201332016A

厚生労働科学研究費補助金

難病・がん等の疾患分野の医療の実用化研究事業
（がん関係研究分野）

進行非小細胞肺癌を対象としたエルロチニブとYM155の分子標的治療薬併用第Ⅰ相試験

平成25年度　総括研究報告書

研究代表者　中　川　和　彦

平成26（2014）年　3月

様式Ａ（８）

厚生労働科学研究費補助金研究報告書

平成 26 年 3 月 31 日

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平成 25 年度厚生労働科学研究費補助金（難病・がん等の疾患分野の医療の実用化研究事業（がん関係研究分野））に係る研究事業を完了したので次のとおり報告する。

研究課題名（課題番号）：　進行非小細胞肺癌を対象としたエルロチニブとYM155の分子標的治療薬併用第I相試験（H24-実用化(がん)一般-004）

国庫補助金精算所要額　：金 ９９，１０２，７４９ 円也（うち間接経費　２５，１７６，０００円）

１．厚生労働科学研究費補助金研究報告書表紙　（別添１のとおり）

２．厚生労働科学研究費補助金研究報告書目次　（別添２のとおり）

３．厚生労働科学研究費補助金総括研究報告書　（別添３のとおり）

４．研究成果の刊行に関する一覧表　（別添５のとおり）

別添１

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別添５

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

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進行非小細胞肺癌を対象としたエルロチニブとYM155の分子標的治療薬併用第I相試験

平成２５年度　総括研究報告書

研究代表者　中川　和彦

平成２６（２０１４）年　３月

別紙２

目　　次

別紙３

厚生労働科学研究費補助金（難病・がん等の疾患分野の医療の実用化研究事業（がん関係研究分野））
総括研究報告書

進行非小細胞肺癌を対象としたエルロチニブとYM155の分子標的治療薬併用第I相試験

研究代表者　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　進行非小細胞肺癌患者を対象に、EGFRチロシンキナーゼ阻害剤(EGFR-TKI)エルロチニブに併用するサバイビン阻害薬YM155の推奨投与量の設定、及び用量制限毒性（DLT）を明らかにし、推奨投与量における安全性と抗腫瘍効果および効果に関わるバイオマーカーを探索する

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西尾　和人　（近畿大学医学部ゲノム生物学教室　教授）
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Ａ．研究目的

EGFR陽性進行非小細胞肺癌患者を対象に、EGFRチロシンキナーゼ阻害剤(EGFR-TKI)エルロチニブに併用するサバイビン阻害薬YM155の推奨投与量の設定、及び用量制限毒性（DLT）を明らかにし、推奨投与量における安全性と抗腫瘍効果および効果に関わるバイオマーカーを探索する。

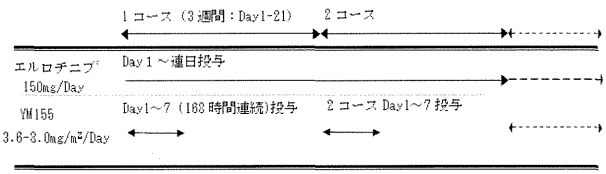
Ｂ．研究方法

[研究計画・方法]
分子標的治療薬併用第Ｉ相臨床試験（医師主導治験）として、EGFR陽性進行非小細胞肺癌に対する化学療法を受ける患者を対象にエルロチニブとサバイビン阻害薬YM155併用投与の両薬剤推奨投与量の設定、用量制限毒性（DLT）および最大耐用量（MTD）を明らかにし、両分子標的治療薬の推奨投与量における安全性と抗腫瘍効果について検討する。

[対象症例]
EGFR陽性進行非小細胞肺癌に対する化学療法を受ける患者、20歳以上、ECOG Performance Status (PS) 0-2、主要臓器機能が保持された症例。患者本人の自由意思による文書同意を必須とする。

【Primary endpoint】
エルロチニブとYM155併用投与の安全性プロファイル（有害事象）、用量制限毒性（DLT : dose limiting toxicity）、最大耐用量（MTD : maximum tolerated dose）および推奨投与量の決定。

【Secondary endpoint】
推奨投与量における安全性と抗腫瘍効果、及び抗腫瘍効果に関わるバイオマーカーの探索。



エルロチニブは1日1錠（150mg）の連日経口投与とし、YM155（アステラス製薬より治験薬剤供給）は（シリンジポンプを用いた）168時間（7日間）の持続点滴静脈内投与とする。併用治療開始時点を1コースday1とする。併用薬エルロチニブは連日経口投与、治験薬YM155は1週間(168時間)投与2週間休薬をもって1コース（21日間隔）とする。以後、腫瘍の増悪・新病変の出現または投与継続が困難な有害事象の発現を認めるまで、1コースを21日間隔として治療を継続する。パート1(dose escalation cohort)の症例では、治験実施計画書に記載のスケジュールにてエルロチニブ及びYM155の薬物動態測定を行う。また同意が得られた患者に対し、抗腫瘍効果に関わるバイオマーカーの探索として1)YM155投与前後における腫瘍組織中のサバイビン蛋白質量の測定とアポトーシス誘導の有無を確認、2)肺癌組織の体細胞変異解析にあたり、LungCarta、Bio-plex (Ligand panel)等のマススクリーニングパネルを用いた半網羅的体細胞変異解析を実施する。

[予定症例数及び研究期間]
医師主導治験による第1相臨床試験として、12-24例。試験期間は2012年12月1日より2015年11月31日（準備期間：1年、登録期間:1年、追跡期間：1年）とする。

[研究体制]
研究代表者（医師主導治験実施責任者）は研究の統括・計画を実施する。研究分担者は近畿大学医学部

腫瘍内科において研究の計画・測定・解析を実施、症例登録を行う。バイオマーカーの測定は近畿大学医学部ゲノム生物学教室で測定する。近畿大学医学部・医学部附属病院および外部CROであるクインタイルズ・ジャパン・データマネジメント部および日本臨床研究オペレーションズ（Japan Clinical Research Operations:JCRO)は近畿大学医学部腫瘍内科と共同して本医師主導治験運用に必須であるセンターデータマネージメント、モニタリング業務、治験薬管理（治験薬剤提供元企業との連携）、CRC業務およびローカルデータマネージメント業務を遂行する。統計解析は近畿大学医学部臨床研究管理センター腫瘍統計学部門および外部CROであるクインタイルズ・ジャパン・データマネジメント部が行う。研究実施環境については研究施設・研究資料・研究フィールド・現在の研究環境の状況等インフラ整備されており問題はない。

（倫理面への配慮）
試験に関係するすべての研究者は、ヘルシンキ宣言および臨床研究に関する倫理指針にしたがって本試験を実施し，以下の事項を厳守する.
1. 登録に先立って、すべてに患者に施設の倫理審査委員会（IRB）承認が得られた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にて取得るする。
2. 個人情報および診療情報などのプライバシーに関する情報は個人の人格尊重の理念の下、厳重に保護され慎重に取り扱われるべきものと認識し、万全な管理対策を講じ、プライバシー保護に努める。データの取り扱いに関しては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ーを確保し，個人情報の保護を厳守する。
本研究に組み込まれるバイオマーカー研究は蛋白発現、体細胞DNAを対象に解析するものであり、「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、その趣旨を踏まえた対応を行う。

