厚生労働科学研究費補助金

がん臨床研究事業

原発不明がんの診断・効果的治療の確立に関する研究

平成19年度～21年度　総合研究報告書

主任研究者　中　川　和　彦

平成22（2010）年　3月

別紙１

厚生労働科学研究費補助金

がん臨床研究事業

原発不明がんの診断・効果的治療の確立に関する研究

平成１９年度～２１年度　総合研究報告書

主任研究者　中川　和彦

平成２２（２０１０）年　３月

別紙２

目　　次

Ⅰ．総合研究報告

原発不明がんの診断・効果的治療の確立に関する研究 ---------- 1

中川　和彦

II．研究成果の刊行に関する一覧表 ---------- 7

III．研究成果の刊行物・別刷 ---------- 11

別紙３

厚生労働科学研究費補助金（がん臨床研究事業）
総合研究報告書

原発不明がんの診断・効果的治療の確立に関する研究

主任研究者　中川　和彦
近畿大学医学部内科学腫瘍内科部門　教授

研究要旨　　臓器別体系を機軸とした我国のがん診療体制における原発不明がんの治療は不適切、かつ遅延することが多い。原発不明がんを対象とした臨床試験の実施により、原発不明がんの診断と治療に関する基本的方針の啓蒙を図る。また画一的な従来の原発不明がん治療戦略に比較して、DNA発現解析により原発巣の推定を行う新しい治療戦略の臨床的有用性を問う第III相比較試験の妥当性を評価するための無作為化臨床第II相試験を実施する。

岡本 勇　（近畿大学医学部内科学腫瘍内科部門准教授）
西尾 和人（近畿大学医学部ゲノム生物学 教授）
河野 勤　（国立がんｾﾝﾀｰ中央病院　乳腺・腫瘍内科）
倉田 宝保（近畿大学医学部内科学腫瘍内科部門准教授）
松本 光史（兵庫県立がんｾﾝﾀｰ腫瘍内科　医長）
武田 晃司（大阪市立総合医療ｾﾝﾀｰ　臨床腫瘍科　部長）
向井 博文（国立がんｾﾝﾀｰ東病院）
三輪 啓介（埼玉医科大学国際医療ｾﾝﾀｰ）
高橋　信　（東北大学加齢医学研究所癌化学療法研究分野）
山本 信之（静岡がんセンター呼吸器内科　部長）
山中 康弘（栃木県立がんセンター薬物療法科部長）
滝口 裕一（千葉大学医学部呼吸器内科　講師）
竹内文乃　（東京大学大学院情報学環・学際情報学府）
南　博信　（神戸大学医学部附属病院　腫瘍内科）
高橋俊二　（財団法人癌研究会有明病院化学療法科）
洪　泰浩　（静岡がんセンター　化学療法科）

A．研究目的

原発不明がんを対象とした臨床試験の実施により、原発不明がんの診断と治療に関する基本的方針の啓蒙を図る。またDNA発現解析により原発巣の推定を行う新しい治療戦略の画一的な従来の原発不明がん治療戦略に対する臨床的有用性を問う第III相比較試験の実施妥当性を無作為化臨床第II相試験にて評価する。

B．研究方法

①第一段階：研究組織と運営組織の確立

1）研究組織：現状では腫瘍内科を有する医療施設は少ない。中心施設となる参加施設を募り共同研究組織を設立し、プロトコール作成を開始する。その後、日本全国のがん薬物専門医に研究協力者を募る。遺伝子発現解析による原発巣の推定には、既存の遺伝子発現解析結果を有する基礎研究者、解析結果から原発巣を推定するアルゴリズムを構築する生物統計家の協力体制を確立する。

2）運営組織：本研究の運営組織として、委託契約を締結して非営利活動法人西日本がん研究機構（NPO-WJOG）のデータセンター機能を使用する。また、病理研究者の本研究への協力を求め、病理診断の中央判定の実施を可能とする。このことにより参加施設の病理診断技術レベルの改善を図る。

3）遺伝子発現解析データベースに基づく原発巣推定のアルゴリズム：近畿大学ゲノム生物学教室西尾和人教授の遺伝子発現解析データを用いて、東京大学大学院医学系研究科健康科学助教の竹内文乃らと共に原発巣推定アルゴリズム作成、検証作業を行う。

②第二段階：臨床試験実施計画書の作成と対象患者選択方法の確立

1）臨床試験プロトコールの作成：臨床試験デザインに関しては参加施設の合意形成が重要である。これまでの原発不明癌を対象にした臨床試験（Single arm phase II studyばかりであるが）において、プラチナ製剤を含む化学療法での生存期間中央値は6-10か月と報告されている。これらのデータより算出した1年生存率35％をコントロール群の1年生存率と仮定する。それに対して今回、DNAチップを用いて原発巣を推定することでより個々の症例において標準的治療法を受ける可能性が高いものと推定し、1年生存率を50％と仮定した。βエラーを0.2、αエラーを0.2とすると登録期間3年、追跡期間2年とした場合、各群57例必要となる。逸脱例も考慮してtotal 120例必要となる。参加施設（14施設）のアンケート調査によると患者集積力は年間80症例であることから本試験は実施可能と判断した。原発不明がんの診療指針の啓蒙のために、今後、更に参加施設を追加する。

2）対象患者選択方法の確立：本研究参加施設の中でも原発不明がんの診断治療の基本方針について相違が存在する可能性がある。病理診断を含めた医学情報に基づいて「予後良好な原発不明がん」を除外す

る統一基準を作成する。
3）試験開始に当たっては、参加施設、班長協力者、効果安全性評価委員会メンバーに集まって頂き、キックオフ・ミーティングを開催する。

③第三段階：臨床試験の実施
1）症例登録とランダム割付：WJOGデータセンターでの中央登録方式とする。登録票記入後、データセンターへFAXにて登録、データセンターより配布された患者識別番号を用いて臨床検体を三菱安全科学研究所または近畿大学医学部ゲノム生物学教室へ送付する。胸水症例では、胸水中のがん細胞を濃縮するために静岡県立静岡がんセンター新規薬剤開発・評価研究部に送付する。遺伝子発現解析結果は近畿大学医学部ゲノム生物学教室に送られ、完成された原発巣推定アルゴリズムを用いて原発巣を推定する。推定結果はWJOGデータセンターに送られ、WJOGデータセンターにて割付された結果を実施施設に通知する。
2）治療方法：
対照治療群：カルボプラチンとパクリタキセルの2剤併用療法
試験治療群：遺伝子発現解析にて推定された原発巣のあらかじめ定められた標準的治療を実施する。
3）予定症例数：120症例（各群60症例）

④実施期間と年次計画
1）一年次：第一、第二段階で示す臨床試験実施の準備を行う。
2）二年・三年次：第三段階であるランダム化臨床第III相比較試験を開始する。中間解析、定期モニタリングを実施する。
3)3年での試験終了は困難である。2年次から症例集積が開始され、最終解析が実施されるまでには最低6年が必要である。

（倫理面への配慮）
本研究では、抗癌剤感受性の高い予後良好な原発不明がん患者が本研究から最大限除外されるよう配慮する。さらに、ヘルシンキ宣言およびわが国の「臨床研究に関する倫理指針」に従い、以下の事項を厳守する。
①研究実施計画書をWJOGプロトコール審査委員会で審査し、各施設のIRB承認の得られた施設のみ症例登録を可能とする。
②全ての患者に説明文書を用いて十分な説明を行い、考慮の時間を設けた後に患者自身の自由意志による同意を文書で取得する。
③データの取り扱いに関して、直接個人を識別できる情報を用いず、データベースのセキュリティを確保し、個人情報の保護を厳守する。
④プロトコール審査委員会、効果・安全性評価委員会を組織し、研究の第三者的監視を行う。
⑤本解析でおこなうマイクロアレイによる遺伝子発現解析はヒトゲノム・遺伝子解析研究に関する倫理指針の対象ではないが、指針の趣旨を尊重し、準じた管理を行うことにより個人情報等倫理的に十分に配慮する。

C．研究結果
＜国内・国外における研究状況＞
①予後不良な「狭義の原発不明がん」に対して海外で実施された臨床第II相試験の多くはプラチナ製剤と新規抗がん剤を併用した化学療法であり、それらの奏効率は22%から55%、MSTは6ヶ月から13ヶ月と報告されている（Hainsworth JD, et al: J Clin Oncol 15: 2385-2393, 1997, Greco FA, et al: J Clin Oncol 20: 1651-1656, 2002, Culine S, et al: J Clin Oncol 21: 3479-3482, 2003）。これらの中で、比較的良好な成績を示したものはプラチナ製剤とタキサン系薬剤の2剤併用療法であった。現在、カルボプラチンとパクリタキセルの2剤併用療法が原発不明がんに対して最も汎用されている治療法である。
②国内での臨床試験は、シスプラチン＋ドセタキセル併用療法の臨床第II相試験のみである。奏効率57%、生存期間中央値12か月と良好な成績を示した（松本光史、他：第4回日本臨床腫瘍学会総会学会誌 p176, 2006）。
③フランスではシスプラチン＋ゲムシタビンとシスプラチン＋CPT-11の比較第II相試験結果に基づき、シスプラチン単剤に対するシスプラチン＋ゲムシタビン併用療法の優位性を検証する臨床第III相試験が実施されている。
④遺伝子発現解析による癌種、組織型の診断技術は近年顕著な発展を示している。原発不明がんの遺伝子発現解析も実施され臨床応用が期待されている。
⑤これまでに得られた本研究結果、進捗状況を説明すると、2008年6月にプロトコール最終版を完成、参加施設のIRB審査に入った。本臨床試験プロトコールは、現在、全14参加施設においてIRBおよび遺伝子倫理委員会を通過し、登録可能となっている。2008年11月より症例登録が開始され、2010年3月31日現在、41症例の症例登録を得ている。DNA発現解析実施施設に検体が到着してから推定原発巣の結果を通知するまでの期間中央値は7日で、次第に期間短縮化が可能となりつつある。また、抽出RNAの収量とその質については近畿大学医学部ゲノム生物学教室において順次モニターされており、これまでのところDNA発現解析をする上で問題はないと判断されている。つまり、原発不明癌患者より腫瘍検体を採取し、解析機関への送付、DNA発現解析の実施、DNA発現解析結果に基づく原発巣の推定、原発巣推定結果の報告、報告結果に基づく無作為化割付、割付結果の参加施設への報告、割付結果に基づく治療の実施という本臨床試験で計画された一連の複雑な実施手続きの実施可能性が明らかとなった。また、一年間で約30症例の登

