別紙5

研究成果の刊行に関する一覧表

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
兵頭一之介	患者および家族が代替治療を望むとき(医療者としてどう対応するか)	池永 昌之，木澤 義之	ギア・チェンジ緩和医療を学ぶ二十一会	医学書院	東京	2004	106-113

雑誌

発表氏名	論文タイトル名	発表誌名	巻・号	ページ	出版年
Muro K Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, Fujita H, Takiyama W, Ohtsu T.	A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer.	Ann Oncol	15(6)	955-9	2004
Nishina T Hyodo I, Miyaike J, Inaba T, Suzuki S, Shiratori Y.	The ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase in tumour tissues of patients with metastatic gastric cancer is predictive of the clinical response to 5'-deoxy-5-fluorouridine.	Eur J Cancer	40(10)	1566-71	2004
谷水正人，佐伯光義，久野梧郎，徳永昭夫，芳仲秀造，木村映善	【ITはあなたのパートナー ベストな選択をするために 診療所編】 地域医療の新たな展開 愛媛情報スーパーハイウェイと愛媛県医師会地域医療情報ネットワーク(EMAネット)	INNERVISION	19(2付録)	18-20	2004
Hirasaki S Tanimizu M, Moriwaki T, Hyodo I, Shinji T, Koide N, Shiratori Y.	Efficacy of clinical pathway for the management of mucosal gastric carcinoma treated with endoscopic submucosal dissection using an insulated-tip diathermic knife.	Intern Med	43(12)	1120-5	2004
Hirasaki S Tanimizu M, Tsuzuki T, Tsubouchi E, Hidaka S, Hyodo I, Tajiri H.	Seronegative alpha-fetoprotein-producing early gastric cancer treated with endoscopic mucosal resection and additional surgery.	Intern Med	43(10)	926-30	2004
Hirao K Hirasaki S, Tsuzuki T, Kajiwara T, Hyodo I	Unresectable alpha fetoprotein-producing gastric cancer successfully treated with irinotecan and mitomycin C after S-1 failure.	Internal Medicine	43(2)	106-10	2004

Shirao K Hoff PM, Ohtsu A, Loehrer PJ, Hyodo I, Wadler S, Wadleigh RG, O'Dwyer PJ, Muro K, Yamada Y, Boku N, Nagashima F, Abbruzzese JL.	Comparison of the Efficacy, Toxicity, and Pharmacokinetics of a Uracil/Tegafur (UFT) Plus Oral Leucovorin (LV) Regimen Between Japanese and American Patients With Advanced Colorectal Cancer: Joint United States and Japan Study of UFT/LV.	J Clin Oncol	22(17)	3466-3474	2004
Shimo K, Mizuno M, Nasu J, Hiraoka S, Makidono C, Okazaki H, Yamamoto K, Okada H, Fujita T, Shiratori Y.	Complement regulatory proteins in normal human esophagus and esophageal squamous cell carcinoma.	J Gastroenterol Hepatol.	19(6)	643-7.	2004
Takenaka R, Okada H, Mizuno M, Nasu J, Toshimori J, Tatsukawa M, Shiratori Y, Wato M, Tanimoto Y.	Pneumocystis carinii pneumonia in patients with ulcerative colitis.	J Gastroenterol.	39(11)	1114-5.	2004
Makidono C, Mizuno M, Nasu J, Hiraoka S, Okada H, Yamamoto K, Fujita T, Shiratori Y	Increased serum concentrations and surface expression on peripheral white blood cells of decay-accelerating factor (CD55) in patients with active ulcerative colitis.	J Lab Clin Med	143(3)	152-8.	2004
Okazaki H, Mizuno M, Nasu J, Makidono C, Hiraoka S, Yamamoto K, Okada H, Fujita T, Tsuji T, Shiratori Y.	Difference in Ulex europaeus agglutinin I-binding activity of decay-accelerating factor detected in the stools of patients with colorectal cancer and ulcerative colitis.	J Lab Clin Med.	143(3)	169-74.	2004
Morita.T, Honke.Y et al	Family Experience with palliative sedation therapy for terminally ill cancer patients	J Pain and Symptom Management	28(6)	557-565	2004
Yamao T Shimada Y, Shirao K, Ohtsu A, Ikeda N, Hyodo I, Saito H, Iwase H, Tsuji Y, Tamura T, Yamamoto S, Yoshida S.	Phase II Study of Sequential Methotrexate and 5-Fluorouracil Chemotherapy Against Peritoneally Disseminated Gastric Cancer with Malignant Ascites: a Report from the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group, JCOG 9603 Trial.	Jpn J Clin Oncol	34(6)	316-22.	2004
Yoshida M Ohtsu A, Boku N, Miyata Y, Shirao K, Shimada Y, Hyodo I, Koizumi W, Kurihara M, Yoshida S, Yamamoto S.	Long-term Survival and Prognostic Factors in Patients with Metastatic Gastric Cancers Treated with Chemotherapy in the Japan Clinical Oncology Group (JCOG) Study.	Jpn J Clin Oncol.	34(11)	654-9	2004

Morita.T, Honke.Y et al	Existential concerns of terminally ill cancer patients receiving specialized palliative care in Japan	Supportive Cancer Care	12	137-140	2004
本家好文	【施設としてのホスピス】 チームケアにおける医師の役割と主張	がん患者と対症療法	15(1)	26-29	2004
森田純子，森ひろみ，兵頭一之介	【コンセンサス 外来化学療法の実際】 外来化学療法のクリニカルパス 消化器癌	コンセンサス癌治療	3(3)	144-147	2004
田中桂子，志真泰夫，本家好文	【呼吸困難のマネジメント】 呼吸困難のマネジメントの指針	ターミナルケア	14(4)	272-274	2004
小原弘之，志真泰夫，本家好文	【呼吸困難のマネジメント】 症状の緩和をどのように行うか 呼吸困難の薬物療法を中心に	ターミナルケア	14(4)	287-292	2004
兵頭一之介	がん医療における代替医療の考え方	ホスピスケア	15(2)	1-17	2004
仁科智裕，兵頭一之介，森脇俊和，日高聡，梶原猛史，筑木隆雄，平尾謙，壺内栄治，那須淳一郎，平崎照士，舛本俊一，久保義郎，栗田啓	フッ化ピリミジン系抗癌剤に治療抵抗性の転移性・再発大腸癌に対するIrinotecan Hydrochlorideを用いた化学療法の治療成績	癌と化学療法	31(9)	1361-1364	2004
森脇俊和，兵頭一之介，仁科智裕，那須淳一郎，日高聡，梶原猛史，筑木隆雄，平尾謙，壺内栄治，山内雄介，平崎照士，舛本俊一，棚田稔	術後再発・転移性膵癌に対するGemcitabine Hydrochlorideの検討	癌と化学療法	31(9)	1373-1376	2004
志真泰夫，山口研成，宮田佳典，兵頭一之介，八木安生，本家好文	末期癌患者における消化管閉塞に伴う消化器症状に対するOctreotide Acetateの臨床試験	癌と化学療法	31(9)	1377-1382	2004
舛本俊一，谷水正人，兵頭一之介	【プライマリケア医のための肝臓疾患診療マニュアル】 肝癌のターミナルケア	治療	86(9)	2529-2534	2004
兵頭一之介	【手術不能進行胃癌への化学療法をどう行うか】 胃癌の化学療法に用いられる主な薬剤とその使い方 今後期待される新しい薬剤	消化器の臨床	7(6)	633-638	2004
多嘉良稔 平儀野剛、東條雅晴、河野恒文、野川享宏、中根比呂志、兵頭一之介、長尾充展、正田孝明	温熱化学療法が有効であった末期胃癌の1例	日本ハイパーサーミア誌	20(3)	179-187	2004
平崎照士，兵頭一之介，梶原猛史，仁科智裕，舛本俊一	超音波内視鏡検査で術前深達度診断が可能であった回腸悪性リンパ腫の1例	日本消化器病学会雑誌	101(1)	41-46	2004
兵頭一之介	がんの補完代替医療(総説)	日本補完代替医療学会誌	1(1)	7-15	2004