C．研究結果
研究計画に関する現在までの研究成果・取組進行状況は以下に示す通りである。平成24年6月27日本研究計画に関する採択通知受領後、直ちに同年 7月より同医師主導治験実施体制準備開始に至り10月23日施設内治験審査委員会（IRB）承認を得たのちに11月22日医薬品医療機器総合機構（PMDA当局）へ治験届を提出、12月10日PMDA当局より審査承認確認を得た。平成24年 12月12日第1回目サイトトレーニング（CRC・薬剤師等を対象）施行、12月20日に治験キックオフミーティングを兼ねた第2回目サイトトレーニング（医師・CRC・看護師・薬剤師等対象）施行、12月21日最終CRFフォーム固定 (クインタイルズ・ジャパン・データマネジメント部)、12月21日アステラス製薬より 近畿大学医学部附属病院薬剤部へ治験薬(YM155)搬入完了、12月25日クインタイルズ・トランスナショナル・ジャパンと同治験委受託契約完了を行った。平成25年1月4日PK（薬物動態測定解析用）用検査キット米国より輸入通関完了 (Advion/Quintiles and PPD, USA)。平成25年1月23日日本臨床研究オペレーションズ（JCRO : Japan Clinical Research Operations)と同治験業務委受託契約完了。平成25年1月25日第1コホート第1症例の治験登録平成25年1月29日第1症例の第1サイクル投与開始。第1コホートレベル（治験薬YM155 3.6 mg/㎡/day）では用量制限毒性（DLT）発現及び臨床上有意な毒性を全3症例において認めず、平成25年3月25日に効果安全性委員会を開催、同委員会の外部委員による審査にて次コホート（第2コホートレベル）への用量増加が承認され、平成25年4月より第2コホートレベル（治験薬YM155 4.8 mg/㎡/day）症例の治験登録が開始となった。第2コホートレベル（治験薬YM155 4.8 mg/㎡/day）において、当初3症例中1例にDLT発現（血清クレアチニン値上昇 2.4mg/dl：治験薬休薬中止にて可逆的回復）を認めた為、効果安全性委員会の確認を経て治験実施計画書に基づき同用量レベルにおいて3症例の追加登録を行った。第2コホートレベルに登録された合計6症例において、DLT発現は結果的に当初の1症例のみであったため、平成26年4月7日に効果安全性委員会を開催、同委員会の外部委員による審査にて次コホート（第3コホートレベル）への用量増加が承認され、平成26年4月7日より第3コホートレベル（治験薬YM155 6.0 mg/㎡/day）症例の治験登録が開始となった。現在第3コホートレベルにおいては2症例が登録され治験薬投与中であり、安全性を慎重に評価観察中である（現在までの治験薬投与症例総数：11名）。
同治験薬剤のCIOMSフォームを用いた海外における有害事象（SAE）報告に関しても近畿大学医学部腫瘍内科、クインタイルズ・ジャパンおよび日本臨床研究オペレーションズ（JCRO)による海外SAE報告プロセスのSOPに従いPMDAへの定期報告を逐一施行している。

D．考察
昨年の報告に引き続き、第1コホートレベルおよび第2コホートレベルでは用量制限毒性（DLT）発現及び臨床上有意な毒性は全9症例中、1症例のみに認められ（血清クレアチニン値上昇 2.4mg/dl：治験薬休薬中止にて可逆的回復）、既に現在までに2回目の外部委員による効果安全性委員会承認を経て治験実施計画書に準じて予定通り第3コホートレベルでの治験実施中である。また、治験薬投与前後の腫瘍組織採取（気管支鏡生検および肝転移部からの経皮的腫瘍針生検等）も既に採取施行可能例には被験者の同意取得のもとに実施されており、抗腫瘍効果に関わるバイオマーカーの探索として1)YM155投与前後における腫瘍組織中のサバイビン蛋白質量の測定とアポ

トーシス誘導の有無を確認、2)肺癌組織の体細胞変異解析にあたり、LungCarta、Bio-plex (Ligand panel)等のマススクリーニングパネルを用いた半網羅的体細胞変異解析を行うための病理組織サンプルを病院病理部にて保管中である。具体的な平成26年度バイオマーカー解析実施計画として、第1四半期（4～6月）：組織採取解析可能症例検体において下記を実施（Survivin IHC、Survivin RT-PCR、LungCarta Panel、Ion Ampliseq Panel（NGS：次世代シーケンサー）、Luminex Panel（血漿タンパク質解析）第2四半期（7～12月）追加解析可能症例検体の測定第3四半期（10～3月）mRNA, IHC, 血漿タンパク質解析結果との相関解析、体細胞遺伝子変異の頻度解析、pre-postにおける比較解析を実施予定である。

Ｅ．結論

本医師主導治験（第Ⅰ相試験）の実施運用に関する施設内インフラ体制は概ね整備が整っている状況となっている。近畿大学医学部附属病院腫瘍内科単施設（1施設）にて同医師主導治験開始後、約1年4か月で第3コホートレベル迄の合計11症例の治験症例登録および治験薬投与開始が実施出来ており、症例集積に関しても予定していた症例集積スピードと差異の無い状況である。用量制限毒性（DLT）発現及び臨床上有意な毒性評価に関しても現在の用量レベルまでは安全性・忍容性を確認済みであり、引き続き平成26年度においても当初の研究計画書・治験実施計画書に基づいた第Ⅰ相試験実施を継続する予定である。

Ｆ．研究発表

第12回日本臨床腫瘍学会学術集会（平成26年7月17-19日：福岡市）インターナショナルセッション（New aspect for molecular mechanism underlying resistance to EGFR-TKIs and ALK-TKIs）において、中間解析データを学会指定演題として英語口演発表予定。

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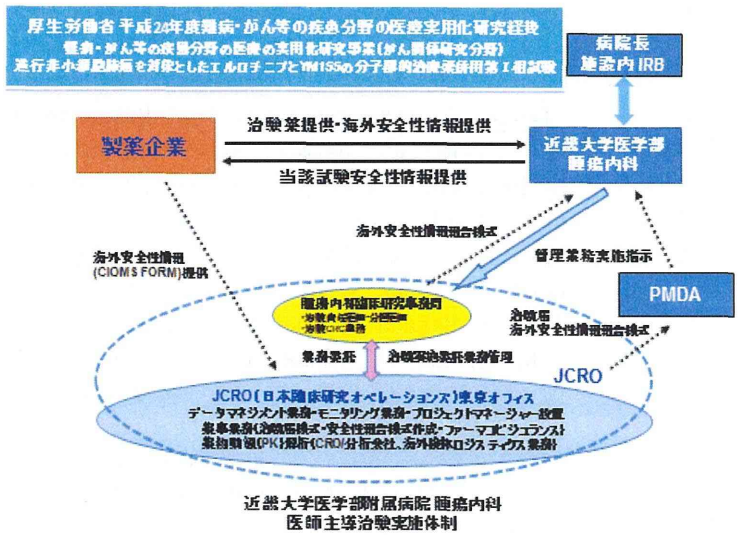
G. 知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　　なし



近畿大学医学部附属病院 腫瘍内科
医師主導治験実施体制

バイオマーカー解析に関する平成25年度取り組み

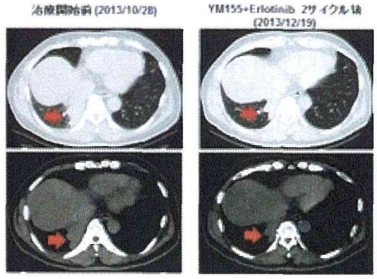
測定項目の準備	■ Survivinの解析(IHC・RT-PCR) 免疫組織染色・RT-PCR測定における測定条件の検討に着手した。 ■ 血漿タンパク質の解析(Luminex) これまでに十分な測定実績を有する。 ■ 体細胞変異解析 次世代シークエンサー(Ion PGM)の稼動開始し、Cancer Panel(体細胞変異測定)の測定が可能となった。
検体の収集	■ 血漿検体・組織検体の収集 症例登録にあわせて検体の集積を開始した。 収集検体 ①組織検体:投与前後のホルマリン固定パラフィン包埋検体 ②血漿検体:PK採血に準じた採血ポイントでの採取(凍結保存)

次年度は、測定項目の解析条件の確定ならびに検体の集積を継続して実施する。

症例登録状況(平成26年5月14日現在)

Level	YM155	Erlotinib	DLT	症例数
1	3.6 mg/m²/day	150 mg/day	なし	3
2	4.8 mg/m²/day	150 mg/day	血清クレアチニン上昇:1例	6
3	6.0 mg/m²/day	150 mg/day	評価中	2

EGFR陽性未小細胞肺がん(肺内転移)
60歳男性 EGFR阻害薬既治療不応症例
YM155 (4.8mg cohort) +エルロチニブ併用2サイクル後



「平成26年度バイオマーカー解析実施計画」

1Q(4~6月):組織採取解析可能症例検体において実施
- Survivin IHC
- Survivin RT-PCR
- LungCarta Panel
- Ion Ampliseq Panel(次世代シーケンサー)
- Luminex Panel(血漿タンパク質解析)

