施設です。

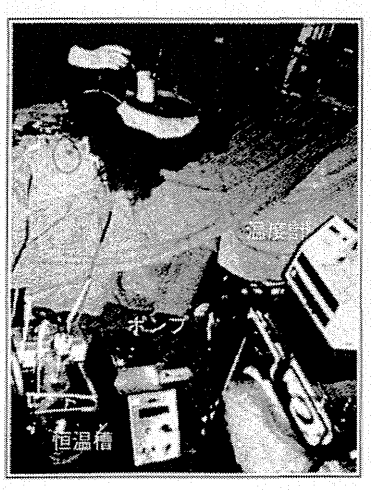
対　象

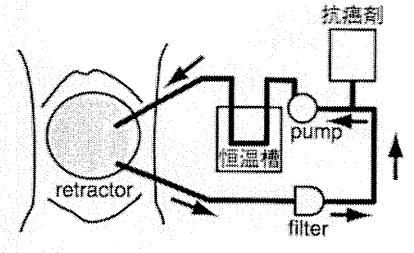
2003年度からは福井大学医学部倫理審査委員会承認を経て，臨床治験として実施計画書に則り十分なICのもとに実施している。20～75歳で腹膜転移以外に非治癒因子のない症例を対象とし，後腹膜癌症をともなう症例，硬化浸潤型の腹膜転移は適応外としている。本稿では，胃癌では最も予後不良であるスキルス胃癌における予防的，治療的HIPEC症例について検討した。大腸癌では，腹膜転移陽性例のみを適応とした。米粒大以上の結節は切除し，小結節散布型の腹膜転移はHIPECにより治療した。

方　法

われわれは，1983年から閉腹法[1]にてHIPECを行ってきた。しかし，閉鎖され限られたスペースを灌流するために，均一な加温が困難であった。横隔膜下腔やダグラス窩など，辺縁部でなおかつ腹膜播種の頻度が高い部分を十分に加温するためには，流入温を高温にせざるを得ず，腸管穿孔などの重篤な合併症が発生した。そこで，1985年，筆者は開腹法HIPECを開発した[2][3]。これにより腹腔は開大し，灌流に十分なスペースが得られ，直視下の撹拌による均一な加温を安全に行うことが可能となった。

施術においては切除再建を先行する。腹膜転移がある症例であっても，リンパ節郭清と必要な合併切除も行い，ほかの非治癒因子を可及的に切除する。腹膜転移も腹膜を含めた可及的な腫瘍減量手術（cytoreductive surgery：CRS）を行う。創縁の皮膚に2号絹糸を14針ほどかけ，Omnitract®開創器のarmに結紮し，腹壁を吊り上げる。シスプラチン（CDDP）/150 mg，マイトマイシンC（MMC）/20 mg，エトポシド（VP-16）/200 mgを含む生食約4Lを恒温槽内で約50℃に加温する。2リットルを腹腔に注ぐことでHIPECを開始する。残りは体外循環ポンプを用いて腹腔内を灌流する（図1）。術中の腹腔内温度を横隔膜下，ダグラス窩，流入温，流出温，体温（食道温，鼓膜温または上大静脈温で持続測定する。途中でCDDP 50mgを追加する。図2に平均的なHIPEC症例における腹腔内各所，流入温，流出温，体温の変化を示す。PC上で43℃における Thermal dose(TD： Equivalent time at 43℃)[4]を計算，積分した数値を表示させる（図3）。治療的HIPECならTDは40分以上，予防的ならTDが20分に至るまで治療を続ける。ヒーターによる流入温と灌流速度を100～500 mL/minで調節し温度管理を行う。流入は灌流液中に注ぎ，用手的に撹拌して腹腔内を均一に42.5℃以上に保つ。決して自分の手を抜かないことが肝要





測温部位
体温（食道，膀胱）
ダグラス窩，左横隔膜窩 42.5～43℃
流入温 50～55℃
恒温槽温 58～59℃

図1　方法
消化管再建後，CDDP 100 mg，MMC 20 mg，VP-16 200 mgを溶解した生食4Lで，42～43℃を保ちながら50分間腹腔内を灌流。途中でCDDP 50 mgを追加する。
（カラーグラビアp2　写真1参照）

である[5]。

腹膜の面積はほぼ体表面積に等しい。広範な熱傷による末梢の血管透過性亢進と血管拡張で循環血漿量が低下し，CDDP の腎毒性と熱障害組織からの腎毒性物質が急性尿細管障害を惹起する。末梢血管抵抗の低下は 48 時間以上続き，心拍出量は 2 倍以上になる。術中から術後数日は十分な細胞外液輸液により腎血流量を維持する。十分な加温をともなう HIPEC の術後には，灌流加温中に体重の 10％程度，術後の 24 時間に体重の 20％程度の大量輸液が必要となり，呼吸循環管理には広範熱傷に準じた綿密な集中管理が必要である[5]。