Morita T Hyodo I, Yoshimi T, Ikenaga M, Tamura Y, Yoshizawa A, Shimada A, Akechi T, Miyashita M, Adachi I.	Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies.	Ann Oncol.	16(4)	640-7	2005
Hirasaki S, Tanimizu M, Tsubouchi E, Nasu J, Masumoto T.	Gastritis cystica polyposa concomitant with gastric inflammatory fibroid polyp occurring in an unoperated stomach	Intern Med.	44(1)	46-9.	2005
Hyodo I Amano N, Eguchi K, Narabayashi M, Imanishi J, Hirai M, Nakano T, Takashima S.	Nationwide Survey on Complementary and Alternative Medicine in Cancer Patients in Japan.	J Clin Oncol.	Feb 22; [Epub ahead of print]		2005
本家好文	放射線科医がはじめた緩和医療	緩和医療学	7(1)	83-86	2005
那須淳一郎, 平家勇司, 谷水正人, 佐々木晴子, 山田純子, 福岡しのぶ, 大住省三, 久保義郎, 青儀健二郎, 新海哲, 高島成光	家族歴調査のシステム化による家族性腫瘍相談室の運営	家族性腫瘍	5(1)	57-60	2005

第十一会

患者および家族が代替医療を望むとき

医療者としてどう対応するか

兵頭一之介

治療法の選択は科学的根拠を有する治療法の情報開示に始まり，患者と十分に相談した結果，合意を得て行われるものである．代替医療は医学的にエビデンスの十分でないものを指す．代替医療の中には，ある程度の科学的エビデンスを有するものから，ほとんどないものまで様々なものがある．

Case

健康食品に期待する癌患者と家族

66歳，男性．3年前に進行結腸癌で切除手術を受けた．2年前に多発性の肝転移と腹部リンパ節転移と診断され，これまでに2種類の化学療法を受けた．3カ月前，増悪が確認され有効な抗癌薬がないことが告げられ，以後，患者は緩和医療を受けることで同意した．前化学療法は両治療とも一時的な効果は認められたが，最終的に癌は進行し，現在，肝腫大と軽度の黄疸がみられ腹痛を訴えている．抗癌薬治療が開始されたときのインフォームド・コンセントの過程で，患者ならびに家族に生存期間中央値が約1～2年と知らされている．患者は，この頃から息子がインターネット販売で購入したキノコ類食品を利用していた．現在，患者のテーブルに置かれたバッグの中には4種類のキノコとサメ軟骨食品および利用者の体験談を掲載した単行本が数冊入れられている．患者から「利用している健康食品の効果がどの程度期待できるのか」との質問があった．

インフォームド・コンセントはとるもの？
インフォームド・コンセントは医療者がとるものではなく，患者や家族から医療者に与えるものである．したがって説明するだけでは不十分で，患者や家族からの問いかけや意見に十分に耳を傾けることが重要になる．

緩和医療の知識

医療者はエビデンスに基づくインフォームド・コンセントを行ったうえで患者の自己選択権を尊重し，可能な限り科学的な治療を提供し客観的な評価を行うよう努めている．その過程では標準的な治療法から始まり代替治療として有用性のエビデンスが劣るものをも提示している．この代替治療の中には有効性が標準治療に劣るものも含まれているが，いまだ標準治療との優劣が明らかにされていない新規の有望な治療法も含まれている．しかし，代替治療といえども現在の科学的評価法によって有効性と安全性が一定の基準で実証されているものしか提示すべきでないことはもちろんである．このように近代西洋医学における代替治療とは，標準治療の代わりに提供することができるだけの科学的検証を受けた治療法を指している．

一方，補完代替医療(CAM : complementary and alternative medicine)とは西洋医学的手法によって有効性や安全性が確認されていない医療と考えられている．代替という用語が同一であるため混乱や誤解を生じやすく，違和感をぬぐえないが，世界的にも名称については同様の状況にある．いずれにしろCAMは西洋医学的手法によって評価されていない医学ということになるが，それでは西洋医学的手法とは何か？　それは臨床試験である．臨床試験の倫理的規範はヘルシンキ宣言(Note 1)に求められ，科学的検証法は近年ICH-GCP(International Conference on Harmonization-Good Clinical Practice)へと結実している(Note 2)．つまりCAMにおいては臨床試験がほとんど行われていないということである．CAMには古くからの経験に基づく療法があったり，自然界の生物を用いたりするものが多く，臨床試験にはなじまないとする意見も多い．確かに瞑想や民族哲学的な療法などに関しては，臨床試験で評価することは困難を伴うが，医学的に臨床試験でしか評価しようのないサプリメントなども存在

Note

1．ヘルシンキ宣言

世界医師会総会において合意された被験者に対する生物医学研究についての国際的な倫理規範．十分な情報の開示と理解のうえに成り立つ自由な自発的同意が基本原則とされた．

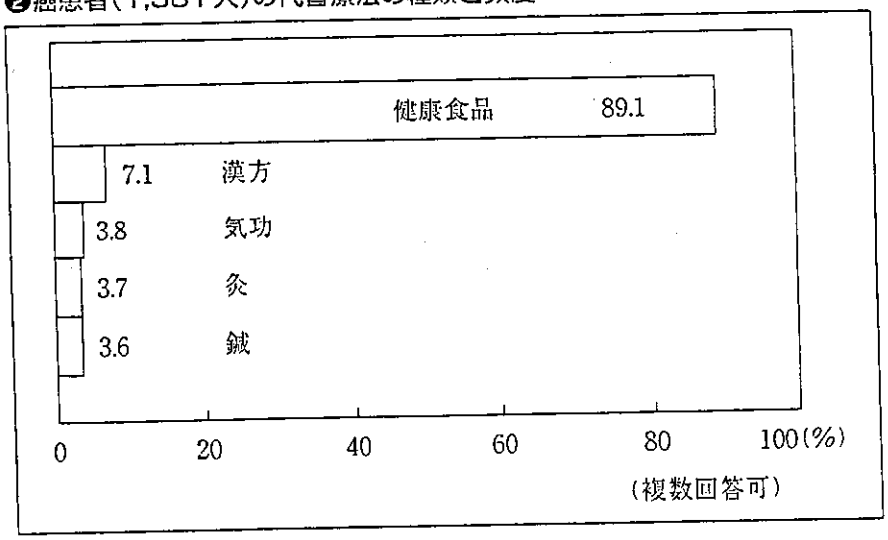
2．ICH-GCP

人に使用する医薬品を承認するための技術的要件を定めた国際的ガイドライン．ICH(International Conference on Harmonization)とは日米欧の三極で臨床試験の整合化を目的として開催された会議．GCP(Good Clinical Practice)とはわが国の臨床試験のための実施基準である．