2Q-3Q(7~12月):追加解析可能症例検体の測定

3Q-4Q:(10~3月)
- mRNA, IHC, 血漿タンパク質解析結果との相関解析
- 体細胞遺伝子変異の頻度解析、pre-postにおける比較解析

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	出版年	巻号	ページ
Takeshi Okuda, Hidetoshi Hayashi, Mitsugu Fujita,Hiromasa Yoshioka,Takayuki Tasaki,Kazuhiko Nakagawa, Amami Kato	Administration of gefitinib via nasogastric tube effectively improved the performance status of a patient with lung adenocarcinoma-derived meningeal carcinomatosis.	Int Canc Conf J.	2014		in press
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Kiyota H, Okamoto I, Takeda M, Daga H, Naito T, Miyazaki M, Okada H, Hayashi H, Tanaka K, Terashima M, Azuma K, Murakami H, Takeda K, Yamamoto N, Nakagawa K.	Phase I and pharmacokinetic study of gefitinib and S-1 combination therapy for advanced adenocarcinoma of the lung.	Cancer Chemother Pharmacol.	2013	71(4)	859-865
Hayashi H, Okamoto I, Taguri M, Morita S, Nakagawa K.	Postprogression Survival in Patients With Advanced Non-Small-Cell Lung Cancer Who Receive Second-Line or Third-Line Chemotherapy.	Clin Lung Cancer.	2013	14(3)	261-266

Int Canc Conf J
DOI 10.1007/s13691-013-0148-0

CASE REPORT

Administration of gefitinib via nasogastric tube effectively improved the performance status of a patient with lung adenocarcinoma-derived meningeal carcinomatosis

Takeshi Okuda · Hidetoshi Hayashi · Mitsugu Fujita · Hiromasa Yoshioka · Takayuki Tasaki · Kazuhiko Nakagawa · Amami Kato

Received: 15 April 2013 / Accepted: 10 December 2013

Abstract Meningeal carcinomatosis (MC) is a refractory disease with a dismal prognosis, and no therapeutic strategy has been established to date. Herein we report a case of lung adenocarcinoma-derived MC in which the patient's performance status was dramatically improved by administration of gefitinib suspension via a nasogastric tube. The patient was a 71-year-old woman who was originally admitted to our hospital for a progressive headache and subsequently presented with severe consciousness disturbance. Cerebrospinal fluid examination and systemic imaging studies revealed MC that was derived from lung adenocarcinoma. Moreover, epidermal growth factor receptor (*EGFR*) mutations were detected in the tumor cells. Since the patient suffered from hydrocephalus, a ventriculoperitoneal shunt was placed. Nevertheless, her consciousness disturbance persisted. Subsequently, gefitinib suspension was prepared and administered via nasogastric tube, which dramatically improved her consciousness level and enabled her to tolerate oral intake. She died 14 months after the disease onset. The observations in this case report suggest that gefitinib might be a therapeutic option for patients with MC derived from cancers harboring *EGFR* mutations even though the patient exhibited severe consciousness disturbance.

Keywords Meningeal carcinomatosis · Lung adenocarcinoma · Gefitinib

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Introduction

Meningeal carcinomatosis (MC) is a refractory disease with a dismal prognosis that occurs in 5–10 % of cancer patients [1]. No therapeutic strategy has been established to date; the median survival time is 4–6 weeks if the disease is left untreated [1]. On the other hand, the recent development of novel chemotherapies has markedly improved the outcome of advanced cancer patients. The advent of molecular-targeted drugs is the most prominent among them, and gefitinib is a representative drug for lung cancer. Gefitinib has been shown to prolong the progression-free survival of patients with lung cancer harboring epidermal growth factor receptor (*EGFR*) mutations compared with standard chemotherapy [2, 3]. However, gefitinib is supplied in a tablet form and therefore needs to be administered orally. For this reason, patients with brain metastasis and/or MC sometimes have difficulty tolerating standard gefitinib treatment because they frequently exhibit consciousness disturbance and/or swallowing difficulty. Herein we report a case of lung adenocarcinoma-derived MC in which the patient's performance status (PS) was dramatically improved by administration of gefitinib suspension via a nasogastric (NG) tube even though the patient exhibited severe consciousness disturbance.

Published online: 24 December 2013

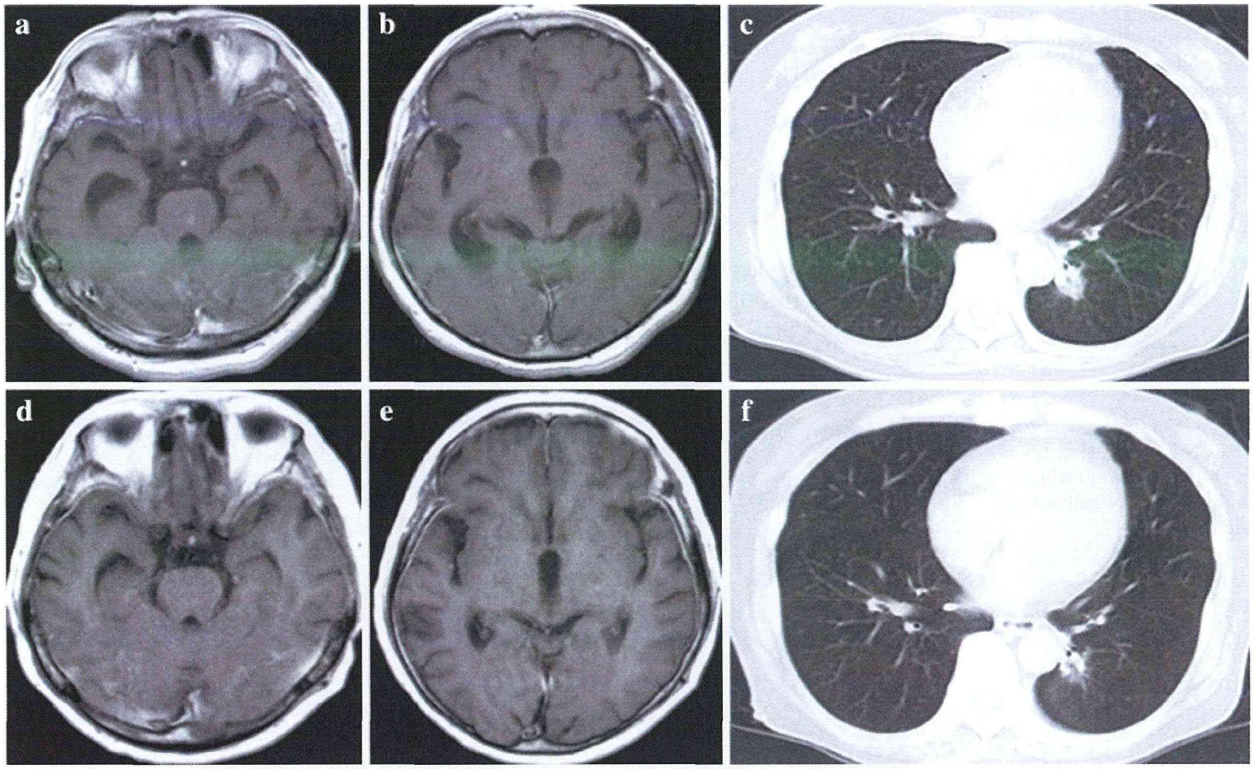

Fig. 1 Imaging studies pre- and post-gefitinib treatment. **a**, **b** T1-weighted gadolinium-enhanced MRI of the head reveals multiple small enhanced lesions. **c** Chest CT shows a mass-like lesion in the left lung S6 with diffuse granular shadows. **d**, **e** T1-weighted gadolinium-enhanced MRI reveals complete disappearance of the enhanced lesions. **f** Chest CT shows a decrease in size of the primary lesion

Case report

The patient was a 71-year-old woman who suffered from a progressive headache that had lasted several weeks. She suddenly presented with consciousness disturbance and was emergently admitted to our hospital. At the time of admission, her consciousness level was lethargic. Her past medical history was unremarkable. Magnetic resonance images (MRI) of the head revealed multiple small enhanced lesions and hydrocephalus (Fig. 1a, b). Cerebrospinal fluid (CSF) examination showed a cell count of 18/3 mm^3, protein 44 mg/dl, glucose 42 mg/dl, and carcinoembryonic antigen (CEA) 54.4 ng/ml (serum CEA 13.5 ng/ml). Adenocarcinoma cells were detected in the CSF. At the same time, computed tomography (CT) revealed a mass-like lesion in the left lung S6 segment along with diffuse granular shadows (Fig. 1c). These findings led us to diagnose MC that was derived from lung adenocarcinoma (cT1N0M1). *EGFR* mutations were also detected in exon 19 in the tumor cells, which was considered an appropriate target of gefitinib treatment.