結　果

1　胃癌予防的 HIPEC の成績（図 4）

いずれも M0H0P0，N ≦ D の切除

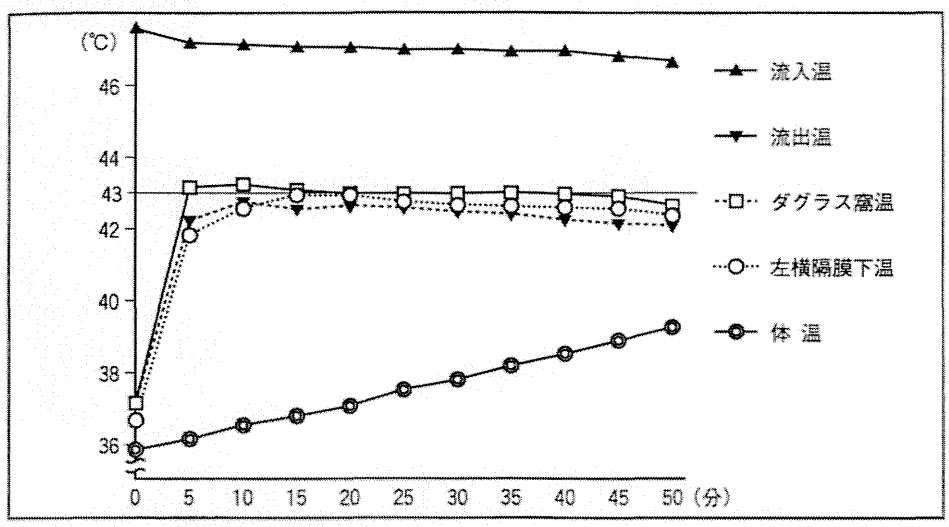


図 2　HIPEC における流入出温，腹腔内温モニタリング結果の 1 例

Thermal dose（分）

	sal500					randa50												
	0	1	3	5	10	15	20	25	30	35	40	45	50	55	60	Thermal dose	MEAN	S.D.	VAR
Douglas	36.9	43.4	42.6	43.5	42.5	42.6	42.5	41.3	42.4	42.6	42.7	42.3	42.4				42.57	0.55	0.302
Thermal dose		1.3	1.1	2.8	2.5	2.9	2.5	0.5	2.2	2.9	3.3	1.9	2.2	0.0	0.0	26.05995			
L-Subphlenic	36.9	42.9	42.9	42.7	42.2	42.4	42.5	41.9	41.4	42.2	42.5	42.7	42.6				42.41	0.434	0.188
Thermal dose		0.9	1.7	1.3	1.6	2.2	2.5	1.1	0.5	1.6	2.5	3.3	2.9	0.0	0.0	22.2091			
Body(Pharyncs)	36.5	36.5	36.7	37.5	37.9	38.4	38.6	38.8	38.9	39.0	39.2	39.4	39.6						
Body(Rectum)	36.6	36.8	37.1	38.1	38.4	38.9	39.3	39.6	39.8	39.9	40.1	40.4	40.5						
In flow temp.	55.7	5.5	53.6	49.9	49.3	49.2	48.8	48.9	49.3	49.3	49.5	49.7	49.8						
Out flow temp.		42.0	42.4	42.1	42.8	42.4	41.8	41.8	42.0	42.4	42.4	42.7	41.9						
Pump flow rate	0.6	0.6	0.5	0.5	0.5	0.5	0.6	0.4	0.4	0.5	0.5	0.4	0.4						
Water bath temp.	58.0	58.0	58.0	58.0	58.0	58.0	58.0	58.0	58.0	58.0	58.0	58.0	58.0						

図 3　Thermal dose（Equivalent time at 43℃＝ TD43）

TD43℃は HIPEC 中 5 分ごとに PC にて計算して積算し，目標時間に達するまで加温を行う。治療的 HIPEC では 40 分以上，予防的 HIPEC では 20 分以上を目標としている。

が行われた症例である。historical control study ではあるが，HIPEC 非施行症例では 5 年生存率が 12.5%であるのに対して HIPEC 群では 50%と，スキルス胃癌では HIPEC 群で有意に腹膜再発予防効果と延命効果を認めた。

2　胃癌治療的 HIPEC の成績（図 5）

リンパ節転移が取りきれない症例では HIPEC を行っても HIPEC 非施行例と予後は変わらない。したがって，P1 であっても N に関しては郭清術を行い，治癒切除が可能となる症例を対象とすべきである。HIPEC 非施行群では郭清をともなう切除は行われてい

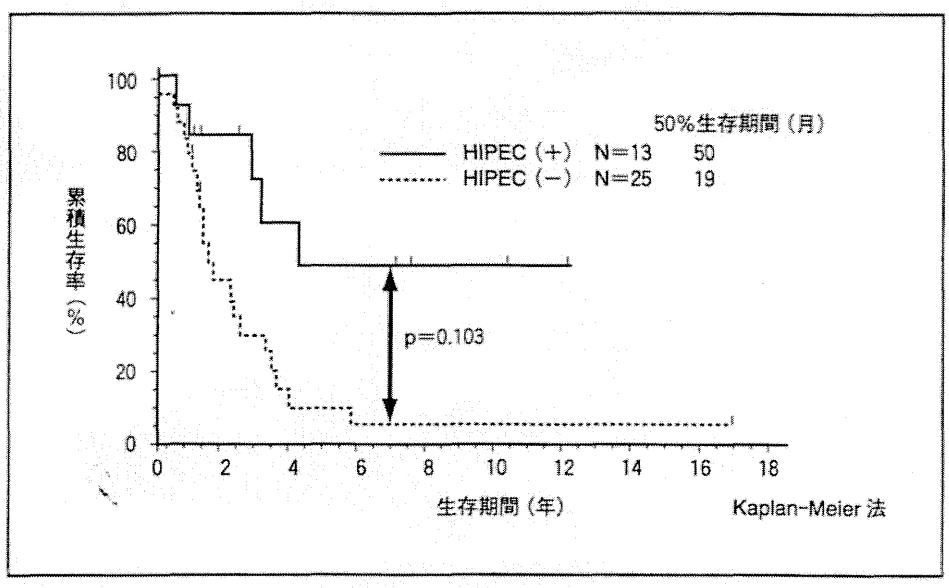


図 4　スキルス胃癌 P0 症例における予防的 HIPEC と予後（H0，リンパ節が根治的に切除しえた症例）

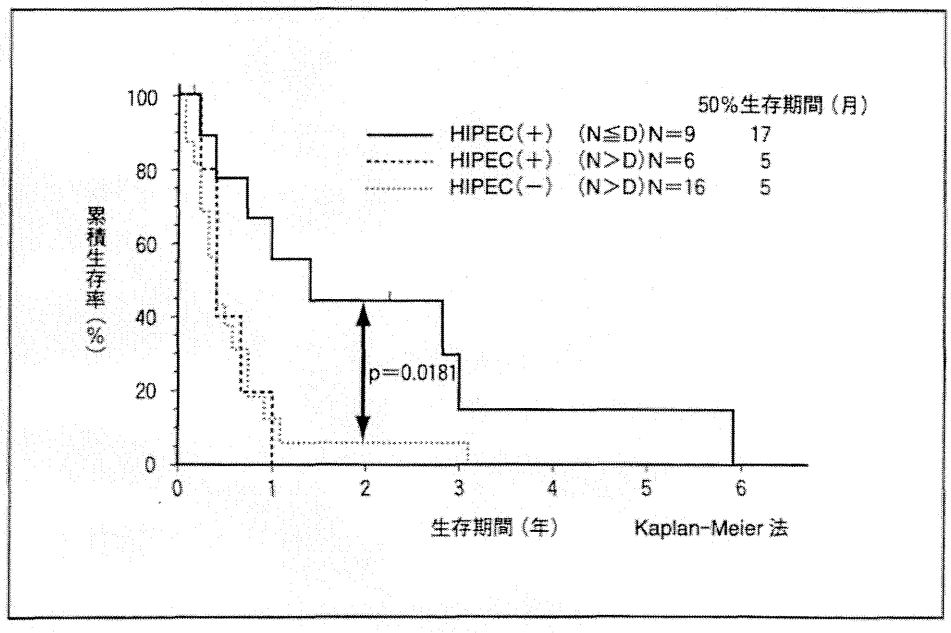


図 5　スキルス胃癌 H0P1 切除症例における治療的 HIPEC と予後

ない。この成績はHIPECの成績というより，スキルス胃癌であってもN2以下の症例におけるHIPECプラス郭清手術の成績というべきである。2年生存率は44%，5年生存率は11%であり，HIPEC非施行，非郭清切除症例に比して有意に延命効果を示した。

3 大腸癌HIPECの成績

14例に施行した。施行例のMSTは25カ月と有意に予後の延長を認めた。5年生存率35%，4例の5年生存，3例の10年生存を得ている（図6）。一方，非施行例ではMSTは8カ月であった。