❶補完代替医療(CAM)の種類

分類と名称	内容
代替医学系 Alternative medical systems	伝統医学系統，民族療法(東洋伝統医学，アーユルヴーダ，ユナニシャーマニズムなど)
精神・身体交流 Mind-body interventions	瞑想，催眠，舞踏，音楽，芸術療法，祈りなど
生物学に基づく療法 (代替バイオ療法) Biologically based therapies	ハーブ，特殊食品，生理活性分子(マグネシウム，メラトニン，ビタミンなど)，サメ軟骨などを利用した治療
指圧など外部からの力で治療する方法 Manipulative and body-based methods	マッサージ，整体，整骨療法など
エネルギー療法 Energy therapies	気功，霊気，タッチング療法，電磁療法

❷癌患者(1,381人)の代替療法の種類と頻度



している(❶)．米国では現在，CAMに関する多くの臨床試験を実施中である．

❶のようにCAMの範疇と考えられる医学体系は多数存在し，哲学的医学体系を構成するものからサメの軟骨やメガビタミンなどの内服治療薬あるいは健

康食品まで様々である．2001～2002年に実施した全国アンケート調査では癌患者の45％がCAMを利用し，その約9割が健康食品であった(❷)．ホスピス・緩和ケア病棟での健康食品利用者はさらに多く60％を超えていた．これまでの調査からCAM利用者の特徴は，高学歴，高収入，女性，若年者，不安の強い患者，有症状の患者とされている．

医療者側としてはCAMを利用する患者にどのように対処すべきか悩み，あるいは無視し関心を示さず放置していることも多い．遺伝子研究は飛躍的に進み，様々な癌の生物学的特性が明らかにされ，分子標的薬も次々に臨床に登場している現代，ますます医学は専門化，分業化し複雑さを増している．このような中でCAMに対して科学的評価を行うだけの価値はなく，人的，経済的医療資源と時間は有効に使われなければならないとする考えは当然である．しかしCAM提供者によるインターネット，新聞広告，体験本などを利用した巧妙な宣伝とインターネット販売をはじめとする通販機構の進歩によりCAM利用者が増加し，それに伴い患者や家族からCAMの有効性についての質問が多くなり，有害反応に対する危惧が増している．次第に臨床医にとって避けて通れない問題となりつつある．全国751人の臨床腫瘍医のアンケート調査結果では，82％が癌で使用される健康食品類には有効性はないと考え，また84％の腫瘍医が抗癌薬との相互作用を危惧している．最近，ハーブの一種であるセントジョーンズ・ワート(西洋オトギリソウ)は抗癌薬のirinotecanから，その活性体であるSN38への変換を低下(42％)させ，抗腫瘍効果を減弱させる可能性が示唆されている(JNCI 94：1187-1181, 2002)．

ギア・チェンジの実際

まず患者が利用しているCAMの内容を調査することが必要である．大多数は健康食品である．一般的に癌に対する効果は直接的なものはなく免疫を介した間接的なものとされ，そのため副作用の心配がないと宣伝されている．しかし，このような内容はまったく医学的にその有用性が検証されたものではないことを認識してもらうことが重要である．医学博士などの肩書き，○○学会での発表や難解な専門用語などは，まったく意味を持たないことを理解してもらう必要がある．また体験談は一方的な医学的に不十分な内容で，追跡ができず，その信憑性は疑わしいこと，場合によっては，捏造も可能であることも伝えることが大切である．また利用するCAMの費用も以上のことから冷静に判断する必要がある．アンケート調査の結果では約6割の患者が癌の治癒や進行抑制を期待して健康食品を利用していた．今後の治療の選択肢が緩和医療しかない

とされた患者や家族が，癌の治癒や増殖抑制を望む精神的背景は十分に理解される必要があり，注意深い対応が必要である．

以上のような内容を患者や家族と十分に話し合ったうえで，健康食品を含むCAMの利用を容認した場合，CAMによる有害事象や通常医療に及ぼす影響を観察し評価することの了承を得ておくことが大切である．同時に十分な緩和治療が提供できているか検討する．

注意すること

医療者に相談なくCAMが利用されている場合があるので，最初に確認する．将来，利用を考慮する場合には相談するよう伝える．また利用に際してはCAMの内容につき医学的にアドバイスできることを伝え，内容によっては患者が希望するCAMの利用を許容し治療経過を観察していくことを伝えておく．

患者は代替医療(多くは健康食品)に期待と疑問を抱きながら使用している場合が多く，医療者の対応は重要であることを認識しておく．CAMを頭ごなしに否定し，毛嫌いし，患者や家族の気持ちを傷つけることのないよう慎重に議論を進める．しかし，CAMが治癒，延命，症状緩和をもたらすものと過度の期待を抱き，通常医療に支障を来す場合がある．このようなときには十分時間をかけて冷静な判断を促す．それでも翻意が困難な場合には，そのうえで医療者として可能な援助を行うことを明確に伝える．

Caseの教訓

質問を受けた主治医は「使用している健康食品が癌の進行抑制や症状緩和に有効であるという医学的な根拠は乏しく，過度の期待は禁物である．経済的負担や摂取の困難さ(食欲不振や悪心をおして多数の健康食品をとる)からくる身体的・精神的負担を考えると中止することをお勧めする」と答えた．患者と息子は主治医の話した内容は十分に理解し忠告に従おうと考えたが，妻は継続を強く希望した．妻は患者に無理を強いていると感じていたが，自分の気持ちをどうしても抑えることができない状態であった．主治医と患者は相談の結果，一種類のみ継続することで妻の同意を得た．

教訓：CAMに関する不確かな都合の良い情報のみが巷にあふれ，大きな混乱を生じている．医療者の適切な認識と有害反応への注意，取り扱い業者に対する当局の適正な規制と指導が必要である．

メールアドバイス

Q 健康食品の中には癌に効果があると宣伝されているものが多数ありますが，違法ではないのですか？

現在，健康食品を定義する法律はなく，一般的に健康維持の目的で用いられ，通常の食品とは異なる形態の粒状，カプセル状などの食品と考えられています．薬理的作用により疾病の予防や改善が期待される食品(高血圧や糖尿病などに良いとされるものなど)で，法的に規定されているものには特定保健用食品があります．2003年10月7日現在，396品目が厚生労働省より認可されています．これはあくまで通常の食品の形をしたもので，錠剤やカプセル状の形態をしていないものとされています．健康食品の効能・効果を謳うことは違法です(薬事法，栄養改善法，景品交換法)．健康食品と呼ばれるものの中には錠剤，カプセル，粉末状のものを業者が健康食品と勝手に名づけて市販しているものが多くあります．現在，このような健康食品に対しては財団法人日本健康・栄養食品協会が含有成分などの製品規格，製造と加工の基準，適切な表示と広告(食品衛生法，薬事法，栄養改善法などに適合しているか)などを審査していますが，実際には無審査の健康食品が非常に多く存在しています．

文　献

1) 兵頭一之介(編)．補完・代替医療．緩和医療学　5：1-43, 2003
最新の代替医療に関する事項が，すべて掲載されているので，この分野に興味のある方はご一読ください．

2) 兵頭一之介，江口研二(共訳)．がん患者・家族との会話技術，南江堂，東京，2001
様々な状況における癌患者・家族とのコミュニケーションの方法が具体的に詳細に記載された翻訳書．会話例が多く掲載されていて読みやすい．癌にかかわる方，ぜひ一度ご覧ください．