Figure 2 shows the clinical course of the patient after the admission. The patient's consciousness level needed to recover for her to receive standard gefitinib treatment orally. Therefore we decided to place a ventriculoperitoneal (VP) shunt to treat the hydrocephalus. Nevertheless, the VP shunt failed to improve her consciousness level. Then, we sought to administer gefitinib suspension to the patient via an NG tube. Gefitinib tablets were finely crushed and suspended in 50 ml of sterile water (Fig. 3), and the patient received 250 mg/day gefitinib via an NG tube. On day 10 after the initiation of gefitinib treatment, her consciousness level improved dramatically, and she was able to tolerate oral intake on the following day. The imaging findings concurrently improved on the follow-up MRIs and CT (Fig. 1d–f). CSF cytology turned out to be negative on day 28. At the same time, CEA levels in the CSF also decreased to 11.3 ng/ml (serum CEA 11.8 ng/ml). The patient recovered with no neurological deficits and no adverse reactions. Gefitinib treatment was continued orally, and the patient was transferred for rehabilitation on day 82. She died 14 months after the disease onset without the cause of death identified.

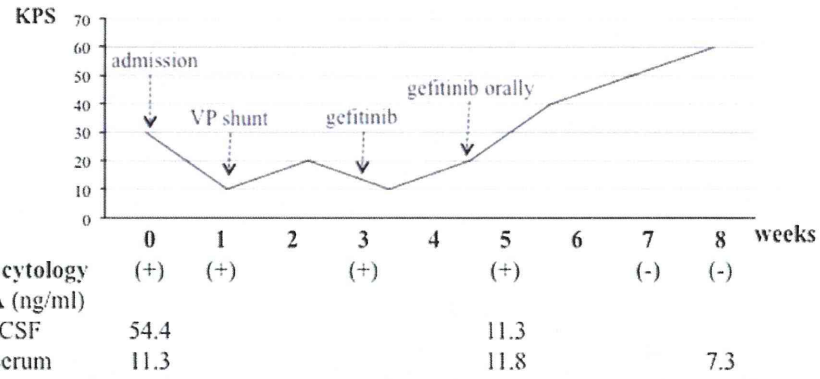

Fig. 2 Clinical course of the MC patient. *KPS* Karnofsky performance status, *CSF* cerebrospinal fluid, *CEA* carcinoembryonic antigen

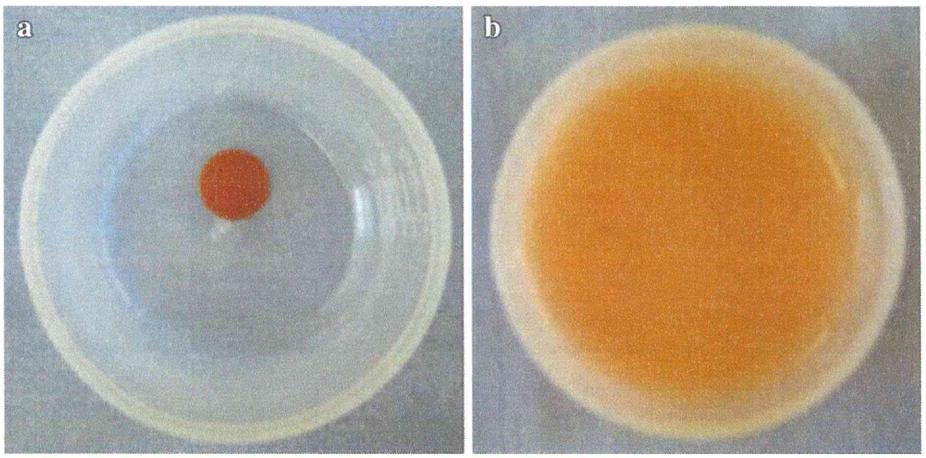

Fig. 3 Gefitinib processing for trans-NG tube administration. **a** Original gefitinib tablet. **b** Suspension of gefitinib in sterile water

Discussion

First-line gefitinib has been shown to improve the outcome of poor PS patients with *EGFR* mutation-positive lung cancers [4]. Therefore, examination of EGFR mutation as a biomarker is recommended in this patient population. However, since gefitinib is supplied in a tablet form and usually administered orally, standard gefitinib treatment is sometimes difficult for those with brain metastasis and/or MC because they frequently exhibit consciousness disturbance and/or swallowing difficulties. To treat these patients harboring *EGFR* mutations, gefitinib can be used in suspension by partially breaking the film coating and adding water [5]. Of note, the tablet film coating is not intended to enable sustained release or provide an enteric coating. Furthermore, administration of gefitinib suspension is comparable to administration of tablets in terms of bioavailability and safety [5]. On the basis of these findings, we postulated that the gefitinib suspension could provide the same therapeutic effect in this patient as the gefitinib tablets. Indeed, this therapeutic strategy successfully improved the patient's PS even though she had exhibited severe consciousness disturbance.

Although gefitinib is a small molecule inhibitor, intrathecal transfer rate is generally very low [6]. Particularly in MC patients, the concentration of gefitinib in the CSF has been reported as less than 1 % of the serum concentration [7, 8]. Nevertheless, the administration of gefitinib suspension improved the patient's PS in this case. We speculate several reasons for this. One is that even a low concentration of gefitinib would be effective against *EGFR* mutation-positive MC. Another reason is that the MC would destroy the blood–brain barrier (BBB) in situ and accelerate the drug transfer to each lesion. Indeed, whole-brain irradiation has been shown to enhance the intrathecal delivery of gefitinib by disruption of the BBB [9].

Erlotinib has been shown to induce higher bioactivities in plasma than gefitinib at similar or even lower doses of administration [10]. In addition, intrathecal gefitinib/erlotinib concentration can be elevated in a dose-escalating manner [7]. These findings suggest that erlotinib can be an alternative option for patients with MC or brain metastases if the primary cancer cells harbor *EGFR* gene mutations. We are currently in the process of determining the therapeutic efficacy of erlotinib for those with brain metastases harboring *EGFR* mutations.

A remaining issue is drug resistance exhibited by cancers. In the case of gefitinib/erlotinib, this typically occurs 8–12 months from the initiation of treatment. Over 50 % of resistance is caused by a mutation in the ATP binding pocket of the EGFR kinase domain involving substitution of a small polar threonine residue with a large nonpolar methionine residue (T790M) [11, 12]. In this regard, commencing treatment with a number of different therapeutic agents with differing modes of action is proposed to overcome the development of T790M and other resistance-conferring mutations [13].

In conclusion, we have reported the case of lung adenocarcinoma-derived MC in which the patient's PS was dramatically improved by the administration of gefitinib via an NG tube. The observations in this case report suggest that gefitinib/erlotinib might be therapeutic options for patients with MC derived from cancers harboring *EGFR* mutations even for the patients exhibiting severe consciousness disturbance.

Acknowledgments We thank Ms. Heather A. Garing at the Children's Hospital of the University of Pittsburgh Medical Center for her writing/proofing assistance.

Conflict of interest The authors declare that we have no conflict of interest.

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Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomised phase 3 study

Kaoru Kubota, Toyoaki Hida, Satoshi Ishikura, Junki Mizusawa, Makoto Nishio, Masaaki Kawahara, Akira Yokoyama, Fumio Imamura, Koji Takeda, Shunichi Negoro, Masao Harada, Hiroaki Okamoto, Nobuyuki Yamamoto, Tetsu Shinkai, Hiroshi Sakai, Kaoru Matsui, Kazuhiko Nakagawa, Taro Shibata, Nagahiro Saijo, Tomohide Tamura, on behalf of the Japan Clinical Oncology Group

Lancet Oncol 2014; 15: 106–13

Published Online December 3, 2013 http://dx.doi.org/10.1016/S1470-2045(13)70511-4

See **Comment** page 13

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Summary

Background Four cycles of etoposide plus cisplatin and accelerated hyperfractionated thoracic radiotherapy (AHTRT) is the standard of care for limited-stage small-cell lung cancer (SCLC). Irinotecan plus cisplatin significantly improved overall survival compared with etoposide plus cisplatin for extensive-stage SCLC. We compared these regimens for overall survival of patients with limited-stage SCLC.