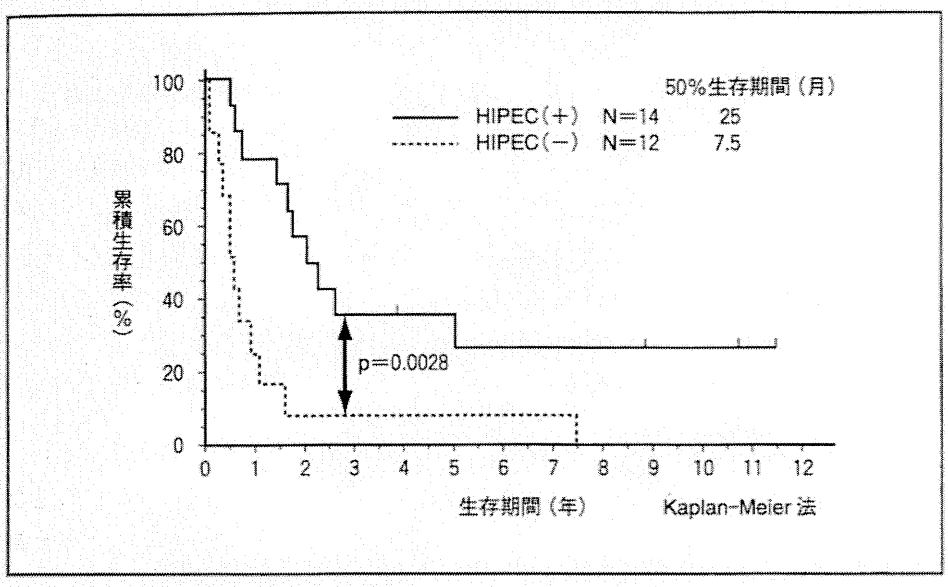


図6 大腸癌H0P1切除症例におけるHIPECと予後

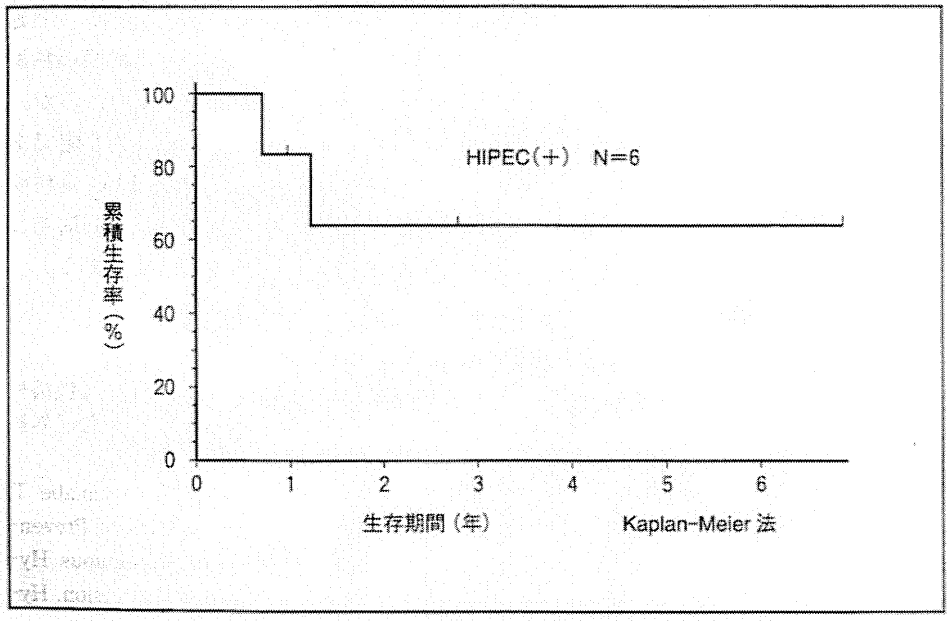


図7 腹膜偽粘液腫症例におけるHIPECと予後
6例中4例が予後不良なPMCA症例，2例は中間型PMCA-Iであった。

4 腹膜偽粘液腫に対するHIPECの成績（図7）

6例中4例が予後不良なperitoneal mucinous carcinomatos（PMCA）症例，2例は中間型PMCA-Iであった。CRSの徹底度が予後に大きく関与する。The Netherlands Cancer Instituteの報告では，腹膜偽粘液腫103例に対するHIPECの成績では，PMCA群のMSTは13カ月，5年生存なし。PMCA-I群のMSTは30カ月，5年生存率42％である。これに比べると良好であったと考えられる。

考　察

癌腹膜転移に対する静脈投与による全身化学療法では，いわゆるblood peritoneal barrier[6][7]のために，抗癌剤は腹膜病変には到達せず，効果を得ることが困難であると考えられた。種々の多剤併用療法も行われたが，腹膜播種症例では延命効果は得られなかった[8][9]。現在われわれも切除不能胃癌でP1症例には積極的に術前タキサン系の腹腔内投与と全身化学療法の併用を行って効果を挙げつつある。

1980年Shiuらはラットの実験腹膜転移腫瘍に抗癌剤の温熱灌流を行った[10]。Sprattらはイヌを用いて安全性の実験を行い[11]，35歳男性の腹膜偽粘液腫症例で初めて臨床応用を行った[12]。各国における外科医の20年以上の研究研鑽の結果，今では腫瘍の可及的CRSとHIPECの併用は，大腸癌，腹膜偽粘液種，虫垂癌，腹膜悪性中皮腫に対しては欧州，特にフランス，イタリア，ベネルクス3国，ドイツ，北欧3国では標準的治療となっている[13]。胃癌，卵巣癌でも現在臨床効果を評価中である[14]。併用する化学療法剤としては，温熱感受性試験の結果などから，CDDP，MMC，VP-16などが温熱により増感されることから用いられる[15]。Losらは，37℃に較べて41.5℃では腹膜腫瘍内のCDDP濃度が4倍になると報告している[16]。温熱療法は腹膜面からの薬剤透過性を高め，抗癌剤の組織内濃度を上げることが期待される。

わが国では古賀らにより始められた[1]HIPECは，一時は多くの施設で行われたが，最近では限られた施設でのみ行われる傾向にある。その原因は，胃癌では多くの施設で有意な効果が認められなかったことと，合併症の頻度が高いことにあると考えられる。Sugerbakerら[17]，米村ら[15]は，HIPECのみの効果では限界があるとして腹膜亜全摘のうえでのHIPECを提唱している。われわれは，できるだけ臓器を温存しつつ，温熱化学による抗腫瘍効果を得るべく術中に十分な加温を行い，播種巣への抗癌剤の浸透性をも期待する。そのために厳重な術後集中管理を行っている。

古賀らは，胃癌で結節型の腹膜播種で径1 mm以上の転移にはHIPECは効果がないとしている[18]。米村らは積極的にsecond look operationを行い，43例中17例に効果を認め，8例で肉眼的組織学的に完全寛解を得て2例で5年生存したと報告した。これらはいずれも結節型であり，瀰漫型ではなかった[15]。Gillyら[19]，藤本ら[20]の報告では，2年生存は47，40％で5年生存はなかった。米村らは2年生存率16％，5年生存率12％であった[21]。腹膜転移陽性胃癌の手術単独症例の1年生存率15％からすれば有効であったといえる。われわれのスキルス型腹膜転移胃癌に対する成績では，HIPEC施行群の2年生存率は44％，5年生存率は11％である。この成績はHIPECというより，スキルス胃癌であってもN2以下の限られた症例におけるHIPECプラス郭清手術の成績というべきと考えられる。