3) 江口研二(編集)．がん治療・臨床試験のインフォームド・コンセント，南江堂，東京 1997
がん治療の臨床試験とインフォームド コンセントに関することについて知りたい方に最適．

4) Gertz MA, Bauer BA. Caring(really) for patients who use alternative therapies for cancer. J Clin Oncol 21：125-128, 2003
アメリカの代替医療に関する現状を簡単に知りたい方は，ぜひお読みください．

まとめ

緩和医療の知識

□代替医療には十分ではないが，ある程度の有効性，安全性に関する西洋医学のエビデンスを有するものと，西洋医学的検証が行われていない補完代替医療(CAM：Complementary and Alternative Medicine)とがある．

□CAMにはどのようなものがあるか知っておく．
わが国の癌のCAMの大部分は健康食品であり，医療者の認識を確認しておく．
健康食品の癌に対する効果に関するエビデンスはほとんどないか，あっても質の低いものしかないことを知っておく．

□インターネットや体験本などの過剰な宣伝により大きな誤解が生じていることが多く，治療法の科学的・医学的評価法を熟知しておくことが必要．

ギア・チェンジの実際

□CAMの内容を調べる．
□CAMの功罪を話し合う．
□患者や家族がCAMを求める精神的背景を分析する．
□CAMの効果と有害事象を観察することを伝える．
□効果と有害事象を多角的に評価する．
□十分な緩和治療が提供できているか検討する．

注意すること

□医療者に相談なくCAMが利用されている場合があるので，最初に確認しておく．
□患者はCAM(多くは健康食品)に期待と疑問を抱きながら使用している場合が多く，医療者の対応は重要であることを認識しておく．
□CAMが治癒，延命，症状緩和をもたらすものと過度の期待を抱き，通常医療に支障を来す場合がある．

Original article

Annals of Oncology 15: 955–959, 2004
DOI: 10.1093/annonc/mdh231

A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer

K. Muro[1]*, T. Hamaguchi[1], A. Ohtsu[2], N. Boku[2], K. Chin[3], I. Hyodo[4], H. Fujita[5], W. Takiyama[6] & T. Ohtsu[7]

[1]*Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo;* [2]*Division of Gastrointestinal Oncology/Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa;* [3]*Department of Medical Oncology, Cancer Institute Hospital, Tokyo;* [4]*Department of Internal Medicine, National Shikoku Cancer Center Hospital, Matsuyama;* [5]*Department of Surgery, Kurume University School of Medicine, Kurume;* [6]*Department of Surgery, Hiroshima City Asa Hospital, Hiroshima;* [7]*Aventis Pharma Ltd, Tokyo, Japan*

Received 22 December 2003; revised 8 February 2004; accepted 17 February 2004

Background: To evaluate the activity and toxicity of docetaxel in patients with metastatic esophageal cancer.

Patients and methods: Eligible patients had histologically confirmed carcinoma of the esophagus with measurable metastatic sites according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients were either chemotherapy-naïve or previously treated with one regimen of chemotherapy. Docetaxel 70 mg/m^2 was administered intravenously over 1–2 h, every 21 days.

Results: Of 52 patients enrolled in this study, three were excluded because they did not receive docetaxel due to worsening condition after enrollment. Thirty-six patients had received prior platinum-based chemotherapy. The majority of patients (94%) had squamous cell carcinoma. Ten of 49 evaluable patients [20%; 95% confidence interval (CI) 10–34%] showed a partial response. Of the 10 partial responses, six patients had received prior platinum-based chemotherapy. Grade 3 or 4 neutropenia was noted in 43 of 49 patients (88%), and nine of 49 patients (18%) developed febrile neutropenia. Twenty-eight of 49 patients (57%) required lenograstim. Grade 3 anorexia and fatigue occurred in nine (18%) and six (12%) patients, respectively. Median survival time was 8.1 months (95% CI 6.6–11.3) and the 1-year survival rate was 35% (95% CI 21–48%).

Conclusions: Docetaxel as a single agent is effective in esophageal cancer, but careful management of neutropenia is needed.

Key words: docetaxel, esophageal cancer, phase II study, RECIST, single agent

Introduction

In the USA, 13 200 new cases of esophageal cancer were diagnosed in 2001, and >90% of patients (12 500) died of their disease, comprising 2% of all cancer deaths [1]. The incidence of esophageal cancer is on the rise, with more cases of adenocarcinoma of the esophagus being reported as compared with squamous cell carcinoma. This phenomenon is a common trend in most Western countries [2]. In Japan, 9991 patients died of esophageal cancer in 1999, accounting for 3.4% of Japanese cancer deaths, which was the sixth leading cause of death in Japanese males. However, in contrast to the West, squamous cell carcinoma is still the most common histological type of esophageal cancer in Japan [3].

Surgery alone as the standard treatment in the management of locally advanced esophageal cancer shows a poor prognosis, with 5-year survival rates of 5–30% [4]. The prognosis is extremely poor, despite treatments with curative intent, because esophageal cancer spreads very quickly to adjacent structures such as the aorta, the trachea and the left main bronchus, and frequently results in lymph node metastases. Therefore, there is a high incidence of residual tumor or recurrence after potentially curative local therapy.

Non-surgical therapies for esophageal cancer include cisplatin, 5-fluorouracil (5-FU), mitomycin C, vindesine [5, 6], paclitaxel [7, 8] and vinorelbine [9]. The combination of cisplatin and continuous-infusion 5-FU is regarded as the standard regimen for both squamous cell carcinoma and adenocarcinoma of the esophagus, with a 25–35% response rate in metastatic disease. However, complete responses are rare, median duration of response is generally short, median survival is only 6–10 months [5, 10–12] and toxicity of cisplatin-based chemotherapy is often substantial. New combination regimens such as paclitaxel–cisplatin–5-FU [8, 13] and irinotecan–cisplatin [14] have not shown improvement in terms of response and survival compared with cisplatin plus 5-FU. A 5-year survival rate of 27% has been reported with chemoradiotherapy [15]. New agents and therapeutic strategies for esophageal cancer are needed urgently.

Docetaxel has shown extensive cytotoxic activity in animal models, as well as antitumor activity against various common cancers in clinical studies [16]. Clinical trials of single-agent

**Correspondence to:* Dr K. Muro, Division of Gastrointestinal Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3542-3815; E-mail: kmuro@ncc.go.jp

docetaxel have been reported in patients with esophageal cancer [17, 18]; however, these single-agent trials had small sample sizes and the results remain controversial. The present phase II clinical trial investigates the clinical activity and tolerability of docetaxel as a single agent in Japanese patients with metastatic esophageal cancer. The dose of docetaxel used, 70 mg/m^2 every 3 weeks, was based on the results of a previous Japanese study [19].

Patients and methods

Inclusion criteria

Each patient was required to meet the following eligibility criteria: histologically proven esophageal cancer; measurable metastatic lesions assessed by Response Evaluation Criteria in Solid Tumors (RECIST) [20]; no more than one prior chemotherapy regimen; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; age 20–74 years; adequate baseline bone marrow function (hemoglobin level ≥9 g/dl, white blood cell count ≥4000/mm^3 and ≤10 000/mm^3, neutrophil count ≥2000/mm^3 and platelet count ≥100 000/mm^3); adequate hepatic function (total bilirubin level ≤1.5 mg/dl, and aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels ≤2.5× the upper limit of normal); adequate renal function (serum creatinine level ≤1.5 mg/dl); adequate respiratory and cardiac function (PaO_2 ≥60 mmHg, normal ECG); a life expectancy of at least 2 months; and written informed consent.

