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２０年度　総括研究報告書

主任研究者　中川　和彦

平成２１（２００９）年　３月

様式A（7）

厚生労働科学研究費補助金研究報告書

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5．研究成果の刊行に関する一覧表　（別添５のとおり）

6．研究成果による特許権等の知的財産権の出願・登録状況

7．健康危険情報

別添１

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研究成果の刊行に関する一覧表

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２０年度　総括研究報告書

主任研究者　中川　和彦

平成２１（２００９）年　３月

別紙２

目　　次

別紙３

厚生労働科学研究費補助金（がん臨床研究事業）
総括研究報告書

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
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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。

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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。当初、申請書に示した参加施設で共同研究組織を設立、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胸部腫瘍臨床研究機構（NPO-WJOG）のデータセンター機能と効果安全性評価委員会による外部評価機能を使用する。また、国立がんセンター中央病院の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教授の保持する過去の遺伝子発現解析データを用いて、アルゴリズム作成とその検証を東京大学伊藤先生らにより作成、検証される。

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（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。したがって1年生存率は35%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0.02、αエラーを0.05とすると登録期間3年、追跡期間2年とした場合、各群77例必要となる。逸脱例も考慮してtotal 160例必要となる。現在の参加施設（14施設）の患者集積力は年間80症例であることから本試験は実施可能である。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考え方の相違が存在する。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へ送付する。遺伝子発現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、データセンターは割付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：160症例（各群80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、定期モニタリングの実施。
3）三年次：最終解析

（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。
＜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（本年度）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。

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。本年度、癌研有明病院が新たに本研究に参加することとなった。

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発現解析実施実施研究所との連携の確認作業を完了した。

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。

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ている。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。これまでの原発不明癌を対象にした臨床試験（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。したがって1年生存率を35%と仮定した。それに対して、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、βエラーを0.2、αエラーを0.2、登録期間3年、追跡期間2年で実施すると見積もった。この場合に必要とされる症例数は各群57例となった。逸脱例も考慮してtotal 120例を登録することとした。2009年3月1日までに9つの参加施設にて審査を終了しており、現在、他5施設での審査結果を待っているところである。すでに審査過程を終了した5施設から8症例の登録を受けている。

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の品質は良好であり、8症例ともに遺伝子発現解析は可能であった。

当初の計画通り、第2年時に当たる本年度内に臨床試験を開始することができた。今後、症例登録を加速させて本臨床試験の完遂を目指す。

F．研究発表

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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（参考）

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ORIGINAL ARTICLE

A phase I escalating single-dose and weekly fixed-dose study of cetuximab pharmacokinetics in Japanese patients with solid tumors

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Abstract

Purpose Cetuximab is a therapeutic immunoglobulin G1 monoclonal antibody that recognizes the epidermal growth factor receptor (EGFR). This phase I dose-escalation study was designed to assess the safety and pharmacokinetics (PK) of cetuximab in Japanese patients with EGFR-expressing, advanced, solid tumors and also to look for evidence of antitumor efficacy.

Patients and methods Thirty patients were enrolled in the study; 29 with colorectal adenocarcinomas and one with an adenocarcinoma of the lung. Patients received an initial/weekly infusion of cetuximab at dose levels of 100/100 (dose level 1), 250/250 (dose level 2), 400/250 (dose level 3), 500/250 (dose level 4) or 400/250 (dose level 5) mg/m^2, for 7 or more weeks, with an interval between the initial and second infusion of 1 (dose level 5 representing the standard regimen) or 2 weeks (dose levels 1–4 of the non-standard regimens).

Results No dose-limiting toxicities (DLTs) were observed during the evaluation period. All patients had at least one adverse event (AE). The most common cetuximab-related AEs were skin toxicity (93% of patients), including acneiform dermatitis (83% of patients). Two patients experienced cetuximab-related grade 3 AEs of skin toxicity and diarrhea after DLT evaluation. C_{max} and $AUC_{0-\infty}$ after the initial infusion showed dose-proportional increases. Mean total body clearance (CL) values decreased with dose at the lower dose levels. At doses of $\geq$400 mg/m^2, CL values appeared to level off. Mean trough concentrations for dose level 5 were constant from week 4 (day 29) onward. Two patients (8%) achieved partial response (at 100/100 mg/m^2). The overall disease control rate (partial response + stable disease) was 58%.

Conclusion The current study demonstrated that cetuximab PK and safety profiles are similar between Japanese and non-Japanese patient populations. It would appear that

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the standard dose of an initial 2-h infusion of 400 mg/m^2 followed thereafter by weekly 1-h infusions of 250 mg/m^2 for non-Japanese patients is feasible for future clinical studies in Japanese patients.