結　語

HIPECは，開腹法の開発により，閉腹法よりも効果的かつ安全に行えた。スキルス胃癌，大腸癌で腹膜転移を認めても，そのほかの非治癒因子が切除可能な場合は，積極的なCRSを行ったうえでHIPECを施行することで延命が得られる症例がある。腹膜偽粘液腫では可及的CRSが必要であるが，HIPECの併用で長期予後が可能である。今後はTDによるHIPECの精度管理を行いながらの他施設共同研究によるエビデンス確立が必要である。

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● 症 例 ●

直腸癌術後多発肝転移再発，門脈腫瘍塞栓に対し三次治療としてPanitumumabが著効した1例

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A Case of Response to Panitumumab as Third-Line Chemotherapy for Multiple Liver Metastases and Portal Venal Tumor Embolus of Rectal Cancer: Youhei Kimura, Takanori Goi, Katsuji Sawai, Atsushi Iida, Kanji Katayama and Akio Yamaguchi (*First Dept. of Surgery, University of Fukui*)

Summary

A 64-year-old man who underwent rectal amputation for rectal cancer was diagnosed with multiple liver metastases and tumor embolus in the portal vein 6 months after operation. Though the patient underwent chemotherapy, mFOLFOX6, and bevacizumab+FOLFIRI, liver metastases were diagnosed as progressive disease (PD). After panitumumab+FOLFIRI was administered for three months as third-line chemotherapy, the tumor embolus completely disappeared, and liver metastases became cytoreductive on CT. The patient was judged to have achieved a partial response (PR). This case indicated that panitumumab was effective as third-line chemotherapy for unresectable recurrent rectal cancer. **Key words**: Rectal cancer, Liver metastasis, Panitumumab (*Received Aug. 8, 2011/Accepted Nov. 17, 2011*)

要旨 症例は64歳，男性。下部直腸癌に対し直腸切断術，D3郭清を施行。最終診断はrectal cancer，Rb，75×45 mm，tub 2，a，ly1，v3，N1，H0，P0，M0，Stage Ⅲa，根治度Aであった。術後より経口剤のUFT/LV療法を行っていた。術後6か月後のフォローアップCTで門脈腫瘍塞栓と切除不能多発肝転移再発を認めたため，mFOLFOX6を開始した。mFOLFOX6を18回終了後に転移巣の増悪を認め，二次治療としてbevacizumab+FOLFIRIを施行するも7回終了後に転移巣の増悪を認めた。次に三次治療としてpanitumumab+FOLFIRIに変更したところ，6回施行後のフォローアップCTで門脈腫瘍塞栓の消失と肝転移巣の縮小を認めた。現在，再発後2年が経過し生存中である。今回われわれは，三次治療としてpanitumumabを上乗せした化学療法を行うことで多発肝転移が著明に改善した症例を経験したので報告する。

はじめに

大腸癌化学療法は，大腸癌治療ガイドライン2010年度版において分子標的治療薬の併用が推奨されている[1]。今回われわれは，分子標的治療薬であるpanitumumabを三次治療として使用し，直腸癌術後多発肝転移に著効した症例を経験したので報告する。

Ⅰ．症 例

患者: 64歳，男性。

現病歴: 2009年2月に下部直腸癌に対し当科で腹会陰式直腸切断術，リンパ節郭清を施行。最終診断はrectal cancer，Rb，75×45 mm，tub 2，a，ly1，v3，N1 (No. 251 2個)，H0，P0，M0，Stage Ⅲa，根治度Aであった(Fig. 1)。退院後は経口のUFT/LV補助療法を行っていたが，術後6か月後にフォローアップCTにて両葉の多発肝転移と門脈腫瘍塞栓を認め，直腸癌術後切除不能多発肝転移再発と診断した。

既往歴: B型肝炎ウイルス陽性。

再発時現症: 表在リンパ節触知せず。下腹部正中に手術痕あり。腹部は平坦・軟，圧痛なし。左下腹部に人工肛門形成状態。

再発時血液検査所見: 血液一般，生化学に異常所見なし。腫瘍マーカーはCEA 9.3 ng/mL (正常値2.5 ng/

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木村 洋平

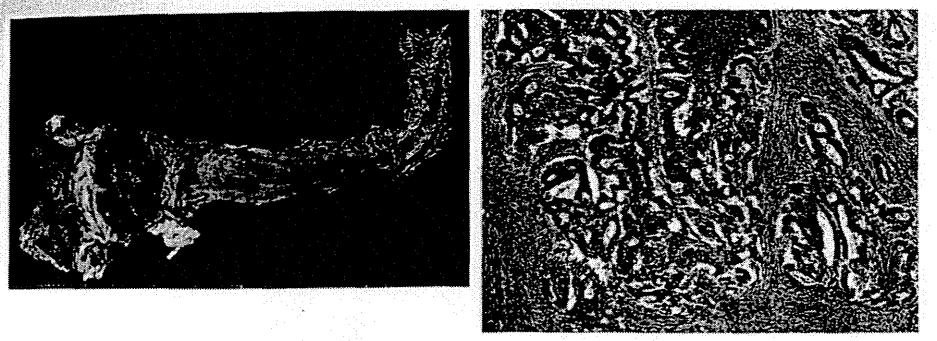

Fig. 1 a: Resected material showing a type 2 tumor on rectum.
b: The microscopic findings (HE×10・original magnification) were moderately differentiated adenocarcinoma (tub 2) and severe vein invasion (v3).

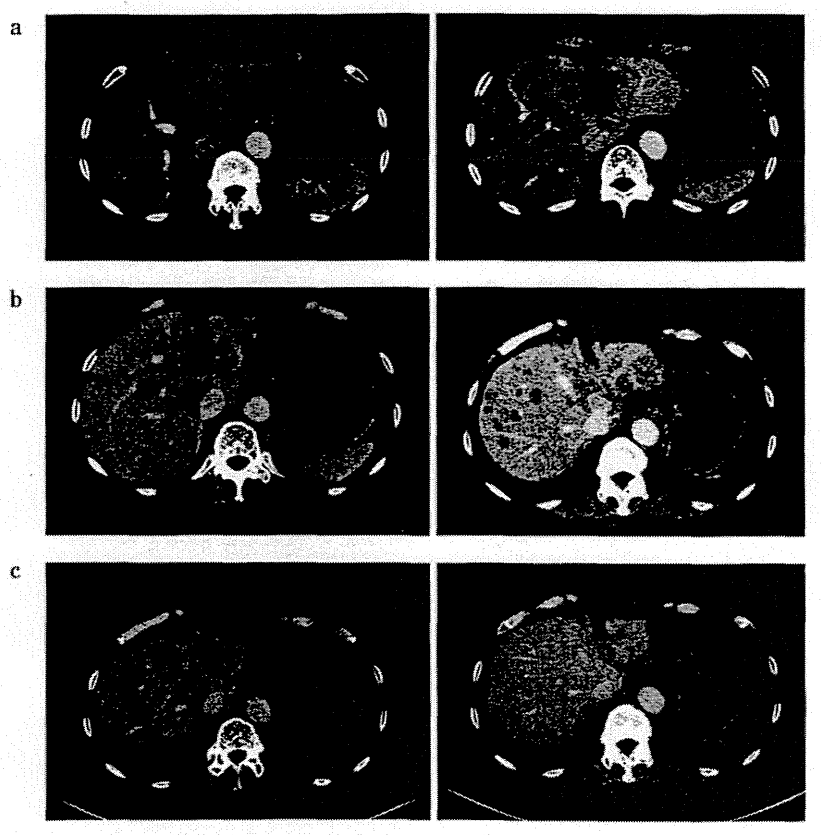

Fig. 2 a: Abdominal CT when first finding multiple liver metastases and left portal vein tumor embolus of rectal cancer.
b: Abdominal CT after 7 times bevacizumab+FOLFIRI chemotherapy. Multiple liver metastases grow bigger.
c: Abdominal CT after 6 times panitumumab+FOLFIRI chemotherapy. Liver metastases were cytoreductive significantly and tumor embolus of left portal vein had disappeared.