Methods We did this phase 3 study in 36 institutions in Japan. Eligibility criteria included age 20–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate organ functions. Eligible patients with previously untreated limited-stage SCLC received one cycle of etoposide plus cisplatin (intravenous etoposide 100 mg/m² on days 1–3; intravenous cisplatin 80 mg/m² on day 1) plus AHTRT (1·5 Gy twice daily, 5 days a week, total 45 Gy over 3 weeks). Patients without progressive disease following induction therapy were randomised (1:1 ratio, using a minimisation method with biased-coin assignment balancing on ECOG performance status [0 *vs* 1], response to induction chemoradiotherapy [complete response plus near complete response *vs* partial response and stable disease], and institution) to receive either three further cycles of consolidation etoposide plus cisplatin or irinotecan plus cisplatin (intravenous irinotecan 60 mg/m² on days 1, 8, 15; intravenous cisplatin 60 mg/m² on day 1). Patients, physicians, and investigators were aware of allocation. The primary endpoint was overall survival after randomisation; primary analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00144989, and the UMIN Clinical Trials Registry, number C000000095.

Findings 281 patients were enrolled between Sept 1, 2002, and Oct 2, 2006. After induction etoposide plus cisplatin and AHTRT, 258 patients were randomised to consolidation etoposide plus cisplatin (n=129) or irinotecan plus cisplatin (n=129). In the etoposide plus cisplatin group, median overall survival was 3·2 years (95% CI 2·4–4·1). In the irinotecan and cisplatin group, median overall survival was 2·8 years (95% CI 2·4–3·6); overall survival did not differ between the two groups (hazard ratio 1·09 [95% CI 0·80–1·46], one-sided stratified log-rank p=0·70). The most common adverse events of grade 3 or 4 were neutropenia (120 [95%] in the etoposide plus cisplatin group *vs* 101 [78%] in the irinotecan plus cisplatin group), anaemia (44 [35%] *vs* 50 [39%]), thrombocytopenia (26 [21%] *vs* six [5%]), febrile neutropenia (21 [17%] *vs* 18 [14%]), and diarrhoea (two [2%] *vs* 13 [10%]). There was one treatment-related adverse event leading to death in each group (radiation pneumonitis in the etoposide plus cisplatin group; brain infarction in the irinotecan plus cisplatin group).

Interpretation Four cycles of etoposide plus cisplatin and AHTRT should continue to be the standard of care for limited-stage SCLC.

Funding National Cancer Center and the Ministry of Health, Labour, and Welfare of Japan.

Introduction

The shift from non-filter to filter tobacco has resulted in a decrease in small-cell and squamous-cell lung cancer, and an increase in adenocarcinoma of the lung.[1] Currently, small-cell lung cancer (SCLC) accounts for 13% of all lung cancer, and about a third of patients with SCLC have limited-stage disease—ie, disease confined to the hemithorax.[2]

Combination chemotherapy is the cornerstone of SCLC treatment, and meta-analyses[3,4] have shown that addition of thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC. Several randomised trials[5–7] have shown that early use of concurrent thoracic radiotherapy results in improved overall survival compared with sequential or late use when etoposide and cisplatin are used as combination

chemotherapy. The US intergroup phase 3 study[8] showed that accelerated hyperfractionated thoracic radiotherapy (AHTRT) with etoposide plus cisplatin for limited-stage SCLC resulted in significantly improved overall survival compared with standard fractionation, once-daily irradiation, with 5-year survival of 26% and 16%, respectively. Thus, etoposide plus cisplatin and AHTRT is now the standard of care in patients with limited-stage SCLC. However, many patients with limited-stage SCLC experience tumour recurrence and die from the disease, showing the need for improved therapy.

The Japan Clinical Oncology Group (JCOG) previously undertook a randomised phase 3 trial[9] (JCOG9511) comparing irinotecan plus cisplatin with etoposide plus cisplatin in patients with extensive-stage SCLC. Response and overall survival were significantly better for patients treated with irinotecan than those treated with etoposide. The result prompted us to explore the use of irinotecan and cisplatin in limited-stage SCLC. A phase 2 study[10] showed that irinotecan and cisplatin after concurrent etoposide plus cisplatin plus AHTRT for limited-stage SCLC was safe with acceptable side-effects, and the 3-year survival of 38% of patients was encouraging.

Therefore, we did a randomised phase 3 trial to compare overall survival of patients with limited-stage SCLC given three cycles of irinotecan plus cisplatin or etoposide plus cisplatin after one cycle of induction etoposide plus cisplatin and concurrent AHTRT.

Methods

Study design and participants

We did this randomised, open-label, phase 3 study in 36 institutions in Japan (appendix). We enrolled patients with histologically or cytologically confirmed limited-stage SCLC—defined as disease confined to one hemithorax, including ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular lymph node metastases. Pleural effusion of less than 1 cm width by chest CT was defined as limited-stage disease; malignant pleural effusion was defined as extensive-stage disease and excluded from the study. Additional eligibility criteria consisted of measurable disease, age 20–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no previous treatment for SCLC, no history of anticancer chemotherapy, 4000 leucocytes per μL or greater, 10^5 platelets per μL or greater, haemoglobin of 90 g/L or greater, serum creatinine of 132·60 μmol/L or less, serum bilirubin of 34·21 μmol/L or less, serum aspartate aminotransferase of 100 IU/L or less, serum alanine aminotransferase of 100 IU/L or less, and partial pressure of oxygen of 9·33 kPa or greater. Consultation with a radiation oncologist was mandated before enrolment. We included patients aged between 20 years and 70 years because the previous JCOG trial[9] (JCOG9511) comparing irinotecan and cisplatin with etoposide plus cisplatin for extensive-stage SCLC included only patients aged 70 years or younger.

Exclusion criteria were active concomitant malignancy, active infection, uncontrolled heart disease or a history of myocardial infarction within the previous 6 months, unstable angina, uncontrollable hypertension or diabetes mellitus, interstitial pneumonia or active lung fibrosis on chest radiograph, psychiatric disease, malignant pericardial effusion, diarrhoea, intestinal obstruction or paralysis, and concurrent administration of any oral or intravenous steroid. We excluded pregnant or lactating women.

All patients enrolled in the study underwent an induction therapy of one cycle of etoposide plus cisplatin with concurrent AHTRT, eligible patients were registered again and randomised to consolidation chemotherapy consisting of three cycles of etoposide plus cisplatin or irinotecan plus cisplatin. The second registration eligibility criteria were: within 49 days from the first registration, ECOG performance status of 0–1, 3000 leucocytes per μL or greater, 10^5 platelets per μL or greater, serum creatinine of 132·60 μmol/L or less, serum bilirubin of 34·21 μmol/L or less, serum aminotransferase of 100 IU/L or less, no fever or diarrhoea within 24 h, no pulmonary infiltration beyond the radiation portal, no active infection, radiation dermatitis or oesophagitis of grade 2 or less, completion of induction chemoradiotherapy, no progressive disease, and tumour response to induction chemoradiotherapy as assessed by chest CT (complete response, near complete response, partial response, or stable disease). Because almost all patients with limited-stage SCLC are admitted to hospital during induction chemoradiotherapy in Japan, chest CT assessment within the specified timeframe was not problematic. The assessment of response to chemoradiation was done after day 23, counted from the start of induction chemoradiotherapy.

The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review boards of the participating institutions. All patients provided written informed consent.