録が得られたことは、今後3年間以内での目標症例数120例の登録可能性を示すことができた。
＜この研究の特色・独創的＞
本研究は、現行の画一的な治療戦略（本研究では、カルボプラチンとパクリタキセルの2剤併用療法）と比較して、遺伝子発現解析により推定された癌種として個別に治療方針を決定する新しい治療戦略の臨床的有用性を評価する先進的な研究であり、世界的にも極めて価値が高い。

D．考察
＜臨床試験を企画・実施すること自体の必要性と期待される成果＞
「原発不明がん」は臓器横断的診療体制をとる診療科（腫瘍内科）でなければ適切な診断・治療ができない象徴的な疾患である。我国の中核病院に臓器横断的診療体制を推進し、それを担う腫瘍内科医を育成するためには、がん治療臨床医が興味を示す優れた臨床研究を実施すること必要である。臨床試験の実施により、「広義の原発不明癌」の中から予後良好な患者群を適切・迅速に選別し、最も効果的な標準治療を実施することにより原発不明がん治療の成績向上が期待できる。
＜臨床試験結果の必要性と結果から期待される成果＞
原発不明がんに対する現行の画一的な治療戦略から、遺伝子発現解析による原発巣の推定を通して、原発不明がん患者に対する個別化治療という新しい治療戦略への転換を促すことが期待される。また、原発不明がん患者の遺伝子発現パターンを知ることにより、原発不明がんについての新しい生物学的理解が得られる可能性がある。

E．結論
初年度の計画として研究組織と運営組織の確立、本臨床試験のデザインを確定し、第２年度にプロトコールを完成、参加施設における審査後、症例登録を開始することを目標とした。そして第3年度には、本格的な症例登録を実施した。
1.　研究組織：原発不明がんの診療を現在実施している13医療実施機関の参加により「原発不明がん共同臨床研究グループ」を設立した。平成20年度、癌研有明病院が新たに本研究に参加することとなったため、参加施設は14施設となった。
2.　運営組織：非営利活動法人西日本がん研究機構（NPO-WJOG）と委託契約を締結し、本研究における登録業務、データマネッジメント業務を委託した。登録、検体送付、結果解析、無作為化に関して、研究事務局、データセンター、実施施設、DNA発現解析実施機関との連携の確認作業を平成20年度に完了した。
3.　遺伝子発現解析データベースに基づく原発巣推定のアルゴリズムに関しては、東京大学生物統計学科伊藤洋一講師及び東京大学医学系研究科博士課程倉橋一成氏により作成された新しいアルゴリズムを本臨床試験にて用いることとした（平成19年度）。
4.　臨床試験プロトコールと患者同意説明文書のひな型を作成し、参加施設に郵送、施設倫理審査員会の審査を受けた（平成20年度）。試験デザインの変更に伴い、本臨床試験での臨床的仮定は以下のごとく変更された。現在までに14の全参加施設にて審査を終了している（平成20年度）。平成20年11月より登録が開始され平成22年3月30日時点で合計41例の症例登録が得られた。原発不明がんの診断と生検材料の送付、症例登録の複雑さを考慮に入れると年間30症例の登録は決して少なく無いと考える（平成21年度）。この症例登録スピードからすると、これから2年半で120症例の登録を終了することが可能と考えられる。
5.　検体からのRNAの抽出とDNA遺伝子発現解析は順調に行われた。組織検体より抽出されたRNAの品質は近畿大学医学部ゲノム生物学教室で評価された。これまで抽出されたRNAの品質は良好であり、41症例全例において遺伝子発現解析は可能であり、発現解析そのものの信頼性は確認できた。

F．研究発表

論文発表
1.
2. Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, Ichinose Y, Katakami N, Yamamoto N, Kudoh S, Sasaki J, Matsui K, Takayama K, Kashii T, Iwamoto Y, Sawa T, Okamoto I, Kurata T, Nakagawa K, Fukuoka M. Randomized Phase III Trial of Platinum-Doublet Chemotherapy Followed by Gefitinib Compared With Continued Platinum-Doublet Chemotherapy in Japanese Patients With Advanced Non-Small-Cell Lung Cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203). J Clin Oncol .28(5):753-60, 2010
3. Takeda M, Okamoto I, Fujita Y, Arao T, Ito H, Fukuoka M, Nishio K, Nakagawa K. De Novo Resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors in EGFR Mutation-Positive Patients with Non-small Cell Lung Cancer. J Thorac Oncol .5(3):399-400, 2010
4. Kaneda H, Arao T, Tanaka K, Tamura D, Aomastu K, Kudo K, De Velasco M A, Mastumoto K, Fujita Y, Yamada Y, Tsurutani J, Okamoto I, Nakagawa K, Nishio K..FOXQ1 is overexpressed in colorectal cancer and enhances tumorigenicity and tumor growth. Cancer Research. 70(5):2053-2063, 2010

5. Takeda M, Okamoto I, Fukuoka M, Nakagawa K. Successful treatment with erlotinib after gefitinib-related severe hepatotoxicity. J Clin Oncol .:in press, 2010
6. Tsujino K, Shiraishi J, Tsuji T, Kurata T, Kawaguchi T, Kubo A, Takada M. Is response rate increment obtained by molecular targeted agents related to survival benefit in the phase III trials of advanced cancer?Ann Oncol .:in press, 2010
7. Kataoka Y, Mukohara T, Shimada H, Saijo N, Hirai M, Minami HAssociation between gain-of-function-mutations in PIK3CA and resistance to HER2-targeted agents in HER2-amplified breast cancer cell lines. Ann Oncol. 21(2):255-62, 2010
8. Nobuyuki Yamamoto, Kazuhioko Nakagawa, Yasumasa Nishimura, Kayoko Tsujino, Miyako Satouchi, Shinzoh Kudoh, Toyoaki Hida, Masaaki Kawahara, Koji Takeda, Nobuyuki Katakami, Toshiyuki Sawa, Soichiro Yokota, Takashi Seto, Fumio Imamura, Hideo Saka, Yasuo IwaPhase III comparative study of a second generation regimen and third generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Oncology Group WJTOG0105. J Clin Oncol.:inpress, 2010
9. "Morita S, Okamoto I, Kobayashi K, Yamazaki K, Asahina H, Inoue A, Hagiwara K, Sunaga N, Yanagitani N, Hida T, Yoshida K, Hirashima T, Yasumoto K, Sugio K, Mitsudomi T, Fukuoka M, Nukiwa T. Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. Clin Cancer Res. 15
10. (13):4493-4498, 2009"
11. Yonemori K, Ando M, Yunokawa M, Hirata T, Kouno T, Shimizu C, Tamura K, Katsumata N, Hirakawa A, Matsumoto K, Yamanaka Y, Arioka H, Fujiwara Y. Irinotecan plus carboplatin for patients with carcinoma of unknown primary site. Br J Cancer. 100(1):18384, 2009
12. Makoto Kodaira, Shunji Takahashi, Shuhei Yamada, Kyoko Ueda, Yuko Mishima, Kengo Takeuchi, Noriko Yamamoto, Yuichi Ishikawa, Masahiro Yokoyama, Takashi Saotome, Yasuhito Terui and Kiyohiko Hatake. Bone metastasis and poor performance status are prognostic factors for survival of carcinoma of unknown primary site in patients treated with systematic chemotherapy. Ann Oncol.:in press, 2009
13. DiMaio, M., Chiodini, P., Georgoulias, V., Hatzidaki, D., Takeda, K., Wachters, FM., Gebbia, V., Smit, EF., Morabito, A., Gallo, C., Perrone, F., Gridelli, C. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 27(11):1836-1843, 2009
14. Okamoto, K., Tsurutani, J., Terashima, M., Okamoto, I., Nakagawa, K. Zoledronic acid-induced regression of multiple metastases at nonskeletal sites. Ann Oncol. 20(4):796-7, 2009
15. Takezawa, K., Okamoto, I., Yonesaka, K., Hatashita, E., Yamada, Y., Fukuoka, M., Nakagawa, K. Sorafenib inhibits non-small cell lung cancer cell growth by targeting B-RAF in KRAS wild-type cells and C-RAF in KRAS mutant cells. Cancer Res. 69(16):6515-21, 2009
16. Kunitoh H, Tamura T, Shibata T, Nakagawa K, Takeda K, Nishiwaki Y, Osaki Y, Noda K, Yokoyama A, Saijo N; JCOG Lung Cancer Study Group, Tokyo, Japan. A phase-II trial of dose-dense chemotherapy in patients with disseminated thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9605). Br J Cancer .101(9):1549-54, 2009
17. Hosoi, F., Izumi, H., Kawahara, A., Murakami, Y., Kinoshita, H., Kage, M., Nishio, K., Kohno, K., Kuwano, M., Ono, M. N-myc downstream regulated gene 1/Cap43 suppresses tumor growth and angiogenesis of pancreatic cancer through attenuation of inhibitor of kB kinase β expression. Cancer Res. 69(129):4983-91, 2009
18. Matsumoto, K., Arao, T., Tanaka, K., Kaneda, H., Kudo, K., Fujita, Y., Tamura, D., Aomatsu, K., Tamura, T., Yamada, Y., Saijo, N., Nishio, K. mTOR signal and hypoxia-inducible factor-1 alpha regulate CD133 expression in cancer cells. Cancer Res. 69(18):7160-4, 2009
19. Minami H, Kawada K, Sasaki Y, Tahara M Igarashi T, Itoh K, Fujii H, Saeki T, Ozawa K Sato HPopulation pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice. Cancer Sci. 100:144-149, 2009
20. Katsumata N, Watanabe T, Minami H, Aogi K, Tabei T, Sano M, Masuda N, Andoh J, Ikeda T, Ishizuka N, Takashima S. Phase III trial of doxorubicin plus cyclophosphamide (A