Keywords Cetuximab · Japanese · EGFR · Safety · Pharmacokinetics · Colorectal

Introduction

Over recent years, the development of rationally selected targeted agents such as monoclonal antibodies and small molecule tyrosine kinase inhibitors has offered new possibilities in relation to improving the efficacy of the standard cytotoxic regimens used in the treatment of metastatic colorectal cancer (mCRC). The epidermal growth factor receptor (EGFR)-targeted immunoglobulin G1 monoclonal antibody cetuximab (Erbitux®) is one such targeted agent.

Cetuximab competitively inhibits the binding of endogenous EGFR ligands and thus prevents receptor dimerization and downstream signaling [1, 2]. Antibody-binding to the tumor cell may also result in a clinically-important antibody-dependent cell-mediated cytotoxicity reaction (ADCC) [3, 4]. Randomized mCRC studies in mainly Caucasian populations have shown that cetuximab, administered in accordance with the standard dosing regimen of an initial 2-h infusion of 400 mg/m^2 of body surface area (BSA) followed thereafter by weekly 1-h infusions of 250 mg/m^2, is effective as monotherapy [5, 6] or in combination with irinotecan [5, 7], following the failure of previous chemotherapy regimens. Furthermore, in the first-line setting, the phase III CRYSTAL study has shown that the addition of cetuximab to infusional 5-fluorouracil/folinic acid/irinotecan (FOLFIRI) significantly improves the response rate, progression-free survival (PFS) time and R0 resection rate in mCRC patients, compared with FOLFIRI alone [8]. Similarly, randomized studies have demonstrated the efficacy of cetuximab in combination with radiotherapy in the treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN) [9] and in combination with platinum-based therapy in the first-line treatment of recurrent and/or metastatic SCCHN [10].

Two recent studies in the US have explored the pharmacokinetics (PK) of single-dose administration of cetuximab in patients with solid tumors, with particular attention paid to the elimination phase [11, 12]. Both studies supported the saturation of EGFR binding at a clinically achievable dose level. A significant association was also noted between cetuximab clearance and both BSA and weight, supporting the use of these parameters in calculating individual cetuximab doses [12]. The primary objective of the current phase I study was to investigate the safety and tolerability of cetuximab in a population of Japanese patients with EGFR-expressing solid tumors. Secondary objectives were to evaluate the PK of cetuximab in Japanese patients the (mirroring the recent US PK analyses with an escalating single dose); expression of human antichimeric antibodies (HACA); the incidence of dose-limiting toxicity (DLT); and the antitumor efficacy of cetuximab.

Patients and methods

Patient eligibility

Only Japanese patients, aged between 20 and 74 years, with a histologically or cytologically confirmed advanced solid EGFR-expressing tumor, refractory to a standard therapy or for which no standard therapy existed, were eligible. They required an Eastern Cooperative Oncology Group performance status of 0–2; a life expectancy of at least 3 months after the start of study; adequate hematological (leukocyte count: $\geq$3,000 and <12,000 mm^{-3}; neutrophil count: $\geq$1,500 mm^{-3}; platelet count: $\geq$100,000 mm^{-3}; hemoglobin: $\geq$9 g/dL), hepatic (aspartate aminotransferase and alanine aminotransferase: $\leq$2.5 times the upper limit of the reference range; serum total bilirubin: $\leq$1.5 times the upper limit of the reference range), and renal (serum creatinine: $\leq$1.5 times the upper limit of the reference range) function. Patients were required to be available for hospitalization until day 22 of the study, to have no carry-over effect from prior therapy and to not have received treatment with blood transfusions, blood products or blood cell factors such as granulocyte colony stimulating factor during 2 weeks prior to enrollment. All patients gave their written informed consent prior to study entry.

Patients were excluded if they had: symptomatic brain metastasis, a previous history of cancerous meningitis, poorly controlled epileptic seizures or clinically significant mental or central nervous system disorders or if they had previously received monoclonal antibody therapy (including cetuximab). They were also ineligible if they had serious cardiac or cardiovascular disease, diabetes mellitus, hypertension, active infection or symptomatic blood coagulation disorder, acute pulmonary disorder, interstitial pneumonia, or pulmonary fibrosis; active, double cancers; a previous history of malignant tumors (other than nonmelanoma skin cancer, uterine cervical carcinoma or gastrointestinal intramucosal carcinoma) with a sign of recurrence within the last 5 years; a large volume of pleural effusion or ascites or were positive for hepatitis B virus, hepatitis C virus or human immunodeficiency virus. Patients were also excluded if they required chronic treatment with systemic steroids; were pregnant or lactating; if they wished to have a child; or if they had an alcohol or drug

addiction or a previous history of drug allergy or anaphylactic symptoms.