Exclusion criteria

Exclusion criteria included: active infection; serious complications (severe heart disease, pulmonary fibrosis, interstitial pneumonitis and tendency to bleeding); neuropathy grade ≥2 by National Cancer Institute–common toxicity criteria (NCI–CTC) version 2.0 [21]; edema grade ≥2 (NCI–CTC); active concomitant malignancy; symptomatic metastases of the central nervous system; pleural or pericardial effusion or ascites that required drainage; history of drug hypersensitivity; pregnant and lactating females; females of childbearing age, unless using effective contraception; concurrent treatment with corticosteroids; and other serious medical conditions.

Before being enrolled in the study, all patients underwent a physical examination and a complete blood cell count with differential serum chemistry analysis, arterial blood sampling, chest X-ray, ECG and computed tomography scan of the abdomen and other target sites.

Treatment plan

Docetaxel 70 mg/m^2 (Taxotere; Aventis Pharma Ltd, Tokyo, Japan) was infused over 1–2 h. Treatment was repeated every 3 weeks and continued unless there was evidence of disease progression or unacceptable toxicity.

The dose of docetaxel was adjusted according to hematological and other toxicities observed in the previous course. Docetaxel 70 mg/m^2 was reduced to 60 mg/m^2, if one of the following occurred: grade 4 neutropenia lasting for 5 days or longer; grade 3 neutropenia with fever with a requirement for intravenous antibiotics lasting for ≥3 days; grade 3 thrombocytopenia lasting ≥5 days; grade 3 thrombocytopenia with bleeding that required platelet transfusion; and grade 3 non-hematological toxicity other than nausea/vomiting, anorexia, fatigue or hypersensitivity. Lenograstim (Neutrogin; Chugai Pharmaceuticals Co., Ltd, Tokyo, Japan) was administered subcutaneously when grade 4 neutropenia or grade 3 neutropenia with fever occurred. If one of the above toxicities occurred at a dose of 60 mg/m^2, docetaxel was discontinued.

No routine premedication for hypersensitivity reactions was given and there was no routine prophylactic administration of antiemetics or granulocyte colony-stimulating factors. When hypersensitivity reactions occurred, docetaxel administration was stopped immediately, and corticosteroids and antihistamines were given. Patients who experienced hypersensitivity reactions were pretreated with these drugs in subsequent courses. Patients who experienced edema or nausea/vomiting were allowed prophylactic administration of corticosteroids or antiemetics, respectively, in subsequent courses.

Criteria for response

Standard clinical measurements and radiological examination were used to assess tumor response according to RECIST. Furthermore, we also used the World Health Organization (WHO) response criteria [22] and a modified criteria of the Japanese Society for Esophageal Diseases [23]. A complete response required disappearance of all evidence of tumor for at least 4 weeks; endoscopic confirmation of no cancer cells was required for patients with primary tumor. A partial response was defined as a >50% reduction in the sum of the longest perpendicular diameters of indicator lesions in WHO criteria, and as a >30% reduction in the sum of the longest diameters of target lesions by RECIST, for a period of at least 4 weeks. Patients were assessed for response every 3 weeks. An independent review committee confirmed the observed responses by radiological and endoscopic examinations.

Statistical methods

The number of patients to be enrolled was planned using a modified multistage Fleming design [24] based on an expected docetaxel response rate of 15% and a non-response rate of 5%, with α error of 0.05 (one-tailed) and β error of 0.2. The required number of patients was 44. An interim analysis was planned when 20–24 patients were enrolled. If none of the first 20–24 patients had a partial or complete response, the trial was to be stopped. If a major objective response was confirmed in any of the first 20–24 patients studied, accrual was to be continued to a total of 44.

Overall survival was measured from the start of the treatment to the date of death or the last confirmed date of survival. The Kaplan–Meier method was used to estimate the overall survival curves. Survival time was censored at the last confirmation date if the patients were alive.

Results

Patient characteristics

Of the 52 patients enrolled in the study from 14 hospitals in Japan between May 2000 and February 2002, the majority were male. Three patients never received docetaxel due to worsening condition after enrollment, and were excluded from the analysis. Thus, 49 patients with metastatic esophageal cancer were evaluable for both the response and toxicity analyses. Patient baseline characteristics are listed in Table 1. The most common histological type seen was squamous cell carcinoma (94%), with lymph nodes (61%) as the main target site of metastases. Ninety per cent of the patients had undergone at least one prior anticancer treatment modality (surgery, chemotherapy, radiotherapy and/or chemoradiotherapy). Prior chemotherapeutic regimens were mostly comprised of 5-FU and platinum combinations.

Response and survival

Response results are summarized in Table 2. There were no complete responses and response rates by both RECIST and WHO criteria were comparable. Ten of the 49 evaluable patients [20%; 95% confidence interval (CI) 10–34%] achieved partial responses using RECIST and 12 (24%; 95% CI 13–39%)partial responses by the WHO criteria. Of the 10 partial responses by RECIST,

Table 1. Baseline patient characteristics ($n = 49$)

Parameter	n (%)
Age (years)	
Median	64
Range	46–73
Sex	
Male	46 (94)
Female	3 (6)
ECOG performance status	
0	28 (57)
1	21 (43)
Histological type	
Squamous cell carcinoma	46 (94)
Adenocarcinoma	1 (2)
Others	2 (4)
Prior treatment status	
Esophagectomy	25 (51)
Chemotherapy	38 (78)
Chemotherapy for metastatic disease	32 (65)
Postoperative adjuvant chemotherapy	6 (12)
Radiotherapy	23 (47)
Chemoradiotherapy	15 (31)
None	5 (10)
Prior chemotherapy regimen	
5-Fluorouracil + cisplatin	25 (51)
5-Fluorouracil + nedaplatin	11 (22)
Others	2 (4)
None	11 (22)
Target site of metastasis	
Lymph nodes	30 (61)
Lung	16 (33)
Liver	11 (22)
Others	6 (12)

ECOG, Eastern Cooperative Oncology Group.

six patients (60%) had prior history of platinum-based treatment. The response rates in patients with prior chemotherapy and with no prior chemotherapy were 16% (six of 38) and 36% (four of 11), respectively. The response rates in target sites of metastases by RECIST were 25% (four of 16) in lung, 18% (two of 11) in liver and 20% (six of 30) in lymph nodes. The duration of response ranged from 1.5 to 14.7 months and the median duration of response was 4.7 months by RECIST. Stable disease and progressive disease were each observed in 19 patients (39%). The survival of 49 evaluable patients is shown in Figure 1. With a median follow-up duration of 7.8 months, the median survival time was 8.1 months (95% CI 6.6–11.3) and the 1-year survival rate was 35% (95% CI 21–48%).

Table 2. Response in assessable patients ($n = 49$)

Type of response	Responders [n (%)]	
	RECIST	WHO
Complete response	0	0
Partial response	10 (20)	12 (24)
Stable disease	19 (39)	15 (31)
Progressive disease	19 (39)	21 (43)
Not evaluated	1 (2)	1 (2)

RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

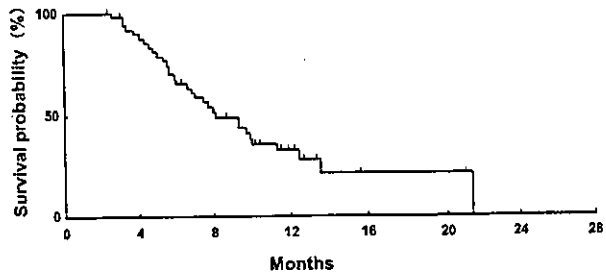


Figure 1. Overall survival for all 49 patients eligible for the study.