C), docetaxel, and alternating AC and docetaxel as front-line chemotherapy for metastatic breast cancer, Japan Clinical Oncology Group Trial (JCOG9802). Ann Oncol . 20 (7):1210-1215, 2009
21. Akihiro Tamiya, Masahiro Endo, Takehito Shukuya, Satoshi Igawa, Asuka Tsuya, Yukiko Nakamura, Haruyasu Murakami, Toshiaki Takahashi, Narikazu Boku, Nobuyuki Yamamoto. Features of gemcitabine-related severe pulmonary toxicity: patients with pancreatic or biliary tract cancer. PANCREAS. 38(7):838-840, 2009
22. Noboru Yamamoto, Tomohide Tamura, Takayasu Kurata, Nobuyuki Yamamoto, Ikuo Sekine, Hideo Kunitoh, Yuichiro Ohe and Nagahiro Saijo. A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancerCancer Chemothr Pharmacol. 65(1):79-88, 2009
23. Tamura K, Okamoto I, Kashii T, Negoro S, Hirashima T, Kudoh S, Ichinose Y, Ebi N, Shibata K, Nishimura T, Katakami N, Sawa T, Shimizu E, Fukuoka J, Satoh T, Fukuoka M . Multicentre prospective phase II trial of gefitinib for advanced non-small cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403). Br J Cancer. 98(5):907-14, 2008
24. Ebi N, Semba H, Tokunaga S, Takayama K, Wataya H, Kuraki T, Yamamoto H, Akamine S, Okamoto I, Nakanishi Y. A phase II trial of gefitinib monotherapy in chemo-na?ve patients > 75 years of age with advanced non-small-cell lung cancer. J Thoracic Oncol. 3(10):1166-71, 2008
25. Ennishi D, Takeuchi K, Yokoyama M, Asai H, Mishima Y, Terui Y, Takahashi S, Komatsu H, Ikeda K, Yamaguchi M, Suzuki R, Tanimoto M, Hatake K. CD5 expression is potentially predictive of poor outcome among biomarkers in patients with diffuse large B-cell lymphoma receiving rituximab plus CHOP therapy. Ann Oncol. 19(11):7823, 2008
26. Okabe, T., Okamoto, I., Tsukioka, S., Uchida, J., Iwasa, T., Yoshida, T., Hatashita, E., Yamada, Y., Satoh, T., Tamura, K., Fukuoka, M., Nakagawa, K. Synergistic antitumor effect of S-1 and the epidermal growth factor receptor inhibitor gefitinib in non-small cell lung cancer cell lines:role of gefitinib-induced down-regulation of thymidylate synthase. Mol Cancer Ther. 7(3):599-606, 2008
27. Ohe, Y., Ichinose, Y., Nakagawa, K., Tamura, T., Kubota, K., Yamamoto, N., Adachi, S., Nambu, Y., Fujimoto, T., Nishiwaki, Y., Saijo, N., Fukuoka, M. Efficacy and Safety of Two Doses of Pemetrexed Supplemented with Folic Acid and Vitamin B12 in Previously Treated Patients with Non-Small Cell Lung Cancer. Clin Cancer Res . 14(13):4206-4212, 2008
28. Iwasa, T., Okamoto, I., Suzuki, M., Nakahara, T., Yamanaka, K., Hatashita, E., Yamada, Y., Fukuoka, M., Ono, K., Nakagawa, K. Radiosensitizing effect of YM155, a novel small molecule urvivin suppressant, in non- small cell lung cancer cell lines. Clinical Cancer Res. 14 (20) :6496-6504, 2008
29. Nakayama, T., Hieshima, K., Arao, T., Jin, Z., Nagakubo, D., Shirakawa, A-K., Yamada, T., Fujii, M., Oiso, N., Kawada, A., Nishio, K., Yoshie, O. Aberrant expression of Fra-2 promotes CCR4 expression and cell proliferation in adult T-cell leukemia. Oncogene. 27(23):3221-32, 2008
30. Honma, K., Iwao-Koizumi, K., Takeshita, F., Yamamoto, Y., Yoshida, T., Nishio, K., Nakagawa, S., Nagahara, S., Kato, K., Ochiya, T. RPN2 gene congers docetaxel resistance in breast cancer. Natuer Med. 14(9):939-48, 2008
31. Yamada, Y., Arao, T., Gotoba, T., Taniguchi, H., Oda, I., Shirao, K., Shimada, Y., Hamaguchi, T., Kato, K., Hamano, T., Koizumi, F., Tamura, T., Saito, D., Shimoda, T., Saka, M., Fukagawa, T., Katai, H., Sasako, M., Nishio, K. Identification of prognostic biomarkers in gastric cancer using endoscopic biopsy samples. Cancer Sci. 99(11):2193-9, 2008
32. Nishio S, Katsumata N, Matsumoto K, Tanabe H, Yonemori K, Kohno T, Shimizu C, Ando M, Kasamatsu T, Fujiwara Y. Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma. Oncol Rep. 19(2):497-503, 2008
33. Yuko Akiyama, Ken-ichi Fujita, Fumio Nagashima, Wataru Yamamoto, Hisashi Endo, Yu Sunakawa, Keishi Yamashita, Hiroo Ishida, Keiko Mizuno, Kazuhiro Araki, Wataru Ichikawa, Toshimichi Miya, Masaru Narabayashi, Kaori Kawara, Minako Sugiyama, Takashi Hirose. Genetic testing for UGT1A1*28 and *6 in Japanese patients who receive irinotecan chemotherapy . Ann Oncol. 19(12):2089-90, 2008

34. Wataru Ichikawa, Kazuhiro Araki, ,Ken-ichi Fujita, Wataru Yamamoto, Hisashi Endo, Fumio Nagashima, Ryuhei Tanaka, Toshimichi Miya, Keiji Kodama, Yu Sunakawa, Masaru Narabayashi, Yuichi Ando, Yuko Akiyama, Kaori Kawara, Yasutsuna Sasaki.Re: UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters.J Natl Cancer Inst .100(3):224-225,2008
35. Riichiroh Maruyama, Yutaka Nishiwaki, Tomohide Tamura, Nobuyuki Yamamoto, Masahiro Tsuboi, Kazuhiko Nakagawa, Tetsu Shinkai, Shunichi Negoro, Fumio Imamura, Kenji Eguchi, Koji Takeda, Akira Inoue, Keisuke Tomii, Masao Harada, Noriyuki Masuda, Haiyi Jiang.Phase III study (V-15-32) of gefitinib (IRESSA) versus docetaxel in previously treated Japanese patients with non-small-cell lung cancerJ Clin Oncol.26(26):4244-4252,2008
36. Akashi,Y., Okamoto,I., Suzuki,M.,Tamura,K., Iwasa,T., Hisada,S., Satoh,T., Nakagawa, K., Ono,K., Fukuoka,M. The novel microtubule-interfering agent TZT-1027 enhances the anticancer effect of radiation in vitro and in vivo. British Journal of Cancer.96(10):1532-1539,2007
37. Wakasugi, T., Izumi, H., Uchiumi, T., Suzuki, H., Arao, T., Nishio, K., Kohno, K.ZNF143 interacts with p73 and is involved in cisplatin resistance.Oncogene.26(36):5194-203,2007
38. Saeki T, Nomizu T, Toi M, Ito Y, Noguchi S, Kobayashi T, Asaga T, Minami H, Yamamoto N, Aogi K, Ikeda T, Ohashi Y, Sato W, Tsuruo T.Dofequidar fumarate (MS-209) in combination with cyclophosphamide, doxorubicin and 5-fluorouracil for patients with advanced cr recurrent breast cancer. J Clin Oncol.25:411-417,2007