mL 以下), CA19-9 11.4 U/mL (正常値 37 U/mL 以下) と CEA 高値であった。

再発時腹部造影 CT (Fig. 2a): 両葉に 5 個の肝転移を認める。また, 門脈左枝根部より腫瘍塞栓と思われる造影剤流入不良領域を認める。

治療経過: 直腸癌術後切除不能多発肝転移, 門脈腫瘍塞栓に対し, 中心静脈埋め込み型カテーテルを挿入し, mFOLFOX6 (*l*-leucovorin 250 mg/日 点滴静注, oxaliplatin 100 mg/日 点滴静注, 5-FU 500 mg/日 静注, 5-FU 3,000 mg 48 時間持続静注) を開始した。mFOLFOX6 を 6 回終了後フォローアップ CT で肝転移巣が縮小しており, Response Evaluation Criteria in Solid Tumors Guideline (RECIST ガイドライン)[2] に基づき partial response (PR) と診断した。その後も mFOLFOX6 を計 18 回施行するもフォローアップ CT で肝転移巣の増悪を認め, progressive disease (PD) と診断した。2010 年 6 月より bevacizumab+FOLFIRI (bevacizumab 250 mg/日 点滴静注, *l*-leucovorin 250 mg/日 点

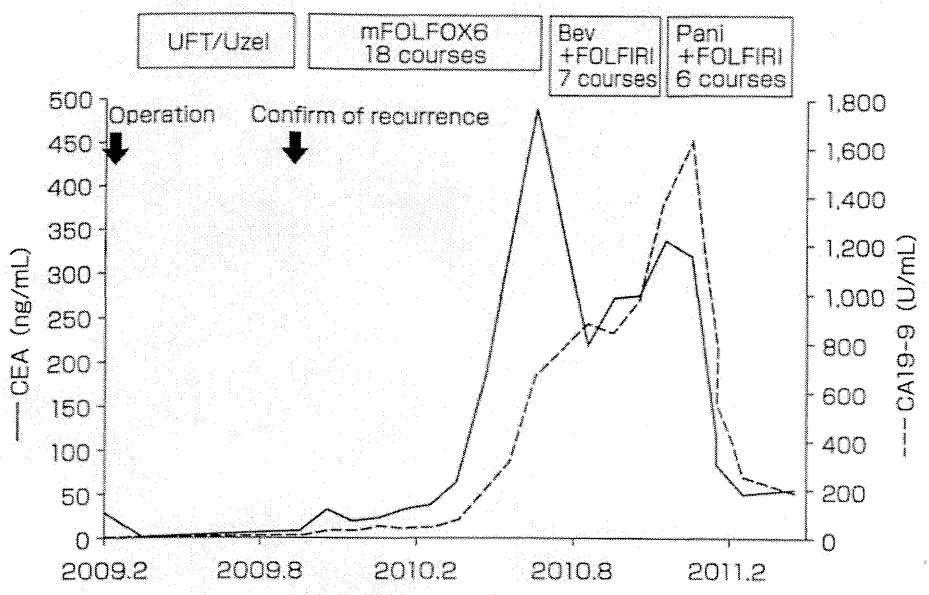

Fig. 3 Clinical course

滴静注，CPT-11 200 mg/日 点滴静注，5-FU 500 mg/日 静注，5-FU 3,000 mg 48時間持続静注）に変更となり計7回施行するも，フォローアップCTで転移巣の増大が認められ（Fig. 2b）PDであった。そこで，三次治療としてFOLFIRIにpanitumumab 300 mg/日を加え化学療法を行うこととなった。*KRAS*遺伝子野生型であり，2010年11月よりpanitumumab+FOLFIRI投与を行ったところ，2回終了時よりGrade 3の痤瘡と爪囲炎を認めたが対処療法にて改善した。以後，計6回化学療法終了後CTを施行したところ両葉の多発肝転移巣は縮小しており，また門脈左枝にあった腫瘍塞栓の消失も認められた（Fig. 2c）。測定可能病変で縮小率が80～90%であり新病変の出現も認められないことより，PRと診断した。現在，再発確認後2年が経過し，panitumumab投与後6か月で生存中である。

Ⅱ．考　察

panitumumabは遺伝子組み換え型ヒト型IgG2モノクローナル抗体であり[3]，大腸癌において抗腫瘍効果が期待できる分子標的治療薬である。本邦では2010年大腸癌治療ガイドラインで一次治療から三次治療までの使用が推奨されているが，有効性や安全性を直接比較した結果は報告されておらず使い分けの明確なコンセンサスは得られていない。また，三次治療としてはpanitumumab単剤投与が推奨されている[4]。一方，2011年米国臨床腫瘍学会（ASCO）において，二次治療でのCPT-11不応例に三次治療として再度CPT-11にpanitumumabを併用した有効性が報告された[5]。また同会で，bevacizumab不応例に対する二次治療としてのFOLFIRIとpanitumumab+FOLFIRIの比較試験においても後者の有用性が示されている[6]。本症例では二次治療にbevacizumabとFOLFIRIを使用しており，その後bevacizumabからpanitumumabに変更したことで門脈腫瘍塞栓の喪失と多発肝転移の縮小を認め，前述二つの比較試験を反映する結果であった。また，三次治療としてFOLFIRIをベースに安全に投与できた症例でもあった。Fig. 3に化学療法の投与歴と大腸癌腫瘍マーカーとの推移を示した。Fig. 3に示すとおり，panitumumab投与前の腫瘍マーカーは漸増しているのに対し，投与後には著明な腫瘍マーカーの低下が認められ，panitumumabの抗腫瘍効果が示された症例であった。

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Polysaccharide K suppresses angiogenesis in colon cancer cells