Toxicity

Docetaxel was generally well tolerated. Hematological and non-hematological toxicities are summarized in Table 3. The most common and severe, but reversible, toxicity of docetaxel on this schedule was neutropenia. Leucocytopenia (grade 3 and 4) and neutropenia (grade 3 and 4) occurred in 36 (73%) and 43 (88%) patients, respectively. Grade 4 leukopenia and grade 4 neutropenia occurred in 12 (24%) and 36 (73%) patients, respectively. Nine patients (18%) developed febrile neutropenia. Dose reductions occurred in 18 of 49 patients (37%) and 53 of 171 courses (31%). The relative dose intensity was 0.893. Lenograstim was given to 28 of 49 patients (57%) and in 99 of entire 171 courses (58%). The median time to the nadir of the neutropenia was 9 days. The median time from the nadir to recovery ($\geq 2000/mm^3$) was 6 days when using lenograstim, as compared with 10 days without lenograstim. Anemia and thrombocytopenia were infrequent and mild.

The non-hematological toxicities were generally mild. Anorexia and fatigue were the most common non-hematological toxicities. Grade 3 anorexia and fatigue occurred in nine (18%) and six (12%) patients, respectively.

Discussion

The present investigation was undertaken to assess the activity and tolerability of docetaxel, administered once every 3 weeks at a dose of 70 mg/m^2, in metastatic esophageal cancer. Single-agent docetaxel in this group of patients demonstrated a response rate of

Table 3. Toxicity in assessable patients

	NCI–CTC grade [*n* (%)]				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3
Hematological toxicity					
Neutropenia	2 (4)	4 (8)	7 (14)	36 (73)	43 (88)
Febrile neutropenia	–	–	8 (16)	1 (2)	9 (18)
Leukopenia	0 (0)	13 (27)	24 (49)	12 (24)	36 (73)
Anemia	8 (16)	19 (39)	3 (6)	3 (6)	6 (12)
Thrombocytopenia	11 (23)	1 (2)	2 (4)	0 (0)	2 (4)
Non-hematological toxicity					
Anorexia	22 (45)	5 (10)	9 (18)	0 (0)	9 (18)
Fatigue	26 (53)	12 (24)	6 (12)	0 (0)	6 (12)
Diarrhea	15 (31)	2 (4)	3 (6)	0 (0)	3 (6)
Nausea	14 (29)	2 (4)	2 (4)	–	2 (4)
Vomiting	6 (12)	2 (4)	0 (0)	0 (0)	0 (0)

NCI–CTC, National Cancer Institute Common Toxicity Criteria.

20–24%, with stable disease observed in 31–39% of patients using the RECIST and WHO criteria. Neutropenia was the most common adverse event, but was well managed with lenograstim.

The response rate of 36% observed in chemotherapy-naïve patients (albeit only 11 patients) is comparable to responses obtained with cisplatin plus 5-FU, the standard treatment in patients with metastatic esophageal cancer. In our study, the response rate of 16% in patients with prior chemotherapy was moderate. Single-agent docetaxel 75–100 mg/m^2 in second-line treatment of esophageal cancer has demonstrated overall response rates of 18–28% [17, 18]. Whereas the phase II trial in France of docetaxel at 100 mg/m^2 every 3 weeks as a second-line chemotherapy showed that docetaxel is an effective treatment for metastatic esophageal cancer in pretreated patients, with an overall response rate of 28% [17], the phase II trial in the USA reported that docetaxel at a dose of 75 mg/m^2 every 3 weeks was ineffective in pretreated patients with adenocarcinoma of the esophagus [18]. However, these single-agent docetaxel trials were limited by their small sample size (n <25). Most of the patients in the current study had squamous cell carcinoma, whereas, all the patients in other studies had adenocarcinoma [18, 25].

Docetaxel was fairly well tolerated. There were no treatment-related deaths. Grade 3 and 4 neutropenia, which was the most common and severe toxicity, was observed in a majority of the patients, but only one-fifth developed febrile neutropenia. Thirty-seven per cent of patients required dose reductions of docetaxel and 57% were given lenograstim for neutropenia. The median time from the nadir to recovery of neutropenia was reduced to 6 days by using lenograstim, as compared with 10 days without lenograstim.

The present investigation assessed docetaxel at a dose of 70 mg/m^2. A previous Japanese phase I trial of docetaxel determined the maximum-tolerated dose to be 70–90 mg/m^2, with neutropenia as the dose-limiting toxicity [26]. Therefore, the recommended dose of docetaxel for phase II trials in Japan is 60 mg/m^2 every 3 weeks, which is lower than the standard dose of 75–100 mg/m^2 used in Western countries. This difference is based on different criteria for dose-limiting toxicities in clinical phase I trials [27], and not to racial differences in docetaxel pharmacokinetics [28]. The tolerability of docetaxel at a dose of 70 mg/m^2 in Japanese population was confirmed by a phase II dose-escalation study in ovarian cancer [19], and consequently the present study was performed at that dose.

The results of this study suggest that single-agent docetaxel 70 mg/m^2 every 3 weeks in metastatic esophageal cancer is an effective feasible schedule under careful management of neutropenia. Future studies of docetaxel alone or in combination in locally advanced esophageal cancer are warranted.

Acknowledgements

This study was supported by a grant from Aventis Pharma Ltd.

References

1. Greenlee RT, Hill-Harmon MB, Murray T et al. Cancer Statistics, 2001. CA Cancer J Clin 2001; 51: 15–36.
2. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol 1999; 26: 2–8.
3. Foundation for Promotion of Cancer Research. Cancer Statistics in Japan Editorial Board. Tokyo, Japan: National Cancer Center 2001.
4. National Cancer Institute. Esophageal Cancer Treatment (PDQ®): Treatment Information for Health Professionals. [On-line]. http://www.cancer.gov/cancerinfo/pdq/treatment/esophageal/healthprofessional/ (2 April 2004, date last accessed).
5. Enzinger PC, Ilson DH, Kelse DP. Chemotherapy in esophageal cancer. Semin Oncol 1999; 26: 12–20.
6. Siewert JR, Stein HJ, Sendler A et al. Esophageal cancer: clinical management. In Kelsen DP, Daly JM, Kern SE et al. (eds): Gastrointestinal

Oncology: Principles and Practice. Philadelphia, PA: Lippincott Williams & Wilkins 1997; pp. 261–287.