G．知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3.その他

なし

別紙４

研究成果の刊行に関する一覧表レイアウト

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, Ichinose Y, Katakami N, Yamamoto N, Kudoh S, Sasaki J, Matsui K, Takayama K, Kashii T, Iwamoto Y, Sawa T, Okamoto I, Kurata T, Nakagawa K, Fukuoka M.	Randomized Phase III Trial of Platinum-Doublet Chemotherapy Followed by Gefitinib Compared With Continued Platinum-Doublet Chemotherapy in Japanese Patients With Advanced Non-Small-Cell Lung Cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203).	J Clin Oncol	28(5)	753-60	2010
Takeda M, Okamoto I, Fujita Y, Arao T, Ito H, Fukuoka M, Nishio K, Nakagawa K.	De Novo Resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors in EGFR Mutation-Positive Patients with Non-small Cell Lung Cancer.	J Thorac Oncol	5(3)	399-400	2010
Kaneda H, Arao T, Tanaka K,Tamura D, Aomastu K, Kudo K, De Velasco M A, Mastumoto K, Fujita Y, Yamada Y, Tsurutani J, Okamoto I, Nakagawa K, Nishio K..	FOXQ1 is overexpressed in colorectal cancer and enhances tumorigenicity and tumor growth.	Cancer Research	70(5)	2053-2063	2010
Takeda M, Okamoto I, Fukuoka M, Nakagawa K.	Successful treatment with erlotinib after gefitinib-related severe hepatotoxicity.	J Clin Oncol		in press	2010
Tsujino K, Shiraishi J, Tsuji T, Kurata T, Kawaguchi T, Kubo A, Takada M.	Is response rate increment obtained by molecular targeted agents related to survival benefit in the phase III trials of advanced cancer?	Ann Oncol		in press	2010
Kataoka Y, Mukohara T, Shimada H, Saijo N, Hirai M, Minami H	Association between gain-of-function-mutations in PIK3CA and resistance to HER2-targeted agents in HER2-amplified breast cancer cell lines.	Ann Oncol	21(2)	255-62	2010
Nobuyuki Yamamoto, Kazuhioko Nakagawa, Yasumasa Nishimura, Kayoko Tsujino, Miyako Satouchi, Shinzoh Kudoh, Toyoaki Hida, Masaaki Kawahara, Koji Takeda, Nobuyuki Katakami, Toshiyuki Sawa, Soichiro Yokota, Takashi Seto, Fumio Imamura, Hideo Saka, Yasuo Iwa	Phase III comparative study of a second generation regimen and third generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Oncology Group WJTOG0105.	J Clin Oncol		inpress	2010
Morita S, Okamoto I, Kobayashi K, Yamazaki K, Asahina H, Inoue A, Hagiwara K, Sunaga N, Yanagitani N, Hida T, Yoshida K, Hirashima T, Yasumoto K, Sugio K, Mitsudomi T, Fukuoka M, Nukiwa T.	Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations.	Clin Cancer Res	15 (13)	4493-4498	2009
Yonemori K, Ando M, Yunokawa M, Hirata T, Kouno T, Shimizu C, Tamura K, Katsumata N, Hirakawa A, Matsumoto K, Yamanaka Y, Arioka H, Fujiwara Y.	Irinotecan plus carboplatin for patients with carcinoma of unknown primary site.	Br J Cancer	100(1)	May-50	2009

Makoto Kodaira, Shunji Takahashi, Shuhei Yamada, Kyoko Ueda, Yuko Mishima, Kengo Takeuchi, Noriko Yamamoto, Yuichi Ishikawa, Masahiro Yokoyama, Takashi Saotome, Yasuhito Terui and Kiyohiko Hatake.	Bone metastasis and poor performance status are prognostic factors for survival of carcinoma of unknown primary site in patients treated with systematic chemotherapy.	Ann Oncol		in press	2009
DiMaio,M.,Chiodini,P.,Georgoulias, V., Hatzidaki,D.,Takeda,K.,Wachters,F M., Gebbia,V.,Smit,EF.,Morabito,A., Gallo,C.,Perrone,F.,Gridelli,C.	Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer.	J Clin Oncol	27(11)	1836-1843	2009
Okamoto,K., Tsurutani,J., Terashima,M., Okamoto,I., Nakagawa,K.	Zoledronic acid-induced regression of multiple metastases at nonskeletal sites.	Ann Oncol	20(4)	796-7	2009
Takezawa,K.,Okamoto,I.,Yonesaka ,K.,Hatashita,E.,Yamada,Y.,Fukuok a,M.,Nakagawa,K.	Sorafenib inhibits non-small cell lung cancer cell growth by targeting B-RAF in KRAS wild-type cells and C-RAF in KRAS mutant cells.	Cancer Res	69(16)	6515-21	2009
Kunitoh H, Tamura T, Shibata T, Nakagawa K, Takeda K, Nishiwaki Y, Osaki Y, Noda K, Yokoyama A, Saijo N; JCOG Lung Cancer Study Group, Tokyo, Japan.	A phase-II trial of dose-dense chemotherapy in patients with disseminated thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9605).	Br J Cancer	101(9)	1549-54	2009
Hosoi, F., Izumi, H., Kawahara, A., Murakami, Y., Kinoshita, H., Kage, M., Nishio, K., Kohno, K., Kuwano, M., Ono, M.	N-myc downstream regulated gene 1/Cap43 suppresses tumor growth and angiogenesis of pancreatic cancer through attenuation of inhibitor of kB kinase β expression.	Cancer Res	69(129)	4983-91	2009
Matsumoto, K., Arao, T., Tanaka, K., Kaneda, H., Kudo, K., Fujita, Y., Tamura, D., Aomatsu, K., Tamura, T., Yamada, Y., Saijo, N., Nishio, K.	mTOR signal and hypoxia-inducible factor-1 alpha regulate CD133 expression in cancer cells.	Cancer Res	69(18)	7160-4	2009
Minami H, Kawada K, Sasaki Y, Tahara M Igarashi T, Itoh K, Fujii H, Saeki T, Ozawa K Sato H	Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice.	Cancer Sci	100	144-149	2009
Katsumata N, Watanabe T, Minami H, Aogi K, Tabei T, Sano M, Masuda N, Andoh J, Ikeda T, Ishizuka N, Takashima S.	Phase III trial of doxorubicin plus cyclophosphamide (AC), docetaxel, and alternating AC and docetaxel as front-line chemotherapy for metastatic breast cancer, Japan Clinical Oncology Group Trial (JCOG9802).	Ann Oncol	20 (7)	1210-1215	2009
Akihiro Tamiya, Masahiro Endo, Takehito Shukuya, Satoshi Igawa, Asuka Tsuya, Yukiko Nakamura, Haruyasu Murakami, Toshiaki Takahashi, Narikazu Boku, Nobuyuki Yamamoto.	Features of gemcitabine-related severe pulmonary toxicity: patients with pancreatic or biliary tract cancer.	PANCREAS	38(7)	838-840	2009
Noboru Yamamoto, Tomohide Tamura, Takayasu Kurata, Nobuyuki Yamamoto, Ikuo Sekine, Hideo Kunitoh, Yuichiro Ohe and Nagahiro Saijo.	A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancer	Cancer Chemothr Pharmacol	65(1)	79-88	2009
Tamura K, Okamoto I, Kashii T, Negoro S, Hirashima T, Kudoh S, Ichinose Y, Ebi N, Shibata K, Nishimura T, Katakami N, Sawa T, Shimizu E, Fukuoka J, Satoh T, Fukuoka M .	Multicentre prospective phase II trial of gefitinib for advanced non-small cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403).	Br J Cancer	98(5)	907-14	2008

Ebi N, Semba H, Tokunaga S, Takayama K, Wataya H, Kuraki T, Yamamoto H, Akamine S, Okamoto I, Nakanishi Y.	A phase II trial of gefitinib monotherapy in chemo-na?ve patients > 75 years of age with advanced non-small-cell lung cancer.	J Thoracic Oncol	3(10)	1166-71	2008
Ennishi D, Takeuchi K, Yokoyama M, Asai H, Mishima Y, Terui Y, Takahashi S, Komatsu H, Ikeda K, Yamaguchi M, Suzuki R, Tanimoto M, Hatake K.	CD5 expression is potentially predictive of poor outcome among biomarkers in patients with diffuse large B-cell lymphoma receiving rituximab plus CHOP therapy.	Ann Oncol	19(11)	Jun-21	2008
Okabe,T.,Okamoto,I.,Tsukioka,S.,Uchida,J.,Iwasa,T.,Yoshida,T.,Hatashita,E.,Yamada,Y.,Satoh,T.,Tamura,K.,Fukuoka,M.,Nakagawa,K.	Synergistic antitumor effect of S-1 and the epidermal growth factor receptor inhibitor gefitinib in non-small cell lung cancer cell lines:role of gefitinib-induced down-regulation of thymidylate synthase.	Mol Cancer Ther	7(3)	599-606	2008
Ohe,Y., Ichinose,Y., Nakagawa,K., Tamura,T., Kubota,K., Yamamoto,N., Adachi,S., Nambu,Y., Fujimoto,T., Nishiwaki,Y., Saijo,N., Fukuoka,M.	Efficacy and Safety of Two Doses of Pemetrexed Supplemented with Folic Acid and Vitamin B12 in Previously Treated Patients with Non-Small Cell Lung Cancer.	Clin Cancer Res	14(13)	4206-4212	2008
Iwasa,T., Okamoto,I., Suzuki,M., Nakahara,T., Yamanaka,K., Hatashita,E., Yamada,Y.,Fukuoka,M., Ono,K., Nakagawa,K.	Radiosensitizing effect of YM155, a novel small molecule urvivin suppressant, in non-small cell lung cancer cell lines.	Clinical Cancer Res	14(20)	6496-6504	2008
Nakayama, T., Hieshima, K., Arao, T., Jin, Z., Nagakubo, D., Shirakawa, A-K., Yamada, T., Fujii, M., Oiso, N., Kawada, A., Nishio, K., Yoshie, O.	Aberrant expression of Fra-2 promotes CCR4 expression and cell proliferation in adult T-cell leukemia.	Oncogene	27(23)	3221-32	2008
Honma, K., Iwao-Koizumi, K., Takeshita, F., Yamamoto, Y., Yoshida, T., Nishio, K., Nakagawa, S., Nagahara, S., Kato, K., Ochiya, T.	RPN2 gene congers docetaxel resistance in breast cancer.	Natuer Med	14(9)	939-48	2008
Yamada, Y., Arao, T., Gotoba, T., Taniguchi, H., Oda, I., Shirao, K., Shimada, Y., Hamaguchi, T., Kato, K., Hamano, T., Koizumi, F., Tamura, T., Saito, D., Shimoda, T., Saka, M., Fukagawa, T., Katai, H., Sasako, M., Nishio, K.	Identification of prognostic biomarkers in gastric cancer using endoscopic biopsy samples.	Cancer Sci	99(11)	2193-9	2008
Nishio S, Katsumata N, Matsumoto K, Tanabe H, Yonemori K, Kohno T, Shimizu C, Ando M, Kasamatsu T, Fujiwara Y.	Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma.	Oncol Rep	19(2)	497-503	2008
Yuko Akiyama, Ken-ichi Fujita, Fumio Nagashima, Wataru Yamamoto, Hisashi Endo, Yu Sunakawa, Keishi Yamashita, Hiroo Ishida, Keiko Mizuno, Kazuhiro Araki, Wataru Ichikawa, Toshimichi Miya, Masaru Narabayashi, Kaori Kawara, Minako Sugiyama, Takashi Hirose.	Genetic testing for UGT1A1*28 and *6 in Japanese patients who receive irinotecan chemotherapy .	Ann Oncol	19(12)	2089-90	2008
Wataru Ichikawa, Kazuhiro Araki, ,Ken-ichi Fujita, Wataru Yamamoto, Hisashi Endo, Fumio Nagashima, Ryuhei Tanaka, Toshimichi Miya, Keiji Kodama, Yu Sunakawa, Masaru Narabayashi, Yuichi Ando, Yuko Akiyama, Kaori Kawara, Yasutsuna Sasaki.	Re: UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters.	J Natl Cancer Inst	100(3)	224-225	2008