Study design

This study was a two-center, phase I dose-escalation study of cetuximab in patients with advanced solid cancer. As this was the first such investigation in Japanese patients, a low dose level of 100 mg/m^2 as an initial dose and 100 mg/m^2 as a repeated weekly dose was selected to begin the study. All patients received 50 mg oral diphenhydramine hydrochloride (H1-antagonist) 30–60 min before each cetuximab infusion as a preventive measure in relation to infusion-related reactions. At first infusion, patients received 100 (dose level 1), 250 (dose level 2), 400 (dose level 3 or 5) or 500 (dose level 4) mg/m^2 of cetuximab as a 2-h intravenous infusion. Subsequent weekly 1-h infusions of 100 (dose level 1) or 250 (dose level 2–5) mg/m^2 of cetuximab began according to the schedule in Fig. 1 and continued to day 50, which was considered to be sufficient to assess cetuximab PK. For dose levels 1–4, patients had a 2-week interval between first and second infusion for the purposes of evaluation of single-dose PK. Patients in dose level 5 received cetuximab according to the standard 400/250 mg/m^2 schedule, with a 1-week interval between first and second infusions, curtailing the collection of single-dose PK at 7 days in this group.

Six patients were assigned to each dose level 1–4, with the first cohort receiving cetuximab at the lowest dose level. If DLT was observed in ≥2 patients during the DLT evaluation period of 6 weeks from the first administration until 1 week after the fifth administration, no further patients were to be enrolled and this dose level was defined as the MTD. Otherwise, the dose was escalated to the next dose level (1–2, 2–3 or 3–4). If the MTD was not established at dose level 4, six patients received the standard 400/250 mg/m^2 regimen at dose level 5. DLT was defined as either: grade 4 or three incidences of grade 3 skin toxicity events, or the omission of three consecutive infusions due to grade 3 skin toxicity; adverse drug reactions ≥grade 3 (except for skin toxicity, electrolyte abnormality, anorexia, nausea, and alkaline phosphatase) or the development of acute pulmonary disease, interstitial pneumonia and other pulmonary symptoms. Infusion-related reactions were not regarded as DLTs as they were considered to be largely dose-independent. If progressive disease (PD) was not observed between the initial dose and fifth administration (or sixth administration for dose level 5), the study medication was to be continued as long as the patient gave consent, again after an observation period of 1 week. During the study period, the following drugs and therapies were not permitted; therapeutic modalities for malignant tumor, other antibody therapy, chemotherapy, hormonal therapy, immunological therapy, radiotherapy, hyperthermia and surgical therapy, and systemic steroids. The drugs and therapies used for symptomatic relief of concurrent diseases or complications were permitted before and during the study with minimal modification of dosage and mode of administration.

Study evaluations

Response was assessed in evaluable patients by the investigators according to RECIST guidelines [ ] and had to be confirmed by a repeated consecutive assessment conducted a minimum of 28 days after the first assessment. Adverse events (AEs) were graded according to the National Cancer Institute—Common Toxicity Criteria version 2 (Japan Clinical Oncology Group—translation version). Safety variables assessed included; AEs, abnormal laboratory values and vital signs (blood pressure, heart rate, respiratory rate, body temperature, 12-lead electrocardiogram, chest X-ray).

Pharmacokinetic analysis

Blood samples (5 mL) were drawn prior to the first cetuximab infusion and at 1, 1:58, 2:30, 3, 4, 6, 8, 24, 48, 96, 168, 264 and 336 h (not 264 and 336 h for dose level 5) after the initiation of infusion. Subsequent samples were taken before cetuximab infusions on days 15 (dose level 5

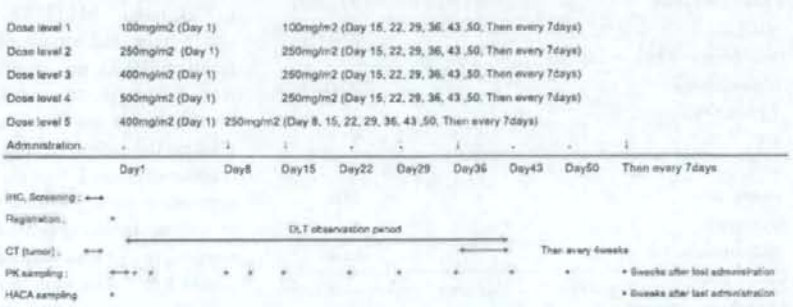

Fig. 1 Dosage and schedule of on-study cetuximab administration

Note: IHC, immunohistochemistry(EGFR), DLT, dose-limiting toxicity, CT, computerized tomography, PK, pharmacokinetics, HACA, human anti-chimeric antibodies.