7. Ajani JA, Ilson DH, Daugherty K et al. Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994; 86: 1086–1091.
8. Adelstein DJ, Rice TW, Rybicki LA et al. Does paclitaxel improve the chemoradiotherapy of loco-regionally advanced esophageal cancer? A non-randomized comparison with fluorouracil-based therapy. J Clin Oncol 2000; 18: 2032–2039.
9. Conroy T, Etienne PL, Adenis A et al. Phase II trial of vinorelbine in metastatic squamous cell esophageal carcinoma. J Clin Oncol 1996; 14: 164–170.
10. Bleiberg H, Conroy T, Paillot B et al. Randomized phase II study of cisplatin and 5-FU versus cisplatin alone in advanced squamous cell esophageal cancer. Eur J Cancer 1997; 33: 1216–1220.
11. Iizuka T, Kakegawa T, Ide H et al. Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal Oncology Group Trial. Jpn J Clin Oncol 1992; 22: 172–176.
12. Hayashi K, Ando N, Watanabe H et al. Phase II evaluation of protracted infusion of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG) Trial (JCOG9407). Jpn J Clin Oncol 2001; 31: 419–423.
13. Ilson DH, Ajani J, Bhalla K et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 1998; 16: 1826–1834.
14. Ilson DH, Saltz L, Enzinger P et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 1999; 17: 3270–3275.
15. al-Sarraf M, Martz K, Herskovic A et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 1997; 15: 277–284.
16. Sparreboom A, van Tellingen O, Nooijen WJ, Beijnen JH. Preclinical pharmacokinetics of paclitaxel and docetaxel. Anticancer Drugs 1998; 9: 1–17.
17. Metges J, Hennequin C, Ychou M et al. Docetaxel as a second-line chemotherapy in metastatic esophageal cancer: a French study. Proc Am Soc Clin Oncol 2001; 20: 160a (Abstr 635).
18. Heath EI, Urba S, Marshall J et al. Phase II trial of docetaxel chemotherapy in patients with incurable adenocarcinoma of the esophagus. Invest New Drugs 2002; 20: 95–99.
19. Fujiwara K, Kohno I, Tanaka K et al. Phase II dose escalation: A novel approach to balancing efficacy and toxicity of anticancer agents. Anticancer Res 1999; 19: 639–644.
20. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92: 205–216.
21. National Cancer Institute. National Cancer Institute Common Toxicity Criteria. [On-line]. http: //ctep.info.nih.gov/reporting/index.html (2 April 2004, date last accessed).
22. Miller AB, Hogestraeten B, Staquet M et al. Reporting results of cancer treatment. Cancer 1981; 47: 207–214.
23. Kanehara S. Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus, 9th edition. Tokyo, Japan: Japanese Society for Esophageal Diseases 1999.
24. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics 1982; 38: 143–151.
25. Einzig AI, Neuberg D, Remick SC et al. Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: the Eastern Cooperative Oncology Group (ECOG) results of the protocol E1293. Med Oncol 1996; 13: 87–93.
26. Taguchi T, Furue H, Niitani H et al. Phase I clinical trial of RP56976 (docetaxel) a new anticancer drug. Gan To Kagaku Ryoho 1994; 21: 1997–2005.
27. Extra JM, Rousseau F, Bruno R et al. Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. Cancer Res 1993; 53: 1037–1042.
28. Tanigawara Y, Sasaki Y, Otsu T et al. Population pharmacokinetics of docetaxel in Japanese patients. Proc Am Soc Clin Oncol 1996; 15: 479 (Abstr 1518).

ELSEVIER

European Journal of Cancer 40 (2004) 1566–1571

European Journal of Cancer

www.ejconline.com

The ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase in tumour tissues of patients with metastatic gastric cancer is predictive of the clinical response to 5′-deoxy-5-fluorouridine

Tomohiro Nishina [a,*], Ichinosuke Hyodo [a], Jiro Miyaike [b], Tomoki Inaba [c], Seiyuu Suzuki [d], Yasushi Shiratori [e]

[a] *Department of Medical Oncology, National Shikoku Cancer Center, 13 Horinouchi, Matsuyama, Ehime 790 0007, Japan*
[b] *Department of Internal Medicine, Saiseikai Imabari Hospital, Japan*
[c] *Department of Internal Medicine, Kagawa Prefectural Central Hospital, Japan*
[d] *Department of Internal Medicine, Sumitomo Beshi Hospital, Japan*
[e] *Department of Medicine and Medical Science, Okayama University Graduate School of Medicine and Dentistry, Japan*

Received 6 October 2003; received in revised form 24 February 2004; accepted 25 February 2004
Available online 7 May 2004

Abstract

The aim of this work was to determine whether intratumour contents of thymidine phosphorylase (TP), which converts 5′-deoxy-5-fluorouridine (5′-DFUR) to 5-fluorouracil, and dihydropyrimidine dehydrogenase (DPD), which degrades 5-fluorouracil to inactive molecules, could be useful in predicting the response of patients with metastatic gastric cancer to chemotherapy using 5′-DFUR. Endoscopic biopsy specimens for the measurement of TP and DPD were obtained from the primary lesions before the start of combination chemotherapy, in which 5′-DFUR, cisplatin and mitomycin C were administered. TP and DPD were measured by enzyme-linked immunosorbent assays after the objective responses to chemotherapy had been confirmed. Twenty five patients were enrolled in this study and data for 22 patients in whom responses were confirmed were analysed. The median levels (ranges) of TP and DPD were 80 (4.9–360) and 44 (15–82) U/mg protein, respectively. The median value (range) of TP to DPD ratios was 1.9 (0.25–5.1). Eight patients with a complete or partial response to chemotherapy had significantly higher TP to DPD ratios than did the remaining patients with stable or progressive disease ($P = 0.014$). When a cut-off level of TP to DPD ratio was defined as the median value, the high-ratio group ($n = 11$) showed a significantly higher response rate (64% vs. 9.1%, $P = 0.024$) than the low-ratio group ($n = 11$). Overall survival of the high-ratio group was significantly longer than that of the low-ratio group (the median survival time; 300 days vs. 183 days, $P = 0.047$). The efficacy of 5′-DFUR could be optimised by preselecting patients with high TP/DPD ratios in their tumour tissues, and this would be applicable to the treatment with capecitabine.

Keywords: Thymidine phosphorylase; Dihydropyrimidine dehydrogenase; Gastric cancer; 5′-Deoxy-5-fluorouridine; Capecitabine; Mitomycin C; Cisplatin; ELISA

1. Introduction

Many methods for predicting the susceptibility of a cancer to various chemotherapy regimens have been investigated. One of the best known is chemosensitivity testing by culturing of tumour cells with the chemotherapeutic agents [1,2]. Another useful approach is the analysis of enzymes involved in the activation or inactivation of chemotherapeutic agents. However, the clinical relevance of such tests has not been established.

Thymidine phosphorylase (TP) is an enzyme involved in pyrimidine nucleoside metabolism. It has been

* Corresponding author. Tel.: +81-89-932-1111; fax: +81-89-931-2428.
E-mail address: tnishina@shikoku-cc.go.jp (T. Nishina).

0959-8049/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.02.019

recently reported that TP is identical to platelet-derived endothelial cell growth factor and has been implicated in angiogenesis [3–5]. It has also been reported that high expression of TP in tumours was indicative of a poor prognosis [6]. TP is expressed in a wide variety of solid tumours (carcinomas of the breast, stomach, colon, pancreas and lung), and its content is higher in tumour tissues than in adjacent normal tissues [7,8]. Capecitabine and 5′-deoxy-5-fluorouridine (5′-DFUR), which is an intermetabolite of capecitabine, are oral prodrugs of 5-fluorouracil (5-FU), and TP is an essential enzyme that converts them to 5-FU [9,10]. High amounts of TP in tumours are suggested to enhance the efficacy of 5′-DFUR [11]. 5′-DFUR is currently being used for the treatment of gastric cancer in Japan [12,13]. Conversely, 5-FU is catabolised to biologically inactive molecules such as dihydrofluorouracil by dihydropyrimidine dehydrogenase (DPD) and DPD reduces the efficacy of 5-FU against tumours [14–16].