Riichiroh Maruyama, Yutaka Nishiwaki, Tomohide Tamura, Nobuyuki Yamamoto, Masahiro Tsuboi, Kazuhiko Nakagawa, Tetsu Shinkai, Shunichi Negoro, Fumio Imamura, Kenji Eguchi, Koji Takeda, Akira Inoue, Keisuke Tomii, Masao Harada, Noriyuki Masuda, Haiyi Jiang.	Phase III study (V-15-32) of gefitinib (IRESSA) versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer	J Clin Oncol	26(26)	4244-4252	2008
Akashi,Y., Okamoto,I., Suzuki,M.,Tamura,K., Iwasa,T., Hisada,S., Satoh,T., Nakagawa,K., Ono,K., Fukuoka,M.	The novel microtubule-interfering agent TZT-1027 enhances the anticancer effect of radiation in vitro and in vivo.	British Journal of Cancer	96(10)	1532-1539	2007
Wakasugi, T., Izumi, H., Uchiumi, T., Suzuki, H., Arao, T., Nishio, K., Kohno, K.	ZNF143 interacts with p73 and is involved in cisplatin resistance.	Oncogene	26(36)	5194-203	2007
Saeki T, Nomizu T, Toi M, Ito Y, Noguchi S, Kobayashi T, Asaga T, Minami H, Yamamoto N, Aogi K, Ikeda T, Ohashi Y, Sato W, Tsuruo T.	Dofequidar fumarate (MS-209) in combination with cyclophosphamide, doxorubicin and 5-fluorouracil for patients with advanced cr recurrent breast cancer.	J Clin Oncol	25	411-417	2007

VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Platinum-Doublet Chemotherapy Followed by Gefitinib Compared With Continued Platinum-Doublet Chemotherapy in Japanese Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203)

Koji Takeda, Toyoaki Hida, Tosiya Sato, Masahiko Ando, Takashi Seto, Miyako Satouchi, Yukito Ichinose, Nobuyuki Katakami, Nobuyuki Yamamoto, Shinzoh Kudoh, Jiichiro Sasaki, Kaoru Matsui, Koichi Takayama, Tatsuhiko Kashii, Yasuo Iwamoto, Toshiyuki Sawa, Isamu Okamoto, Takayasu Kurata, Kazuhiko Nakagawa, and Masahiro Fukuoka

From the Department of Clinical Oncology, Osaka City General Hospital; Department of Respiratory Medicine, Osaka City University Medical School, Osaka; Department of Thoracic Oncology, Aichi Cancer Center, Nagoya; Departments of Biostatistics and Preventive Services, Kyoto University School of Public Health, Kyoto; Department of Thoracic Oncology, National Kyushu Cancer Center, Department of Clinical Medicine, Faculty of Medical Science, Research Institute for Diseases of the Chest, Kyushu University, Fukuoka; Department of Thoracic Oncology, Hyogo Cancer Center, Akashi; Division of Respiratory Medicine, Kobe City General Hospital, Kobe; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi; Department of Respiratory Medicine, Kumamoto University, Kumamoto; Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino; Department Medical Oncology, Toyama University Hospital, Toyama; Department of Medical Oncology, Hiroshima City Hospital, Hiroshima; Department of Respiratory Medicine and Oncology, Gifu Municipal Hospital, Gifu; Department of Medical Oncology, Kinki University School of Medicine, Osaka-Sayama; Department of Cancer Chemotherapy Center, Osaka Medical College, Takatsuki, and the Kinki University School of Medicine, Sakai Hospital, Sakai, Japan.

Submitted April 23, 2009; accepted September 10, 2009; published online ahead of print at www.jco.org on December 28, 2009.

This study is registered with UMIN-CTR [http://www.umin.ac.jp/ctr/index.htm, identification number C000000035].

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Koji Takeda, MD, 2-13-22 Miyakojimahondohri, Miyakojima-ku, Osaka 534-0021, Japan; e-mail: kkk-take@ga2.so-net.ne.jp.

0732-183X/10/2805-753/$20.00

DOI: 10.1200/JCO.2009.23.3445

See accompanying editorial on page 713 and article on page 744

ABSTRACT

Purpose
Gefitinib is a small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase. We conducted a phase III trial to evaluate whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Chemotherapy-naïve patients with advanced stage (IIIB/IV) NSCLC, Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function were randomly assigned to either platinum-doublet chemotherapy up to six cycles (arm A) or platinum-doublet chemotherapy for three cycles followed by gefitinib 250 mg orally once daily, until disease progression (arm B). Patients were stratified by disease stage, sex, histology, and chemotherapy regimens. The primary end point was overall survival; secondary end points included progression-free survival, tumor response, safety, and quality of life.

Results
Between March 2003 and May 2005, 604 patients were randomly assigned. There was a statistically significant improvement in progression-free survival in arm B (hazard ratio [HR], 0.68; 95% CI, 0.57 to 0.80; $P < .001$); however, overall survival results did not reach statistical significance (HR, 0.86; 95% CI, 0.72 to 1.03; $P = .11$). In an exploratory subset analysis of overall survival by histologic group, patients in arm B with adenocarcinoma did significantly better than patients in arm A with adenocarcinoma (n = 467; HR, 0.79; 95% CI, 0.65 to 0.98; $P = .03$).

Conclusion
This trial failed to meet the primary end point of OS in patients with NSCLC. The exploratory subset analyses demonstrate a possible survival prolongation for sequential therapy of gefitinib, especially for patients with adenocarcinoma.

J Clin Oncol 28:753-760. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the most common cancer worldwide, with an estimated 1.2 million new cases globally (12.3% of all cancers) and 1.1 million deaths (17.8% of all cancer deaths) in 2000.[1] The estimated global incidence of non–small-cell lung cancer (NSCLC) in 2000 was approximately 1 million, which accounted for approximately 80% of all cases of lung cancer.[1] Treatment of advanced NSCLC is palliative; the aim is to prolong survival without leading to deterioration in quality of life.[2] The recommended first-line treatment of advanced NSCLC currently involves up to six cycles of platinum-based combination chemotherapy, with no single combination recommended over another.[3,4] Recently, combination chemotherapy of pemetrexed plus cisplatin was significantly superior to gemcitabine plus cisplatin in nonsquamous NSCLC.[5]

Gefitinib is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that blocks the signal transduction pathways

Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma

SHIN NISHIO[1,3], NORIYUKI KATSUMATA[1], KOJI MATSUMOTO[1], HIROSHI TANABE[1], KAN YONEMORI[1], TSUTOMU KOHNO[1], CHIKAKO SHIMIZU[1], MASASHI ANDO[1], TAKAHIRO KASAMATSU[2] and YASUHIRO FUJIWARA[1]

Departments of [1]Medical Oncology and [2]Gynecologic Oncology, National Cancer Center Hospital, Tokyo 104-0045, Japan

Received July 23, 2007; Accepted October 22, 2007

Abstract. The aim of this study was to evaluate the clinicopathological prognostic factors in patients with stage IVb cervical carcinoma (CC). All patients with stage IVb CC included in the study were diagnosed from 1997 to 2006 at the National Cancer Center Hospital. We retrospectively examined clinicopathological parameters in these patients, including the efficacy of chemotherapy. Survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using a Cox's proportional hazard model. Thirty-six patients (median age 54 years) were diagnosed with stage IVb CC. The median progression-free survival and overall survival were 3.8 and 11.1 months, respectively. As initial treatment, 4 patients underwent hysterectomy, 13 received chemotherapy, 17 received radiotherapy, and the remaining 2 patients refused treatment. A total of 21 patients received chemotherapy, of which 13 were initial cases, 7 were persistent/recurrence cases, and 1 was a postoperative adjuvant case; 15 patients were never treated with chemotherapy. On univariate analysis, poor performance status (PS) and non-chemotherapy groups were considered poor prognostic factors, respectively. On multivariate analysis, poor PS (p=0.007; hazard ratio, 2.64) and non-chemotherapy (p=0.016; hazard ratio, 6.03) were independent prognostic factors of survival, respectively. Poor PS and non-chemotherapy groups were found to have poor prognosis in patients with stage IVb CC. Chemotherapy may improve the survival for stage IVb CC.