Procedures

Induction chemotherapy consisted of intravenous cisplatin 80 mg/m² on day 1 and intravenous etoposide 100 mg/m² on days 1–3. AHTRT was begun on day 2 of induction chemotherapy and administered twice daily, 5 days a week, (1·5 Gy per fraction, with 6 h or more between fractions) to a total dose of 45 Gy in 3 weeks. 30 Gy was delivered with 6–10 MV photons using anterior–posterior opposed fields that included the primary tumour; metastatic lymph nodes; and regional nodes, excluding the contralateral hilar nodes. Supraclavicular lymph nodes were also included when involved. A booster dose of 15 Gy was delivered to the primary tumour and metastatic lymph nodes. Conventional two-dimensional radiograph simulation and three-dimensional CT simulation were allowed for treatment planning; PET scanning was not required. The clinical target volume was equal to the gross tumour volume, including the primary tumour and metastatic nodes (1 cm or greater in shortest dimension).

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See Online for appendix

The planned target volumes for the primary tumour, metastatic lymph nodes, and regional nodes were defined as clinical target volume plus adequate margins (typically 0·5–1·0 cm laterally and 1·0–2·0 cm craniocaudally). The volume of the lung unaffected by cancer to receive 20 Gy or more was kept to 35% or less when three-dimensional CT simulation was used. Lung heterogeneity corrections were not used. If grade 3 non-haematological side-effects (excluding hyponatraemia, nausea, vomiting, and appetite loss), performance status of 3, grade 2 pneumonitis or pulmonary infiltrates, or a fever of 38·0°C or more developed, radiotherapy was withheld until recovery. Quality assurance reviews were done and the results are reported elsewhere.[11]

In the consolidation chemotherapy stage, patients assigned to etoposide plus cisplatin received intravenous cisplatin 80 mg/m² on day 1 and intravenous etoposide 100 mg/m² on days 1–3, repeated every 3 weeks for three cycles. Patients assigned to irinotecan plus cisplatin were treated every 3–4 weeks for three cycles; this regimen consisted of intravenous irinotecan 60 mg/m² on days 1, 8, and 15 and intravenous cisplatin 60 mg/m² on day 1. The doses of cisplatin were the same as in the previous JCOG trial (JCOG9511) in extensive-stage SCLC.[9]

If the leucocyte count decreased to less than 3000 leucocytes per μL or the platelet count fell below 10^5 platelets per μL on the first day of etoposide plus cisplatin or irinotecan plus cisplatin, chemotherapy was withheld until the counts recovered to above these cutoffs. Administration of irinotecan was skipped on day 8 or 15, or on both days, if the leucocyte count was less than 2000 leucocytes per μL, the platelet count was below 10^5 platelets per μL, or if there was any diarrhoea irrespective of grade, or a fever of 37·5°C or more. The dose of etoposide in subsequent cycles was reduced by 20 mg/m² from the planned dose if grade 4 leucopenia, grade 4 thrombocytopenia, or grade 3 non-haematological side-effects (excluding nausea, vomiting, appetite loss, hyponatraemia, and creatinine) developed. The dose of irinotecan in subsequent cycles was reduced by 10 mg/m² from the planned dose if grade 4 leucopenia or grade 4 thrombocytopenia, grade 2 or 3 diarrhoea, or grade 3 non-haematological side-effects (excluding nausea, vomiting, hyponatraemia, and creatinine) developed. The dose of cisplatin was reduced by 10 mg/m² if serum creatinine was higher than 132·60 μmol/L but not exceeding 176·80 μmol/L. Cisplatin was not administered if creatinine was higher than 176·80 μmol/L. Treatment was stopped in patients with non-haematological side-effects of grade 4.

Administration of granulocyte colony stimulating factor (G-CSF) was prohibited on the same days as chemotherapy or radiotherapy. Primary prophylactic G-CSF was not administered. For patients who had developed grade 4 neutropenia or grade 3 febrile neutropenia during previous cycles of chemotherapy, secondary prophylactic G-CSF administration was allowed. Prophylactic antibiotics were not administered.

Prophylactic cranial irradiation (25 Gy in ten fractions) was undertaken for patients showing a complete response or near complete response, defined as a reduction of 70% or more in the sum of the longest diameters of the target lesions.

Before enrolment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, arterial blood gas, biochemical laboratory examinations, chest radiograph, electrocardiogram, chest CT scan and whole-brain CT or MRI, abdominal ultrasound or CT, and isotope bone scans. Data regarding the time interval between diagnosis and start of concurrent chemoradiotherapy were not collected. Blood cell counts, differential white cell counts and other laboratory data were obtained weekly during induction chemoradiotherapy. All patients were reassessed at the end of consolidation chemotherapy with the same imaging assessments as at the time of enrolment. For efficacy assessments after the end of study treatment, patients were monitored once a month for 1 year and once every 3 months after 1 year. If progression was suspected on the basis of worsening symptoms or abnormal laboratory test values, the site of suspected progression was examined. If recurrence or progression was established, restaging including chest CT, brain MRI or CT, abdominal ultrasound or CT, and bone scintigraphy were done.

Responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Response was defined as the proportion of patients whose best overall response was complete reponse or partial response according to RECIST. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 2.0. Serious adverse events were defined as grade 4 non-haematological or grade 5 adverse events.

Randomisation and masking

After induction chemoradiotherapy, eligible patients were randomly assigned in a 1:1 ratio to receive either three cycles of consolidation etoposide plus cisplatin or irinotecan plus cisplatin at the JCOG Data Center. Randomisation was done using a minimisation method with biased-coin assignment balancing on ECOG performance status (0 *vs* 1), response to induction chemoradiotherapy (complete response plus near complete response *vs* partial response and stable disease) and institution. Patients, treating physicians, and individuals assessing outcomes and analysing data were not masked to treatment allocation.

Statistical analysis

The primary endpoint was overall survival after randomisation. The planned sample size for randomisation was 250 and the expected number of events was 223, with a one-sided α of 2·5% and at least 70% power to detect a difference between groups, assuming 30·0% 3-year survival with etoposide plus cisplatin versus 42·5% with

iriontecan plus cisplatin. Final analysis was planned 5 years after completion of accrual. Secondary endpoints were adverse events associated with induction chemoradiotherapy, adverse events associated with consolidation chemotherapy, late radiation morbidity after thoracic irradiation, adverse events during treatment with prophylactic cranial irradiation, incidence of serious adverse events, and progression-free survival after randomisation.

Progression-free survival was calculated from the date of randomisation until the date of documented progression or death (in the absence of progression). Overall survival was calculated from the date of randomisation until the date of death from any cause. Both intervals were estimated by the Kaplan-Meier method.

Three interim analyses were scheduled. The first interim analysis was to assess the futility of the trial after half the planned sample size was randomised. The second interim analysis was planned immediately after patient accrual was completed to decide whether the preplanned follow-up was necessary in terms of efficacy. The third interim analysis was planned 2 years after completion of accrual, with the same aim as the second interim analysis. Results of the interim analyses were reviewed by the JCOG Data and Safety Monitoring Committee and investigators were masked to the results. Multiplicity for analyses of the primary endpoint was adjusted with the O'Brien-Fleming type α-spending function.[12]

The primary endpoint, overall survival after randomisation, was analysed with the log-rank test, stratified by ECOG performance status (0 *vs* 1) and response to induction chemoradiotherapy (complete response plus near complete response *vs* partial response plus stable disease). Hazard ratios (HR) were estimated with a Cox regression model, stratified by the same factors as the log-rank test. Unstratified log-rank tests and unstratified Cox regression models were used for all other analyses. The efficacy analyses were by modified intention to treat, including all patients enrolled at the second registration who did not violate any inclusion criteria. Safety analyses included all patients enrolled at the second registration who received at least one dose of study drug. Analyses were done by the JCOG Data Center using SAS (version 9.2).