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Abstract. The protein-bound polysaccharide K (PSK) is used as a non-specific immunotherapeutic agent for the treatment of colon cancer. Little research, however, has been conducted on its association with angiogenesis, which is a prognostic factor markedly correlated with hematogenous metastases. We therefore decided to investigate the action of PSK on angiogenic growth factors, angiogenesis inhibitors and angiogenesis in colon cancer cells. Reverse transcription-polymerase chain reaction (RT-PCR) was used to investigate changes in HIF-1α mRNA expression. PCR array was used to investigate changes in angiogenic growth factors and angiogenesis inhibitors, as well as the expression of related genes. Colon cancer cells were cultured with or without PSK for 48 h. The following day, cells were cultured for two days at 37˚C in new complete media. The resulting culture medium was placed in the chamber of a tube formation system in order to investigate tube formation. Investigation of HIF-1α mRNA expression in colon cancer cell lines and in cells cultured under identical conditions with added PSK revealed a significant decrease in expression, as well as a decrease in angiogenic growth factors and related genes in PSK-treated colon cancer cell lines. By contrast, levels of angiogenesis inhibitors and related genes were higher in the PSK-treated colon cancer cell lines. Investigation of tube formation revealed that elongation was inhibited in the medium of the PSK-treated colon cancer cell lines in comparison to the medium of the non-treated colon cancer cell lines. PSK suppresses angiogenic growth factors and related genes, enhances angiogenesis inhibitors and related genes and ultimately suppresses angiogenesis in colon cancer cells.

Introduction

Polysaccharide K (PSK; Kureha Chemical Industry Co., Ltd., Tokyo, Japan) is a protein-bound polysaccharide widely used as a non-specific immunotherapeutic agent and is derived from the cultured mycelia of *Coriolus versicolor*. This protein-polysaccharide complex, which has a molecular weight of approximately 940,000 Da, contains approximately 38% protein and a saccharide portion consisting of a glucan with approximately 75% glucose and smaller amounts of mannose, xylose and galactose (1). To date, PSK has been administered primarily to patients with gastric cancer, colon cancer and other gastrointestinal malignancies. Torisu *et al* reported that patients with curatively resected colon cancer had a significantly improved survival rate when treated with PSK (2). Yoshitani and Takashima (3) and Ohwada *et al* (4), who used PSK in combination with anticancer agents to treat curatively resected patients, also reported significantly improved survival in the patients who received PSK compared with those who did not.

The following main mechanisms of action of PSK on malignancies have been identified to date: i) direct apoptosis induction, inhibition of cellular infiltration and enhancement of MHC class-I expression; ii) enhancement of natural killer, cytotoxic T and lymphokine-activated killer activation and regulation of cytokine production; and iii) suppression of TGF-β production and reduction of oxidative stress (5-8). PSK also has a variety of immunostimulatory effects as a biochemical response modifier. Liver, lung and other hematogenous metastases are considered to be prognostic factors in colon cancer. Hematogenous metastases of colon cancer are generally believed to occur when cancer cells detach from the primary tumor, invade the capillaries and spread systemically via the portal and greater circulatory systems prior to adhering to vascular endothelial cells in the target organ, escaping and infiltrating outside blood vessels and proliferating (9,10). Previous characterization of the mechanisms of metastasis has identified key angiogenic growth factors in this process (11-13). Therefore, we investigated the changes induced by PSK in angiogenic growth factors, angiogenesis inhibitors and related genes in colon cancer cells, and whether PSK suppresses angiogenesis.

Materials and methods

Cell culture and PSK stimulation. Human colorectal cancer cell lines, SW620, HT29 and HCT116 (obtained from European collection of cell cultures, UK), were cultured at 37˚C in 5% CO_2 in RPMI-1640 medium containing 10% fetal bovine serum (14). Cells were seeded ($5x10^5$) into 6-cm dishes in triplicate with PSK for 2 days.

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Key words: colon cancer, polysaccharide K, angiogenesis

Cell viability. Apoptosis was detected by flow cytometry using Annexin V Detection kit (Nanjing KeyGen Biotech, Nanjing, China). Briefly, cells were double stained with Annexin V-TIRIC for 15 min at 37˚C. After cells were washed thrice in PBS, we detected non-red cells under a fluorescent microscope.

Reverse transcription-polymerase chain reaction (RT-PCR) analysis. The total RNA was extracted from the colorectal cancer cells using guanidinium-thiocyanate (15,16). Single strand cDNA was prepared from 3 μg of total RNA using Moloney murine leukemia virus reverse transcriptase (Takara Bio, Inc., Shiga, Japan). The primers for PCR amplification of the HIF-1α gene-coding regions were as follows: 5' primer; HIF-1α -AX,GGACAAGTCACCACAGGA, 3' primer; HIF-1α-BX,GGAGAAAATCAAGTCGTG. GAPDH amplification was used as an internal PCR control with 5'-GGGGAGCCAAAAGGGTCATCATCT-3' as the sense primer and 5'-GACGCCTGCTTCACCACCTTCTTG-3' as the antisense primer. A total of 23 cycles of denaturation (94˚C, 1 min), annealing (50˚C, 1.5 min) and extension (72˚C, 2 min) were carried out in a thermal cycler (PTC-100, Programmable Thermal Controller, NJ Research Inc., MA, USA). The PCR products (10 μl) which demonstrated the relevant bands in RT-PCR analysis were sequenced by electrophoresis in 1.2% agarose gel. The sequencing was performed on PCR products that showed the bands in RT-PCR analysis.

RT2 Profiler™ PCR array and real-time PCR. Total RNA was extracted from colon cancer cells using guanidinium-thiocyanate. Real-time PCR was performed according to the manufacturer's instructions included with the RT2 Profiler PCR array system (angiogenic growth factors and angiogenesis inhibitors; PCR array: catalog no. PAHS-072A; SA Bioscience, Valencia, CA, USA). The data were analyzed using Excel-based PCR array data analysis templates.

In vitro tube formation assay. Following preparation of the cells described above, the medium was removed from all dishes and replaced with fresh complete medium. After two days, each culture fluid was collected and added to wells of an angiogenesis kit (Kurabo Company, Japan). Fields from each sample were photographed and total tube length was analyzed by the MacSCOPE program (Mitani Company, Tokyo, Japan). The control tube areas were defined as 100% tube formation and the percent increase in tube formation as compared with the control was calculated for each sample (17).

Statistical considerations. Other characteristics of the two treatment methods were compared using the Chi-square test. $P<0.05$ was considered to indicate a statistically significant result.

Results

Cell viability. The colon cancer cells analyzed under a fluorescence microscope using the Annexin-V assay demonstrated no increased cell apoptosis and death in samples treated with PSK (100 or 300 μg/ml) compared with untreated cells. Cells treated with 500 μg/ml demonstrated an increase in cell apoptosis and death (Table I).

Table I. Cell viability following exposure to PSK.

PSK (μg/ml)	Annexin V staining (%)
0	3.2
100	3.5
300	3.8
500	10.0

PSK, polysaccharide K.

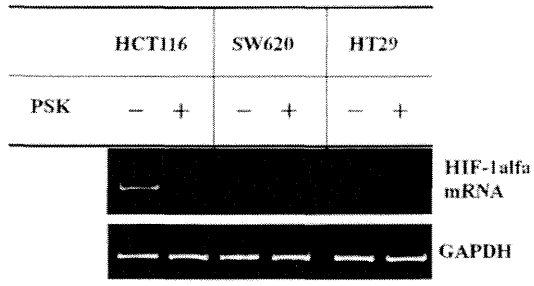

Figure 1. The expression of HIF-1α mRNA was detected in colon cancer cell lines. The HIF-1α mRNA expression in colon cancer cell lines treated with PSK was decreased. PSK, polysaccharide K.