Correspondence to: Dr Shin Nishio, [3]*Present address*: Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
E-mail: nishio_shin@hotmail.com

Key words: stage IVb cervical carcinoma, prognostic factor, chemotherapy, performance status

Introduction

Cervical carcinoma is the main cause of death in females throughout the world, despite the fact that a useful screening method has been established (1). In stage I/II patients, conventional treatments such as surgery and radiotherapy have achieved good results. In stage III/IV patients, various treatments such as the combination of surgery and radiotherapy, radiotherapy, and chemoradiation therapy are being examined, though their long-term results are still poor (2,3). The 5-year survival of stage IVb patients ranges from 0 to 44%, and approximately 50% of these patients show a fatal outcome within 1 year (4-6). No standard therapy has been established, and palliative surgery, radiotherapy, and best supportive care (BSC) have been performed as initial treatment. However, since stage IVb cervical carcinoma is a systemic disease, surgery and radiotherapy are useful for local control, but are insufficient. In addition, BSC is not effective for the severe local pain characteristic of this disorder (7). Since 1990, chemotherapy has been employed as a type of BSC in patients with good general condition and organ function (8). However, as this therapy targets the relief of symptoms and improvements in quality of life (QOL), regimens with less toxic low-dose agents were initially administered (9). No randomized comparative study has examined whether chemotherapy for stage IVb cervical carcinoma prolongs survival compared to BSC.

Several studies have investigated single-agent chemotherapy for cervical carcinoma, and reported that the response rates to cisplatin, ifosfamide, paclitaxel, vinorelbine and topotecan of 20-30% (5,8,10-12), 14-40% (13-15), 17% (16), 15% (17,18) and 12-19% (19,20), respectively. Cisplatin has been the most frequently used agent, and has achieved the highest response rate. Therefore, cisplatin has been employed as a key drug for more than 20 years. However, the response to single-agent cisplatin has been limited, and combination chemotherapy with other agents has been administered to achieve improvement in prognosis, exceeding the enhancement of its toxicity. Result of recent phase III studies have indicated that combination regimens with cisplatin/paclitaxel (21) or cisplatin/topotecan (22) are more effective than single-agent cisplatin.

A few studies have reported that factors affecting the prognosis of stage IVb cervical carcinoma include main organ

metastases, multiple lymph node metastases, poor performance status (PS), and non-squamous cell carcinoma (23-29). According to some studies, the results of surgery combined with radiotherapy or radiotherapy alone are relatively good in stage IVb cervical carcinoma patients with para-aortic lymph node metastases alone (30-33). However, chemotherapy for stage IVb patients with cervical/mediastinal lymph node or main organ metastases, without surgery and radiotherapy, has been reported to have only slight effect.

In this study, we retrospectively investigated the clinicopathological features of stage IVb cervical carcinoma, and evaluated the efficacy of chemotherapy for this stage of cancer.

Patients and methods

Patients with stage IVb cervical carcinoma were diagnosed and treated in the National Cancer Center Hospital between April 1997 and March 2006. Stage was evaluated according to the FIGO staging. We rectrospectively reviewed the medical chart of these patients.

Treatment. Therapeutic strategies were selected for individual patients. For surgery, total hysterectomy (radical hysterectomy in some patients) and bilateral salpingo-oophorectomy were performed. Pelvic and/or para-aortic lymphadenctomy were performed in some patients. For radiotherapy, the area of external irradiation was established as the entire pelvic region from the closed pore to the L4/5 lumbar vertebrae, with a radiation dose of 2 Gy per treatment (total dose, 50-60 Gy). When the cumulative dose reached 20-30 Gy, external irradiation was combined with high-dose intra-cavity irradiation, with a central shield, at a radiation dose of 5 Gy (total dose, 20-25 Gy). When imaging findings suggested para-aortic lymph nodė metastases, biopsy was performed. After a definitive diagnosis of metastases was made, the irradiation field was extended to include the para-aortic node. For chemotherapy, eligible patients participated in a phase II clinical study with an in-house protocol that we previously reported, including paclitaxel (PTX)/carboplatin (CBDCA) therapy (Kitagawa R, *et al*, Proc ASCO 22: abs. 5048, 2004) (PTX, 175 mg/m^2, CBDCA AUC5, day 1, every 3 weeks for 6 cycles), and carboplatin (CBDCA)/irinotecan (CPT) therapy (Hori S, *et al*, Proc ASCO 21: abs. 835, 2002) (CBDCA AUC5, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles). For patients with PS of 3, weekly PTX/CBDCA therapy (PTX 80 mg/m^2, CBDCA AUC2, continuous administration for 20 weeks) was administered. In 1 patient with small cell carcinoma, cisplatin (CDDP)/CPT therapy (CDDP, 60 mg/m^2, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles) was administered as postoperative adjuvant therapy.

Best supportive care (BSC) was defined as treatment targeting the relief of symptoms without surgery, radiotherapy or chemotherapy, as described above.

Evaluation. Pretreatment clinical evaluation was repeated before each treatment cycle with the exception of radiography or CT/MRI imaging, which was repeated at least every other treatment cycle. Treatment was continued until disease progression or adverse effects precluded further administration. The response to treatment, in terms of the best response achieved in a given patient, was assessed using standard clinical criteria. A complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. A partial response (PR) was defined as a >50% reduction in the product of perpendicular diameters obtained from the measurement of each lesion, sustained for at least 4 weeks. Progressive disease (PD) was defined as a >50% increase in the product of perpendicular diameters of any lesion documented within 2 months of study entry or the appearance of any new lesion within 8 weeks of study entry. Stable disease (SD) was any condition not meeting any of the above three criteria. Overall survival was measured as the observed length of life from protocol entry to death or (for living patients) date of last contact. Progression-free survival was measured from the date of initiation of protocol to the first progression or death, or to the date of last contact for patients who were alive and progression-free.

Persistent disease was defined as carcinoma at a pelvic site known to be previously involved within 6 months of staging. Recurrent disease was classified as a new tumor in the extrapelvic area or pelvic disease >6 months after staging in a location previously tumor-free. Persistent or recurrent disease was documented by surgical exploration, biopsy or progression on imaging studies. The time of recurrence or death was calculated from the date of original staging. The end of the follow-up period was March 2006.

Statistical analysis. Statistical analysis was performed using SPSS. The impact of clinical and pathologic risk factors on survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using Cox's proportional hazard model. P-values <0.05 were considered significant.

Results

Thirty-six patients were treated between April 1997 and March 2006. Table I shows the patient characteristics. The median age was 54 years. In 34 patients, PS was almost 0, 1 or 2. In the remaining 2 patients, PS was 3. As initial treatment, surgery was performed in 4 patients, radiotherapy in 17, and chemotherapy in 13. BSC was performed in two patients who did not wish to receive aggressive treatment. Histopathologically, 18 patients had squamous cell carcinomas, 16 had adenocarcinomas and 2 had small cell carcinomas. The median primary tumor diameter was 4.1 cm, with a maximum of 7.7 cm. In addition, a bulky mass was detected in 28 patients. In 13 patients, hydronephrosis was noted, with 8 of these having bilateral hydronephrosis. The number of distant metastases was 1 in most patients, but 3 or 4 in some patients. The metastatic lesion sites included the para-aortic node in 7 patients and the main organs in 8 patients. Table II shows the sites of distant metastases (including duplicating patients). In the abdominal cavity, para-aortic lymph node metastases were detected in 18 patients (50%), comprising the highest percentage. In the extraperitoneal region, supraclavian lymph node metastases were detected in 13 patients (36%). Among main organ metastases, liver metastases were detected in 7

Table I. Patient characteristics.

Age (year), median (range)	54 (28-77)
PS 0/1/2/3	5/18/11/2
No. of patients	36
Initial treatment	
Surgery	4
Radiotherapy	17
Chemotherapy	13
Best supportive care	2
Pathology	
Squamous cell carcinoma	18
Adenocarcinoma	16
Small cell carcinoma	2
Primary tumor size (cm), median (range)	4.1 (2.1-7.7)
Bulky mass >4 cm	
Negative	8
Positive	28
Hydronephrosis	
Negative	23
Unilateral	5
Bilateral	8
No. of distant metastases	
1	20
2	13
3	2
4	1
Site of distant metastases	
Para-aortic lymph node only	7
Distant lymph node only	7
Organ metastases only	1
Para-aortic lymph node + Distant lymph node	10
Para-aortic lymph node + Organ metastases	1

Table II. Distant metastases in patients.

Metastatic sites	n (%)
Intra-abdominal metastases	
Para-aortic lymph node	18 (50)
Liver	7 (19)
Spleen	2 (5.5)
Small intestine	1 (2.7)
Extra-abdominal metastases	
Lung	4 (11)
Bone	2 (5.5)
Supraclavicular lymph node	13 (36)
Mediastinal lymph node	2 (5.5)
Inguinal lymph node	2 (5.5)

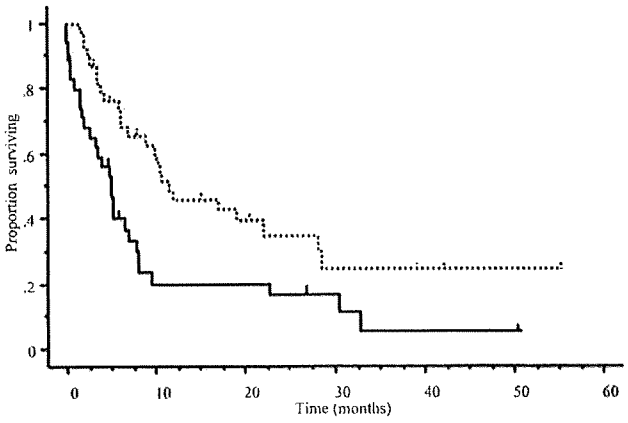

Figure 1. Kaplan-Meier analysis of progression-free survival (solid line) and overall survival (dotted line). Vertical bars indicate censored cases.