This trial was registered with ClinicalTrials.gov, number NCT00144989 and UMIN Clinical Trials Registry, number C000000095.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

281 patients were enrolled between Sept 1, 2002, and Oct 2, 2006. Four patients were shown to be ineligible after the first registration, three did not receive study treatment because of progressive disease, and two did not receive AHTRT, one because of an inappropriate radiation field and one because of an allergy to etoposide (figure 1). After the induction etoposide plus cisplatin plus AHTRT, 258 patients were enrolled at the second registration and

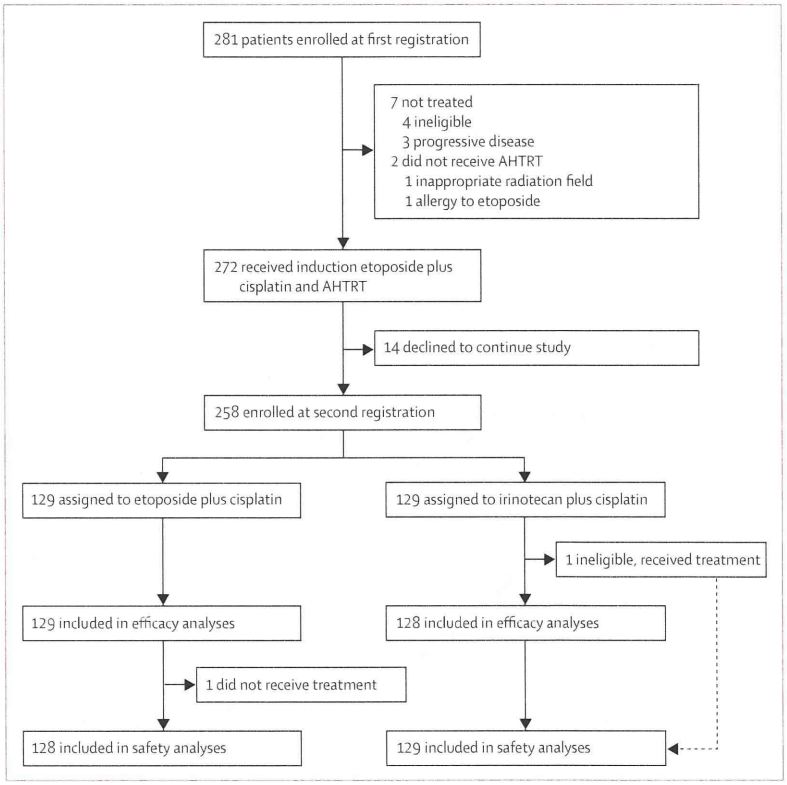

Figure 1: **Trial profile**
AHTRT=accelerated hyperfractionated thoracic radiotherapy.

	First registration (n=281)	Second registration	
		Etoposide and cisplatin (n=129)	Irinotecan and cisplatin (n=129)
Age (years)	61 (32–70)	60 (32–70)	62 (39–70)
Sex			
Men	228 (81%)	103 (80%)	106 (82%)
Women	53 (19%)	26 (20%)	23 (18%)
ECOG performance status			
0	170 (60%)	86 (67%)	85 (66%)
1	111 (40%)	43 (33%)	44 (34%)
Response to induction chemoradiotherapy*			
Complete response	..	3 (2%)	4 (3%)
Near complete response	..	28 (22%)	26 (20%)
Partial response	..	92 (71%)	87 (67%)
Stable disease	..	6 (5%)	12 (9%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *According to Response Evaluation Criteria In Solid Tumors (version 1.0).

Table 1: **Characteristics of patients**

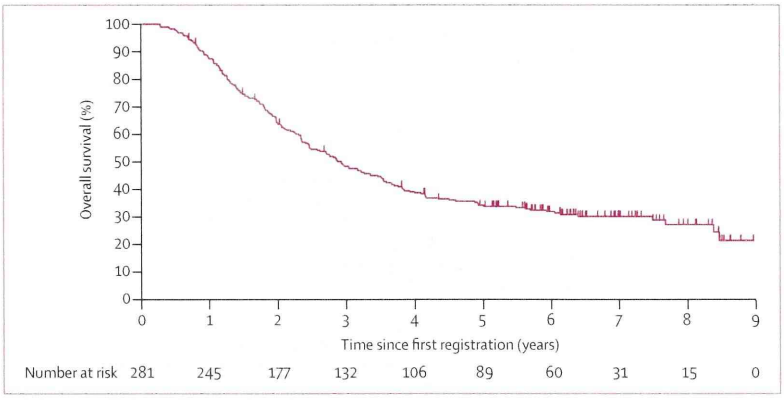

Figure 2: **Overall survival after first registration**
*One-sided p value from stratified log-rank test, with Eastern Cooperative Oncology Group performance status and response to induction chemoradiotherapy as strata.

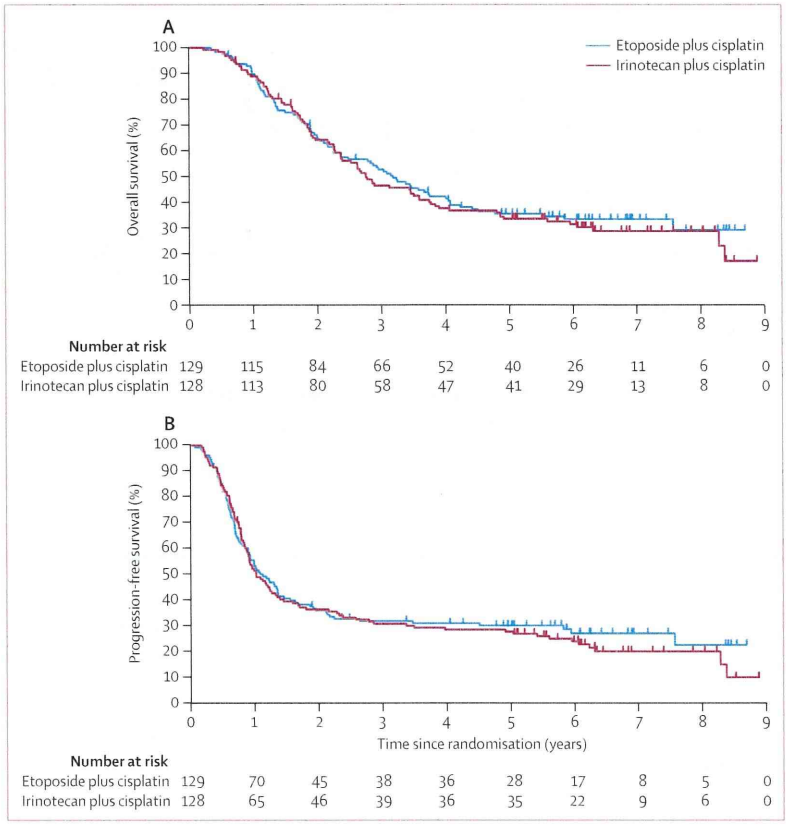

Figure 3: **Overall survival (A) and progression-free survival (B) after randomisation**
*p value from unstratified log-rank test.

randomised to consolidation etoposide plus cisplatin (n=129) or irinotecan plus cisplatin (n=129). One patient in the irinotecan plus cisplatin group was shown to be ineligible after the second registration because of contralateral hilar node metastasis, this patient was excluded from the efficacy analyses, but included in the safety analyses. Table 1 shows the characteristics of the patients.

Of 129 patients who were randomised to the etoposide plus cisplatin group, 116 patients (90%) received three cycles of consolidation chemotherapy, four (3%) received two cycles, eight (6%) received one cycle, and one (1%) had no consolidation therapy. In the irinotecan plus cisplatin group, 110 of 128 (86%) patients received three cycles of consolidation chemotherapy, six (5%) received two cycles, 12 (9%) received one cycle. The main reasons for non-completion of three cycles of consolidation chemotherapy in the both groups were adverse events (eight patients in the etoposide plus cisplatin group, 12 patients in the irinotecan plus cisplatin group) and patient refusal because of adverse events (nine patients in the etoposide plus cisplatin group, 14 patients in the irinotecan plus cisplatin group); one patient in each group did not complete consolidation chemotherapy because of progressive disease. In the etoposide plus cisplatin group, 115 (89%) of 129 patients received at least 70% of the planned of dose of etoposide, and 116 (90%) of 129 received at least 70% of the planned dose of cisplatin; in the irinotecan plus cisplatin group, 88 (69%) of 128 received at least 70% of the planned dose of irinotecan and 110 (86%) of 128 received at least 70% of the planned dose of cisplatin. Prophylactic cranial irradiation was administered to 76 patients in the etoposide plus cisplatin group and 73 in the irinotecan plus cisplatin group.