Recently, it was revealed that the efficacy of 5′-DFUR was correlated with the ratio of TP to DPD (TP/DPD) activity in human cancer xenograft models [17]. Furthermore, a clinical study using 5′-DFUR in adjuvant chemotherapy showed that patients with a high TP/DPD ratio in gastric cancer tissues had longer disease-free survival than did the patients with a low TP/DPD ratio [18]. Thus, the efficacy of 5′-DFUR is strongly influenced by the contents of TP and DPD in the tumour tissues. Recently, convenient enzyme-linked immunosorbent assays (ELISA) for measuring TP and DPD in human cancer tissues were developed [7,8]. The TP and DPD contents determined by each ELISA showed good correlation in clinical samples of tumour tissues with those determined by enzyme-activity assays [7,8]. This enabled us to measure those enzymes quantitatively in small portions of biopsy specimens, some comprising as little as 10 mg of tissue.

On the basis of these data, we conducted a prospective multicentre trial to investigate the relation between TP and DPD in tumour tissues measured by ELISA and the efficacy of 5′-DFUR.

2. Materials and methods

2.1. Patient population and eligibility

Patients were eligible for this study if they met the following inclusion criteria: (a) Patients having histologically proven gastric adenocarcinoma; (b) patients with advanced or recurrent gastric cancer with measurable metastatic lesions; (c) biopsy specimens taken from the primary lesion for the TP and DPD assays; (d) patients not less than 20 years old; (e) performance status of 0–2 (Eastern Cooperative Oncology Group); (f) no prior 5′-DFUR administration; (g) no severe major organ dysfunction; (h) no severe complications; (i) expected to survive more than 8 weeks and (j) written informed consent obtained.

The institutional review board of each participating institution approved this study.

2.2. Treatment methods

The treatment regimen was as follows: 5′-DFUR, 1200 mg/m^2 per day, was given orally from days 1 to 5; cisplatin, 10 mg/m^2 per day, was given by 30-min intravenous drip infusion on days 1 and 4; mitomycin C (MMC), 5 mg/m^2 per day, was given by bolus intravenous injection on day 8. This treatment was repeated every 2 weeks and was continued until progression or until occurrence of unacceptable adverse reactions.

2.3. Response criteria and treatment evaluation

The response to treatment was evaluated according to revised World Health Organisation criteria (Response Evaluation Criteria in Solid Tumours) every 4–6 weeks [19]. The response of each patient to the treatment was assessed by a group of extramural reviewers. All adverse reactions were graded according to the National Cancer Institute Common Toxicity Criteria version 2.

2.4. Preparation of biopsy specimens

Fresh endoscopic biopsy specimens (at least five biopsy samples from each patients) taken for the measurement of TP and DPD were sampled from primary lesions before the start of chemotherapy, after informed consent had been obtained. Samples from each patient were immediately frozen and stored at −80 °C. After the response to chemotherapy had been confirmed, each specimen was homogenised in a 10-fold volume of 10 mM Tris–HCl buffer (pH 7.4) containing 15 mM NaCl, 1.5 mM $MgCl_2$ and 50 μM potassium phosphate, then centrifuged at 10,000*g* for 15 min. The supernatant was stored at −80 °C. The protein concentration in the supernatant extracted from the tumour tissue was determined using a DC Protein Assay Kit (Bio-Rad Laboratories, Hercules, CA).

2.5. TP ELISA

TP in tumour tissues was measured by ELISA [7], and the enzyme contents were expressed as U/mg protein, where 1 U was equivalent to the amount of TP generating 1 μg of 5-FU in 1 h. The interassay precision of TP ELISA had a coefficient of variation (CV) of 8.6%.

2.6. DPD ELISA

DPD in tumour tissues was measured by a sandwich ELISA using two monoclonal antibodies specific to human DPD [8]. Enzyme contents were expressed as U/mg protein, where 1 U was equivalent to the amount of DPD catabolising 1 pmol of 5 FU/min. The interassay precision of DPD ELISA had a CV of 2.5%.

2.7. Statistical analysis

Differences among TP and DPD contents and TP/DPD ratios were analysed using the Mann–Whitney U test. Differences in response rates were analysed using Fisher's exact test. Overall survival rate was determined using the Kaplan–Meier method, and the log-rank test was used to calculate the difference in survival between the groups. P-values $\leqslant 0.05$ were regarded as statistically significant. All analyses were performed using SPSS software (version 11.5J; SPSS Inc., Tokyo).

3. Results

3.1. Case analysis and background factors

A total of 25 eligible patients was enrolled in the study between April 1999 and March 2002. Three patients could not have their responses evaluated because 5′-DFUR could not be administered sufficiently, due to gastrointestinal stenosis, and their treatments were terminated or changed too early. Responses to the chemotherapy were confirmed for 22 patients, and TP and DPD in the biopsy specimens from these patients were determined by ELISA. The backgrounds of these patients are shown in Table 1.

Table 1
Patient characteristics

Characteristics	Number of patients ($n = 22$)
Age (years)	
Median	66
Range	32–78
Sex	
Male	13
Female	9
Performance status (ECOG)	
0	10
1	10
2	2
Prior treatment	
Chemotherapy	3
Target lesion	
Lymph node	18
Liver	7
Lung	1
Histopathological type	
Differentiated	12
Undifferentiated	10

ECOG, Eastern Cooperative Oncology Group.

3.2. Response to chemotherapy and toxicity

The responses to treatment were: complete response (CR) one, partial response (PR) seven, stable disease (SD) six and progressive disease (PD) eight. The overall response rate was 36% (8/22). Grade 3 or 4 toxicity was caused by anorexia (4%), neutropenia (28%), anaemia (8%) and thrombocytopenia (12%). There were no treatment-related deaths.

3.3. Relationship between TP and DPD and responses to chemotherapy

The values of TP, DPD and TP/DPD ratios for each patient are plotted in Fig. 1(a), (b) and (c), respectively. The median TP for all 22 patients was 80 U/mg protein (range 4.9–360 U/mg protein) and that of DPD was 44 U/mg protein (range 15–82 U/mg protein). The median TP/DPD ratio was 1.9 (range 0.25–5.1). Neither TP nor DPD contents were significantly different between the responder (CR + PR) and the non-responder (SD + PD) groups ($P = 0.25$ and $P = 0.23$, respectively) (Fig. 1(a) and (b)). There was a considerable overlap for the distribution of TP/DPD ratios between responders and non-responders, but the ratios were significantly higher in the responder group than in the non-responder group ($P = 0.014$) (Fig. 1(c)). When a cut-off level for TP and DPD contents was assigned as the median value, there were no significant differences in response rates between the high- and low-level groups (response rate for TP, 55% vs. 18%, $P = 0.18$; response rate for DPD, 27% vs. 46%, $P = 0.66$). However, when the median value of the TP/DPD ratios was designated as a cut-off level, the high TP/DPD ratio group had a significantly higher response rate than did the low ratio group (64% vs. 9.1%, $P = 0.024$) (Table 2).

There was no significant correlation between the TP/DPD ratios and the severity of toxicities.

3.4. Survival

Only one patient was alive for 630 days up to the final follow-up time and the remaining patients were all dead due to tumour progression. The overall median survival time (MST) was 240 days. When each cut-off level for TP and DPD was assigned as the median value, there were no significant differences in survival between the high- and low-level groups (MST for TP, 207 days vs. 284 days, $P = 0.91$; MST for DPD, 240 days vs. 207 days, $P = 0.62$). When the median value