Table III. Characteristics of 21 patients with chemotherapy.

	n=21
Indication for therapy	
Initial case	13
Persistent/recurrence case	7
Postoperative case	1
Regimens	
Paclitaxel/carboplatin	9
Irinotecan/carboplatin	9
Weekly paclitaxel/carboplatin	2
Irinotecan/cisplatin	1

patients, comprising the highest percentage, followed by lung metastases in 4 patients. The median progression-free survival and overall survival were 3.8 months and 11.1 months, respectively (Fig. 1).

We examined the effects of chemotherapy on stage IVb cancer (Table III). Chemotherapy was administered to 21 patients, 13 of whom were undergoing initial treatment, 7 of whom had persistent/recurrence, and 1 of whom was undergoing postoperative therapy. The regimens consisted of paclitaxel/carboplatin in 9 patients, irinotecan/carboplatin in 9, weekly paclitaxel/carboplatin in 2, and cisplatin/irinotecan in 1. In 2 patients, including 1 undergoing postoperative adjuvant therapy, chemotherapy was discontinued due to adverse effects. For lesions that could be measured, the response rate was 61.9% (95% CI, 41.1-82.6) including 4 patients with CR and 9 patients with PR (Table IV).

We compared survival in the chemotherapy and non-chemotherapy groups. The median survivals of the chemotherapy and non-chemotherapy groups were 11.1 and 5.1 months, respectively, with a significant difference (p=0.0055) (Fig. 2).

We also compared survival between initial chemotherapy and initial other treatment groups. The median survivals in the initial chemotherapy and initial other treatment groups

Table IV. Response rate of chemotherapy (n=21).

Response (%)					
CR	PR	SD	PD	NE	RR
4	9	4	1	3	61.9%
					(95% CI, 41.1-82.6%)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; RR, response rate.

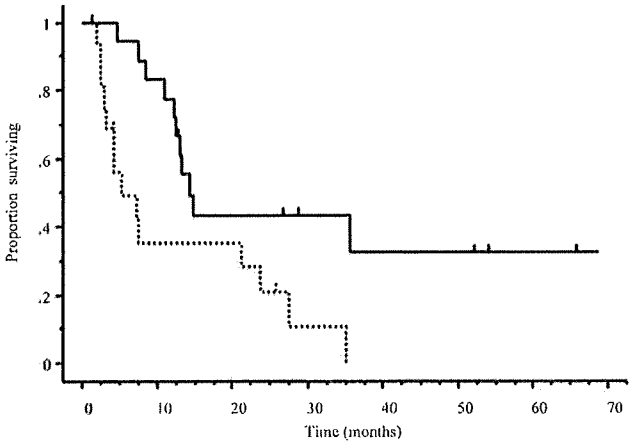

Figure 2. Kaplan-Meier analysis of overall survival according to with/without chemotherapy in stage IVb cervical carcinoma. Chemotherapy group (solid line) is significantly better prognosis (p=0.0055) than non-chemotherapy group (dotted line). Vertical bars indicate censored cases.

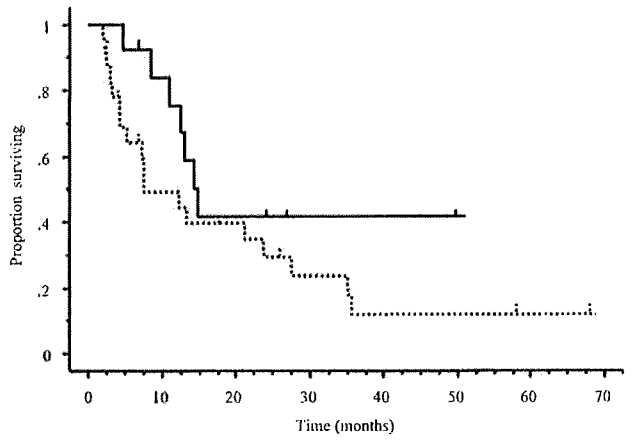

Figure 3. Kaplan-Meier analysis of overall survival according to with/without initial chemotherapy in stage IVb cervical carcinoma. There are no statistical differences (p=0.09) between initial chemotherapy group (solid line) and other initial treatment group (dotted line). Vertical bars indicate censored cases.

were 13.2 and 7.5 months, respectively, but it did not reach statistical significant (p=0.09) (Fig. 3). Two patients treated by chemotherapy alone as an initial treatment have survived

Table V. Prognostic factors of overall survival.

	Univariate	Multivariate		
Factor	P-value	P-value	HR	95% CI
Age ≥50	0.171	0.506	1.36	0.54-3.43
PS (0 and 1 vs. 2 and 3)	0.005	0.007	2.64	1.42-4.91
Pathology (SCC vs. non-SCC)	0.638	-	-	-
Organ metastases (0 vs. ≥1)	0.792	-	-	-
No. of distant metastases (1 vs. ≥2)	0.109	0.546	1.22	0.63-2.35
Bulky mass	0.478	-	-	-
Chemotherapy	0.011	0.016	6.03	1.97-18.37

disease-free for 51.8 and 68.6 months, respectively. One patient had stage IVb CC with para-aortic lymph node metastases while the other had stage IVb CC with subclavian lymph node metastases and mediastinal lymph node metastases. Both patients were administered paclitaxel/carboplatin for 6 cycles. After 6 cycles, the primary lesion and metastatic site exhibited complete response.

We analyzed chemotherapy, age, PS, histological type, main organ metastases, number of distant metastases, and bulky masses as prognostic factors. On univariate analysis, poor PS and non-chemotherapy groups were prognostic factors. On multivariate analysis, a poor PS (p=0.007; hazard ratio, 2.64; 95% CI, 1.42-4.91) and non-chemotherapy groups (p=0.016; hazard ratio, 6.03; 95% CI, 1.94-18.37) also affected overall survival (Table V).

Discussion

The prognosis of stage IVb cervical carcinoma is poor in patients with systemic metastases. No treatment has been established. In the NCI-PDQ, it is described that therapeutic strategies for this stage of cancer include palliative radiotherapy, chemotherapy as a regimen designed by a clinical study, and chemotherapy with cisplatin, which has previously been reported (34).

In stage IVb patients with para-aortic lymph node metastasis alone, surgery with postoperative radiotherapy and extended radiotherapy achieved a 5-year survival rate of 50% (30-33), and radical surgery may also be an option. However, since most metastases involve the main organs, it is difficult to control them by local treatment, and chemotherapy is indicated for most patients (4).

Various regimens of chemotherapy for this stage of cancer, including single-agent, have been investigated. In particular, cisplatin has most frequently been employed, and yields the highest response rate as a single-agent. It has therefore been

used as a key drug for more than 20 years (5,8,10-12). However, since the efficacy of cisplatin as a single-agent persists for only 6 months, combination regimens have been administered to improve in the prognosis to an extent exceeding the enhancement of its toxicity. In the 1990s, many phase II clinical studies investigated combination regimens with 2-4 agents including cisplatin. Cisplatin with ifosfamide (IFM) yielded the second highest response rate, and bleomycin (BLM), which has commonly been employed to treat other cancers due to its similar high response rate and low toxicity. The usefulness of IP (IFM + CDDP) (35) and BIP (BLM + IFM + CDDP) (36) regimens has also been examined. Some regimens have achieved a response rate of 60% or higher; however, these regimens for the non-advanced and locally advanced stages are quite toxic and shorten the survival of some patients. In addition, no comparative study has been conducted, and the evaluation of each regimen has been insufficient. In the latter half of the 1990s, combination regimens with new agents were designed, and the need for a standard therapy was emphasized.

Recently, carboplatin (37-39), topotecan (19,20) and paclitaxel (40-42) have also been reported to be tolerable and efficacious. Complete responses have also been observed with topotecan and paclitaxel. However, topotecan has greater toxicity than carboplatin or paclitaxel. Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel or topotecan is a reasonable approach in patients with recurrent disease. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S).

Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel (21) and cisplatin/topotecan (22) have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the two-drug combination yielded a higher response rate (36 versus 19%) and improved progression-free survival (4.8 versus 2.8 months; $p<0.001$), although no improvement has been seen in median survival (21). Another randomized phase III GOG study investigated the combination of cisplatin and topotecan versus cisplatin alone for persistent/recurrent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was superior to single-agent cisplatin with respect to overall response rate (27 versus 13%; $p=0.004$), progression-free survival (4.6 versus 2.9 months; $p=0.014$), and median survival (9.4 versus 6.5 months; $p=0.017$) (22). A phase II study assessed cisplatin and gemcitabine in patients with advanced, persistent/recurrent cervical cancer; 17 patients were evaluated (43). The response rate was 57% in patients who had not previously received radiotherapy, and there was 1 complete response of 14 months. Paclitaxel and carboplatin have recently been assessed for recurrent or persistent cancer of the cervix; 4 of 15 patients had a complete response and 5 showed a partial response for an overall response rate of 60% (39). The median survival of all 15 patients treated was 17 months (range, 4-39 months). The combination of vinorelbine and cisplatin has also been assessed in 42 patients with recurrent or metastatic cervical cancer; the overall response rate was 48% (44). The GOG is currently conducting a phase III trial (GOG204) to assess 4 cisplatin-doublet regimens in patients with advanced metastatic or recurrent cancer (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisiplatin/vinorelbine).