Of 281 patients who entered into the first registration, median follow-up for the 88 censored patients was 6·3 years (IQR 5·6–7·2); median overall survival was 2·9 years (95% CI 2·5–3·5), 3-year overall survival was 48·4% (95% CI 42·4–54·1), and 5-year overall survival was 34·3% (28·7–39·9; figure 2). Of 257 patients included in the final analysis of the primary outcome, median follow-up for the 84 censored patients was 6·2 years (IQR 5·4–7·0); there were 173 events. In the etoposide plus cisplatin group, median overall survival was 3·2 years (95% CI 2·4–4·1), 3-year overall survival was 52·9% (95% CI 43·9–61·1), and 5-year overall survival was 35·8% (27·4–44·1). In the irinotecan plus cisplatin group, median overall survival was 2·8 years (95% CI 2·4–3·6), 3-year overall survival was 46·6% (37·7–55·1) and 5-year overall survival was 33·7% (25·5–42·0; HR 1·09 [95% CI 0·80–1·46]; p=0·70 from one sided stratified log-rank test; figure 3A). The results of the unstratified analysis did not differ from those of the stratified analysis (data not shown).

Figure 3B shows the Kaplan-Meier curves for progression-free survival in the two groups. Median progression-free survival was 1·1 years (95% CI 0·9–1·4) in the etoposide plus cisplatin group and 1·0 years (0·9–1·4) in the irinotecan plus cisplatin group (HR 1·10; 95% CI 0·83–1·45; p=0·74 from one sided unstratified log-rank test). In the etoposide group, 3-year progression-free survival was 32·0% (95% CI 24·1–40·1) and 5-year progression-free survival was 30·2% (22·4–38·3). In the irinotecan plus cisplatin group, these were 30·8% (23·0–38·9) and 27·7% (20·2–35·6), respectively.

	Etoposide plus cisplatin plus AHTRT*				Consolidation chemotherapy							
	Grade 1–2	Grade 3	Grade 4	N	Etoposide plus cisplatin				Irinotecan plus cisplatin			
					Grade 1–2	Grade 3	Grade 4	N	Grade 1–2	Grade 3	Grade 4	N
Leucopenia	16 (6%)	148 (54%)	109 (40%)	273	12 (9%)	81 (63%)	34 (27%)	128	28 (22%)	76 (59%)	25 (19%)	129
Anaemia	86 (32%)	1 (<1%)	0	273	76 (59%)	33 (26%)	11 (9%)	128	72 (56%)	42 (33%)	8 (6%)	129
Thrombocytopenia	108 (40%)	20 (7%)	0	273	56 (44%)	22 (17%)	4 (3%)	128	28 (22%)	6 (5%)	0	129
Neutropenia	12 (4%)	57 (21%)	203 (74%)	273	6 (5%)	33 (26%)	87 (68%)	128	28 (22%)	62 (48%)	39 (30%)	129
Hypoalbuminaemia	194 (72%)	0	..	271	102 (80%)	0	..	127	109 (84%)	0	..	129
Bilirubin	72 (26%)	1 (<1%)	0	272	20 (16%)	0	0	128	21 (16%)	0	0	129
Aspartate aminotransferase	54 (20%)	1 (<1%)	0	273	19 (15%)	1 (1%)	0	128	29 (22%)	0	0	129
Alanine aminotransferase	91 (33%)	4 (1%)	0	273	38 (30%)	1 (1%)	0	128	47 (36%)	0	0	129
Creatinine	67 (25%)	0	0	273	55 (43%)	0	0	128	35 (27%)	0	0	129
Fever	75 (27%)	0	0	274	28 (22%)	1 (1%)	0	128	33 (26%)	0	0	129
Alopecia	207 (77%)	..	..	270	94 (76%)	..	..	123	93 (74%)	..	..	126
Weight loss	43 (16%)	0	..	274	17 (13%)	0	..	128	20 (16%)	1 (1%)	..	129
Anorexia	158 (58%)	22 (8%)	1 (<1%)	274	82 (64%)	12 (9%)	0	128	78 (60%)	16 (12%)	0	129
Diarrhoea	28 (10%)	3 (1%)	0	274	10 (8%)	2 (2%)	0	128	68 (53%)	13 (10%)	0	129
Dysphagia–oesophageal†	229 (84%)	5 (2%)	0	274	34 (27%)	0	0	128	34 (26%)	1 (1%)	0	129
Nausea	139 (51%)	17 (6%)	..	274	82 (64%)	7 (5%)	..	128	82 (64%)	7 (5%)	..	129
Stomatitis or pharyngitis	38 (14%)	1 (<1%)	0	274	16 (13%)	0	0	128	15 (12%)	0	0	129
Vomiting	53 (19%)	3 (1%)	0	274	26 (20%)	3 (2%)	0	128	21 (16%)	5 (4%)	0	129
Febrile neutropenia	..	67 (25%)	0	271	..	21 (16%)	0	128	..	18 (14%)	0	129
Infection with grade 3 or 4 neutropenia	0	37 (14%)	0	272	0	15 (12%)	0	128	0	8 (6%)	0	129
Infection without neutropenia	7 (3%)	11 (4%)	1 (<1%)	274	11 (9%)	4 (3%)	0	128	16 (12%)	8 (6%)	0	129
Pneumonitis or pulmonary infiltrates	2 (1%)	1 (<1%)	0	274	9 (7%)	1 (1%)	0	128	16 (12%)	0	0	129

Data were missing for some patients. AHTRT=accelerated hyperfractionated thoracic radiotherapy. *Including two patients who did not undergo radiotherapy. †Related to radiation.

Table 2: Adverse events

The two groups did not differ in terms of sites of primary failure. Of 175 patients who had disease progression, in the etoposide plus cisplatin group, 30 had local progression within the radiation field, seven had local progression outside of the radiation field, 26 had progression to the brain, and 35 had systemic progression to other sites; in the irinotecan plus cisplatin group, 27 had local progression within the radiation field, six had local progression outside of the radiation field, 33 had progression to the brain, and 38 had systemic progression to other sites (some patients had progression to more than one site).

In a planned subgroup analysis, women in the etoposide plus cisplatin group had improved overall survival compared with those in the irinotecan plus cisplatin group (median overall survival not reached, 5-year overall survival 55·3% [95% CI 33·8–72·3] *vs* median overall survival 2·4 years [1·6–3·4], 5-year overall survival 26·1% [10·6–44·7] in the irinotecan group; unstratified HR 2·56; 95% CI 1·20–5·44, one-sided p=0·99) whereas outcomes for men did not differ between the groups (0·90; 0·65–1·24, one-sided p=0·25). Other prespecified subgroup analyses, including age (≤60 years old *vs* >60 years old), stage by UICC-TNM 7th edition (≤IIIA *vs* ≥IIIB), ECOG performance status (0 *vs* 1), response to induction chemoradiotherapy (complete response plus near complete response *vs* partial repsonse plus stable disease), bodyweight loss during 6 months (≤5% *vs* >5%), and smoking history (<20 packs per year *vs* ≥20 packs per year) did not differ between the two groups (data not shown).

Of 129 eligible patients randomised to the etoposide plus cisplatin group, 128 (99·2%) had an overall response (24 complete response; 54 near complete response; 50 partial response); of 128 patients in the irinotecan plus cisplatin group, 123 (96·1%) had an overall response (30 complete response; 57 near complete response; 36 partial response).

Table 2 shows side-effects associated with concurrent chemoradiotherapy and consolidation chemotherapy. During consolidation chemotherapy, the most common adverse events of grade 1 or 2 were hypoalbuminaemia (102 [80%] in the etoposide plus cisplatin group *vs* 109 [84%] in the irinotecan plus cisplatin group) and alopecia (94 [76%] *vs* 93 [74%]). The most common adverse events of grade 3 or 4 were neutropenia (120 [95%] in the etoposide plus cisplatin group *vs* 101 [78%] in the irinotecan plus cisplatin group), anaemia (44 [35%] *vs* 50 [39%]), thrombocytopenia (26 [21%] *vs* six [5%]), febrile neutropenia (21 [17%] *vs* 18 [14%]), and diarrhoea (two [2%] *vs* 13 [10%]). 12% of patients in the in the etoposide plus cisplantin group and 6% in the irinotecan plus cisplatin group had infection with grade 3 or 4 neutropenia. However, grade 3 febrile neutropenia did not differ between the two groups. Grade 3 or 4 leucopenia was less frequent in the