HIF-1α mRNA expression with PSK exposure in colon cancer cell lines. RT-PCR was used to investigate HIF-1α mRNA expression in colon cancer cell lines. The results are shown in Fig. 1. Although the expression of HIF-1α mRNA was detected in colon cancer cell lines, the addition of PSK suppressed HIF-1α mRNA expression in colon cancer cell lines.

Expression of angiogenic growth factors in colon cancer cell lines treated with PSK. PCR array was used to investigate how the addition of PSK to colon cancer cell lines affected levels of angiogenic growth factors and related genes. A comparison of levels in these cells to those in untreated colon cancer cell lines cultured is listed in Table II. Typical genes that were expressed at lower levels included gastrin-releasing peptide (GRP), interleukin 8 (IL8) and platelet-derived growth factor β polypeptide (PDGFB) in HCT116, EGF-like repeats and discoidin I-like domains 3 (EDIL3) in SW620 and chemokine (C-X-C motif) ligand 9 (CXCL9), fibroblast growth factor binding protein 1 (FGFBP1) and interleukin 8 (IL8) in the HT29 cell line. Numerous other angiogenic growth factors and the expression of related genes were reduced in all cell types.

Expression of angiogenesis inhibitors in colon cancer cell lines treated with PSK. PCR array was used to investigate how the addition of PSK to colon cancer cell lines affected levels of angiogenesis inhibitors and related genes. A comparison of levels in these cells to those in untreated colon cancer cell lines cultured at 20% CO_2 is listed in Table III. Typical genes

Table II. Representative list of downregulated genes in PSK-stimulated cells (angiogenic growth factors and related genes).

Cell line	Gene Bank	Description	Ratio
HCT116	Hs.153444	GRP, gastrin-releasing peptide	-5.2635
	Hs.624	IL8, interleukin 8	-4.0425
	Hs.1976	PDGFB, platelet-derived growth factor β polypeptide	-4.9113
SW620	Hs.482730	EDIL3, EGF-like repeats and discoidin I-like domains 3	-11.0357
HT29	Hs.77367	CXCL9, chemokine (C-X-C motif) ligand 9	-28.9895
	Hs.1690	FGFBP1, fibroblast growth factor binding protein 1	-4.4097
	Hs.624	IL8, interleukin 8	-19.315

PSK, polysaccharide K.

Table III. Representative list of upregulated genes in PSK-stimulated cells (angiogenesis inhibitors and related genes).

Cell line	Gene Bank	Description	Ratio
HCT116	Hs.522632	TIMP1, TIMP metallopeptidase inhibitor 1	5.7541
SW620	-	-	-
HT29	Hs.673	IL12A, interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)	17.1
	Hs.644596	TNNI3, troponin I type 3 (cardiac)	4.1713

PSK, polysaccharide K.

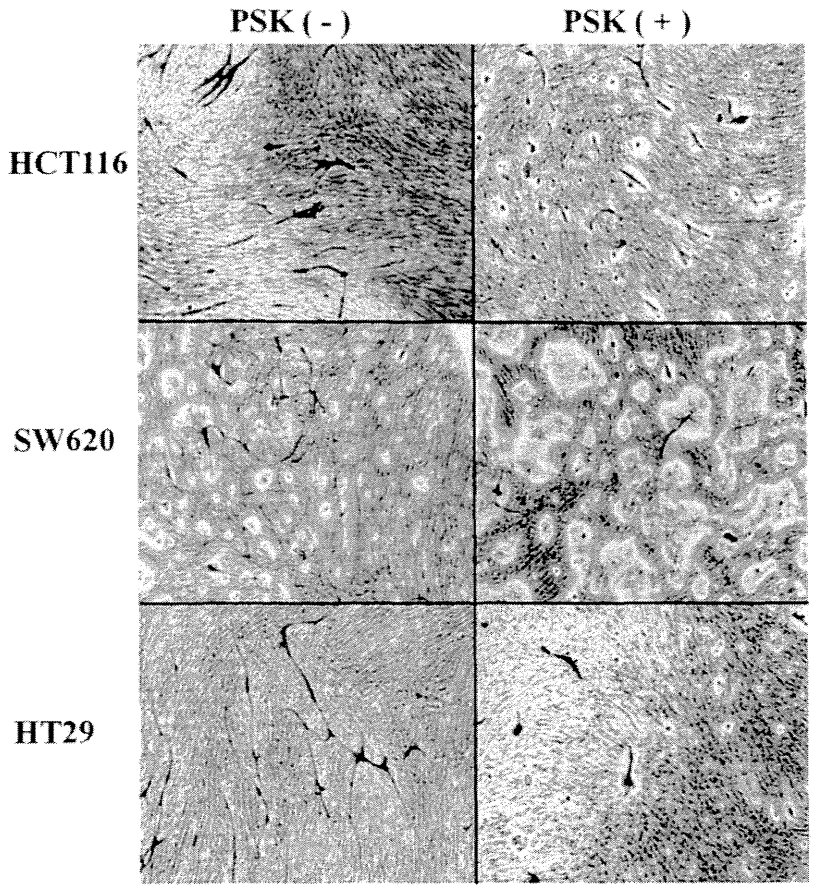

Figure 2. Tube formation in PSK-stimulated colon cancer cells. PSK-treated or untreated colon cancer cell lines were applied to the wells of a tube formation assay to investigate the effects on elongation of tube formation. The length was significantly decreased in PSK-stimulated colon cancer cells compared with untreated cells. PSK, polysaccharide K.

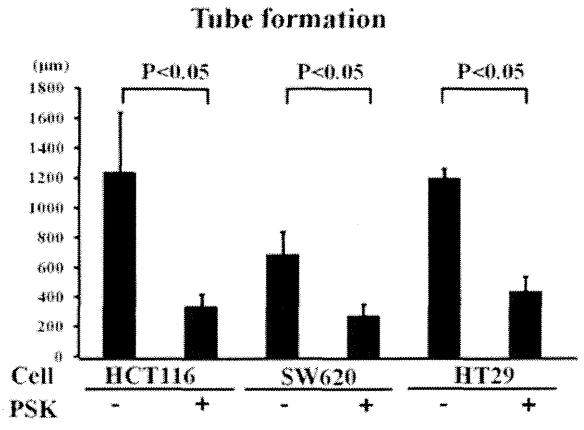

Figure 3. Evaluation of the tube formation in PSK-stimulated colon cancer cells. With tube elongation in the medium of untreated colon cancer cell lines taken to be 100%, the elongation of the PSK-treated cell lines was 40% in SW620, 27% in HCT116 and 36.5% in HT29. PSK, polysaccharide K.

that were expressed at higher levels included TIMP metallopeptidase inhibitor (TIMP1) in HCT116 and interleukin 12A (IL12A) and troponin I type 3 (TNNI3) in the HT29 cell line. There were no typical genes with an altered expression pattern in the SW620 cell line.