In our hospital, we conducted an in-house clinical study. For eligible patients, paclitaxel/carboplatin or irinitecan/carboplatin therapy was administered. Adverse effects were within the permissible ranges, and there were no treatment-related deaths, as reported in other studies. Response rate as an end-point was also similar to or exceeded that previously reported, suggesting the usefulness of these treatment options in chemotherapy for cervical carcinoma. In patients with poor PS, weekly paclitaxel/carboplatin therapy was safe. Several reports have indicated that the hematological toxicity of this therapy is lower than that of tri-weekly therapy, and that the therapeutic effects of these two regimens are similar (45,46). Weekly paclitaxel/carboplatin therapy may be useful for treating stage IVb cancer patients with poor PS.

In patient with this stage of cancer, nephropathy is frequent, making cisplatin administration difficult in many cases. Carboplatin can be administered to patients with nephropathy, without hydration. Considering the adverse effects, less toxic agents should be reviewed.

In this study, two patients treated by chemotherapy alone as an initial treatment have survived disease-free for 51.8 and 68.6 months, respectively. For patients with recurrence who desired sequential treatment, chemotherapy was administered when we considered them eligible. Considering that the prognosis was significantly better than that in the non-chemotherapy group, chemotherapeutic intervention may be useful in stage IVb patients who have undergone initial treatment and in those with persistent/recurrent metastases.

Eligible, consenting patients should be enrolled in clinical trials employing new drugs and/or strategies. Since there is as yet no evidence for the curative potential of chemotherapy in cervical cancer and no established survival benefit, and uncertainty exists as to how often response translates into symptom relief ('palliation'), non-protocol therapy should not be encouraged. Nevertheless, for a patient who is ineligible or unwilling to participate in a study but who wants treatment, there may still be an indication for chemotherapy giving 'psychological support' or hope. When such a patient insists on treatment and seeks untested remedies rather than a hospice if orthodox chemotherapy is not offered, single-agent cisplatin or carboplatin may be justified, with due attention being paid to contraindications and the toxic side effects. An interval response assessment and finite period of treatment are indicated. Objective benefit is possible, but not likely.

Prognostic factors for stage IVb cervical carcinoma include PS, age, histological type, main organ metastases, and distant metastases (23-29). In this study, univariate and multivariate analysis revealed that non-chemotherapy and poor PS influenced prognosis. In patients with poor PS, it is difficult to continue treatment, and chemotherapy may exceed cancer control due to systemic disease. However, we can not conclude the efficacy of chemotherapeutic intervention, as this study was a retrospective study and involved only a small number of patients. Previously, surgery and radiotherapy have been selected for this stage of cancer. The results of chemotherapy for initial treatment were similar to those for conventional treatment, suggesting the efficacy of chemotherapy as initial

treatment. However, a randomized comparative study should be conducted to demonstrate its efficacy.

In conclusion, the prognosis of stage IVb cervical carcinoma remains poor. Chemotherapy may improve the survival of patients with stage IVb CC.

Acknowledgments

This work was supported by The Supporting Fund of Obstetrics and Gynecology Kurume University.

References

1. Sasieni PD, Cuzick J and Lynch-Farmery E: Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Coordinating Network for Cervical Screening Working Group. Br J Cancer 73: 1001-1005, 1996.
2. Wong LC, Ngan HY, Cheung AN, Cheng DK, Ng TY and Choy DT: Chemoradiation and adjuvant chemotherapy in cervical cancer. J Clin Oncol 17: 2055-2060, 1999.
3. NCI Clinical Alert Urges New Standard of Care for Invasive Cervical Cancer, URL:http://www.nci.nih.gov/clinicaltrials/developments/cervical-cancer-alert0600.
4. Omura GA: Current status of chemotherapy for cancer of the cervix. Oncology 6: 27-32, 1992.
5. Omura GA: Chemotherapy for stage IVb or recurrent cancer of the uterine cervix. J Natl Cancer Inst Monogr 21: 123-126, 1996.
6. Lea JS, Sheets EE, Wenham RM, Duska LR, Coleman RL, Miller DS and Schorge JO: Stage IIB-IVB cervical adenocarcinoma: prognostic factors and survival. Gynecol Oncol 84: 115-119, 2002.
7. Cleeland CS: Pain assessment in cancer. In: Effect of Cancer on Quality of Life. Osoba D (ed). CRC Press, Boston, MA, pp293-306, 1991.
8. Thigpen T: The role of chemotherapy in the management of carcinoma of the cervix. Cancer J 9: 425-432, 2003.
9. Thigpen JT, Vance R, Puneky L and Khansur T: Chemotherapy as a palliative treatment in carcinoma of the uterine cervix. Semin Oncol 22: 16-24, 1995.
10. Thigpen T, Shingleton H, Homesley H, Lagasse L and Blessing J: Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II trial of the Gynecologic Oncology Group. Cancer 48: 899-903, 1981.
11. Bonomi P, Blessing J, Stehman FB, DiSaia PJ, Walton L and Major FJ: Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 3: 1079-1085, 1985.
12. Thigpen JT, Blessing JA, DiSaia PJ, Fowler WC Jr and Hatch KD: A randomized comparison of rapid versus prolonged (24 h) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Gynecol Oncol 32: 198-202, 1989.
13. Coleman RE, Harper PG, Gallagher C, *et al*: A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother Pharmacol 18: 280-283, 1986.
14. Meanwell CA, Mould JJ, Blackledge G, Lawton FG, Stuart NS, Kavanagh JJ, Latief TN, Spooner D and Chetiyawardana AD: Phase II study of ifosfamide in cervical cancer. Cancer Treat Rep 70: 727-730, 1986.
15. Sutton GP, Blessing JA, McGuire WP, Patton T and Look KY: Phase II trial of ifosfamide and mesna in patients with advanced or recurrent squamous carcinoma of the cervix who had never received chemotherapy: a Gynecologic Oncology Group study. Am J Obstet Gynecol 168: 805-807, 1993.
16. McGuire WP, Blessing JA, Moore DH, Lentz SS and Photopulos G: Paclitaxel has moderate activity in squamous cervix cancer: a Gynecologic Oncology Group study. J Clin Oncol 14: 792-795, 1996.
17. Morris M, Brader KR, Levenback C, Burke TW, Atkinson EN, Scott WR and Gershenson DM: Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. J Clin Oncol 16: 1094-1098, 1998.
18. Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB and Menzin A: Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 92: 639-643, 2004.
19. Bookman MA, Blessing JA, Hanjani P, Herzog TJ and Anderson WA: Topotecan in squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 77: 446-449, 2000.
20. Muderspach LI, Blessing JA, Levenback C and Moore JL Jr: A phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 81: 213-215, 2001.
21. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF and Rocereto TF: Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 22: 3113-3119, 2004.
22. Long HJ III, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA and Fiorica JV: Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol 23: 4626-4633, 2005.
23. Leath CA III, Straughn M Jr, Kirby TO, Huggins A, Partridge EE and Parham GP: Predictors of outcomes for women with cervical carcinoma. Gynecol Oncol 99: 432-436, 2005.
24. Kastritis E, Bamias A, Efstathiou E, Gika D, Bozas G, Zorzou P, Sarris K, Papadimitrou C and Dimopoulos MA: The outcome of advanced or recurrent non-squamous carcinoma of the uterine cervix after platinum-based combination chemotherapy. Gynecol Oncol 99: 376-382, 2005.
25. Sommers GM, Grigsby PW, Perez CA, Camel HM, Kao MS, Galakatos AE and Lockett MA: Outcome of recurrent cervical carcinoma following definitive irradiation. Gynecol Oncol 35: 150-155, 1989.
26. Yamamoto K, Yoshikawa H, Shiromizu K, Saito T, Kuzuya K, Tsunematsu R and Kamura T: Pulmonary metastasectomy for uterine cervical: a multivariate analysis. Ann Thorac Surg 77: 1179-1182, 2004.
27. Brader KR, Morris M, Levenback C, Levy L, Lucas KR and Gershenson DM: Chemotherapy for cervical carcinoma: factors determining response and implications for clinical trial design. J Clin Oncol 16: 1879-1884, 1998.
28. Potter ME, Hatch KD, Potter NY, Shingleton HM and Baker VV: Factors affecting the response of recurrent squamous cell carcinoma of the cervix to cisplatin. Cancer 63: 1283-1286, 1989.
29. Seki M, Nakagawa K, Tsuchiya S, Matsubara T, Kinoshita I, Weng SY and Tsuchiya E: Surgical treatment of pulmonary metastases from uterine cervical cancer. Operation method by lung tumor size. J Thorac Cardiovasc Surg 104: 876-881, 1992.
30. Lovecchio JL, Averette HE, Donato D and Bell J: Five-year survival of patients with periaortic nodal metastases in clinical stage IB and IIA cervical carcinoma. Gynecol Oncol 34: 43-45, 1989.
31. Varia MA, Bundy BN, Deppe G, Mannel R, Averette HE, Rose PG and Connelly P: Cervical carcinoma metastatic to para-aortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group Study. Int J Radiat Oncol Biol Phys 42: 1015-1023, 1998.
32. Grigsby PW, Lu JD, Mutch DG, Kim RY and Eifel PJ: Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes: phase II study of the RTOG 92-10. Int J Radiat Oncol Biol Phys 41: 817-822, 1998.
33. Grigsby PW, Heydon K, Mutch DG, Kim RY and Eifel P: Long-term follow-up RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. Int J Radiat Oncol Biol Phys 51: 982-987, 2001.
34. NCI Cancer Topics Cervical Cancer (PDQ®): Treatment URL: http://www.nci.nih.gov/cancertopics/pdq/treatment/health-professional/.
35. Omura GA, Blessing JA, Vaccarello L, Beman ML, Clarke-Pearson DL, Mutch DG and Anderson B: Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 15: 165-171, 1997.
36. Bloss JD, Blessing JA, Behrens BC, Mannel RS, Rader JS, Sood AK, Markman M and Benda J: Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 20: 1832-1837, 2002.