Tube formation in colon cancer cell lines treated with or without PSK. The medium from PSK-treated colon cancer cell lines was applied to the wells of a tube formation assay to investigate the effects of PSK on the elongation of tube formation. Tube elongation in the medium of untreated colon cancer cell lines was taken to be 100%, elongation was 40% in SW620, 27% in HCT116 and 36.5% in HT29 cells cultured in the medium of PSK-treated colon cancer cell lines (Figs. 2 and 3). Elongation was therefore significantly less than that observed in the medium of non-treated colon cancer cell lines.

Discussion

PSK, derived from the cultured mycelia of *C. versicolor*, is widely used as a nonspecific immunotherapeutic agent (1,5-8). The efficacy of PSK has been demonstrated to increase survival in patients with gastrointestinal malignancies, including gastric and colon cancer. Hematogenous metastases are considered to be a prognostic factor in colon cancer, and PSK is believed to act in the process leading to these metastases, thereby increasing survival (2-4). It has been reported that the occurrence of hematogenous metastases in colon cancer is closely correlated with increased angiogenesis, and angiogenic growth factors and angiogenic growth inhibiting factors likely contribute to the induction and propagation of angiogenesis and may eventually promote hematogenous metastases (9-13).

We investigated how the addition of PSK to the medium of cultured colon cancer cell lines affects the expression of the HIF-1α gene, which is closely associated with the expression of angiogenic growth factors, in addition to angiogenic growth factors and angiogenesis (18-23).

The expression of HIF-1α mRNA was detected in colon cancer cell lines, but the addition of PSK suppressed HIF-1α mRNA expression. The HIF-1α gene is believed to activate the production of numerous angiogenic growth factors, and has various effects on cancer, regulating at least 70 genes, most of which promote cancer (18-23). Also HIF-1α gene, oncogene and tumor suppressor gene intricately linked with the expression of angiogenic growth factors and angiogenesis inhibitors (24). A PCR array was then used to investigate the affected angiogenic growth factors and angiogenesis inhibitors. Although the suppression of genes differed between the cell lines studied, the addition of PSK suppressed numerous angiogenic growth factors and increased levels of angiogenesis inhibitors.

When the untreated colon cancer cell lines were used in a tube formation system, tube formation was promoted. By contrast, when the PSK-treated colon cancer cell lines were used, tube formation was reduced, which indicates that PSK acts to suppress angiogenesis in the strains of colon cancer cells studied.

The effects of PSK identified in the present study include the suppression of HIF-1α gene expression, the suppression of angiogenic growth factors and the enhancement of angiogenesis inhibitors in colon cancer cells. These findings demonstrate the potential of PSK to ultimately suppress angiogenesis.

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Research Article Open Access

Retrospective Analysis of Chemotherapy-Induced Nausea and Vomiting (CINV) in Colorectal Cancer Patients Treated with Antiemetics

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Abstract

Purpose: The aim of this retrospective study was to clarify the effect of the antiemetics for chemotherapy-induced nausea and vomiting associated with FOLFOX chemotherapy.

Methods: Fifty patients were given FOLFOX as chemotherapy for colorectal cancer, and granisetron were used as first-line antiemetics. The severity of CINV was evaluated using (1) questioning, (2) Common Terminology Criteria for Adverse Events version 4.0, and (3) Multinational Association of supportive care in cancer method for patient self-assessment. When a patient indicated that another antiemetic was desired, granisetron was switched to palonosetron.

Results: Forty two patients did not express a desire for another antiemetic, but eight patients expressed a desire for it. They were evaluated as Grade 2 according to the CTCAE 4.0. The MAT method identified a score of 6 points or more. Granisetron was switched to palonosetron as a second-line antiemetic. The severity of CINV decreased to Grade 1 or less, while the MAT method score decreased to 0 points in 3 patients and ≤ 4 points in 5 patients. None of the 8 patients expressed a desire for another antiemetic.

Conclusion: Granisetron/palonosetron can be thought to have improved the patients' QOL, relieved their anxiety, and contributed to continuation of the chemotherapy.

Keywords: Colorectal cancer; Chemotherapy; Chemotherapy-induced nausea and vomiting; Antiemetic; Palonosetron; Granisetron

Abbreviations: QOL: Quality of Life; CTCAE: Common Terminology Criteria for Adverse Events; CINV: Chemotherapy-Induced Nausea and Vomiting

Introduction

The last 10 years have seen striking advances in chemotherapy for unresectable, advanced, recurrent colorectal cancer. In the early 2000s, the Median Survival Time (MST) was about 14-17 months [1,2], whereas survival has been steadily extended since then, recently reaching approximately 30 months [3,4]. However, conversely, chemotherapy-related adverse reactions due to chemotherapy have become an issue, and it is not unusual for such reactions to decrease patients' Quality of life (QOL). Nausea and vomiting rank high on the list of such chemotherapy-related adverse reactions that especially impact on the daily life of patients and cause anxiety [5,6]. Granisetron is a first-generation 5-HT3 receptor antagonist and commonly used as a first-line antiemetic. Palonosetron is a second-generation 5-HT3 receptor antagonist that has recently (April, 2010) gone on the market in Japan. Compared with the first-generation antiemetic, granisetron, palonosetron is characterized by stronger affinity for the 5-HT3 receptor and a plasma half-life that is 40 hours longer [7]. For these reasons, palonosetron is said to show both acute(up to 24 hours postchemotherapy) and delayed (after 24 hours postchemotherapy) antiemetic activity. However, there have not yet been any reports of studies that investigated the efficacy of palonosetron, the second-generation 5-HT3 receptor antagonist, in colorectal cancer patients who did not respond sufficiently to the first-generation antiemetic, granisetron. The present retrospective study aimed to clarify the efficiency of the antiemetics.

Materials and Methods

Prior to being given FOLFOX as chemotherapy for unresectable, advanced, recurrent colorectal cancer, 50 patients were given granisetron (0.75 mg, intravenous) and dexamethasone (4 mg, intravenous) as first-line antiemetics to suppress Chemotherapy-Induced Nausea and Vomiting (CINV). On days 2-4 after starting the chemotherapy, dexamethasone (4 mg) was administered orally (Figure 1). Following the chemotherapy, the following were done: (1) the patient was questioned (i.e., asked whether another antiemetic was desired), (2) the severity of nausea and/or vomiting was evaluated using CTCAE version 4.0 (CTCAE 4.0), and (3) the Multinational Association of supportive care in cancer (MAT) method developed by Multinational Association of Supportive Care in Cancer (MASCC) was used for patient self assessment and recording of the severity of nausea and vomiting [8].

Results

Forty-two patients did not express a desire for another antiemetic. The CTCAE 4.0 classification of nausea/vomiting was Grade 1 or less. The MAT method showed that nausea/vomiting was a score of 3 points or less. Eight patients expressed a desire for another antiemetic (Table 1). Using the CTCAE 4.0, nausea was rated as Grade 2 in all 8 patients, while vomiting was rated as Grade 2 in 3 patients, Grade 1 in 4 patients,

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