厚生労働科学研究費補助金

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その他、がんに対する標準的治療法の確立に関する研究

平成14年度～16年度　総合研究報告書

主任研究者　福　岡　正　博

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平成１４年度から実施した厚生労働科学研究費補助金（ がん臨床 研究事業）に係る研究事業を完了したので、次のとおり報告する。

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１．厚生労働科学研究費補助金総合研究報告書表紙　（別添１のとおり）

２．厚生労働科学研究費補助金総合研究報告書目次　（別添２のとおり）

３．厚生労働科学研究費補助金総合研究報告書　（別添３のとおり）

４．研究成果の刊行に関する一覧表　（別添４のとおり）

５．研究成果による特許権等の知的財産権の出願・登録状況
（総合研究報告書の中に書式に従って記入すること。）

別紙１

厚生労働科学研究費補助金

がん臨床研究事業

その他、がんに対する標準的治療法の確立に関する研究

平成１４年度～１７年度　総合研究報告書

主任研究者　福岡　正博

平成１７（２００５）年　３月

別紙２

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別紙3

厚生労働科学研究費補助金（がん臨床研究事業）
総合究報告書

その他、がんに対する標準的治療法の確立に関する研究

主任研究者　福岡　正博　近畿大学医学部・教授

研究要旨： 切除不能限局型進行Ⅲ期非小細胞肺癌の治療成績向上を目的とし、新しく開発された分子標的薬の上皮成長因子受容体（EGFR）チロシンキナーゼ阻害剤であるゲフィチニブ（イレッサ）を組み込んだ新しい治療法を考案し、第Ⅲ相試験を計画したが、ゲフィチニブによる間質性肺障害（ILD）などの問題が発生したため、当初の計画を変更せざるを得なくなった。そこで、まずゲフィチニブと胸部放射線照射（TRT）の併用の安全性を確認する２つの試験から開始こととした。いずれも切除不能Ⅲ期非小細胞肺癌を対象とし、試験１はTRTとゲフィチニブの同時併用療法、試験２はシスプラチンとビノレルビンの併用化学療法後にゲフィチニブとTRTの併用を実施する方法である。試験1は平成15年8月から開始し現在まで9例実施しILDが2例に見られたが、現在も症例を追加中であり実施可能と考えている。試験2はJCOGの審査委員会の承認が得られ、平成16年8月から開始し、現在まで国立がんセンター中央、東病院において4例が治療終了ないし治療中である。この4例の安全性が確認されれば施設を拡大して38症例において安全性と効果を検討することになっている。これらの試験が平成17年度中に終了すれば、シスプラチンとビノレルビン併用化学療法後にゲフィチニブとTRTを併用する治療法（ゲフィチニブ群）とシスプラチンとビノレルビン併用化学療法とTRT同時併用療法（標準治療群）の無作為化第Ⅲ相試験を実施する予定である。

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Ａ．研究目的

肺癌の死亡数は悪性腫瘍死の第1位であり、毎年55,000人以上が肺癌で死亡している。肺癌の80%は非小細胞肺癌（NSCLC）で、その治療成績は極めて不良である。近年、分子標的薬として開発された上皮成長因子受容体（EGFR）チロシンキナーゼ阻害剤のゲフィチニブがNSCLCの2^{nd}-line治療として有効であることが認められ承認された。切除不能Ⅲ期NSCLCの標準的治療は現在化学療法と胸部放射線療法（TRT）の併用である。前臨床試験においてEGFR阻害剤と放射線照射に強い相乗効果が見られることから、EGFRターゲットの薬剤であるゲフィチニブとTRTの併用治療には大きな期待がかけられている。そこで本研究では切除不能限局型Ⅲ期NSCLCの治療成績向上を目的とし、化学療法、TRTにゲフィチニブを組み込んだ新しい治療法を考案し、その安全性と効果を検討することとした。

Ｂ．研究方法

本研究はゲフィチニブの承認と同時に計画・申請した。申請時の計画では切除不能Ⅲ期NSCLCを対象に化学放射線治療（シスプラチンとビノレルビンとTRT同時併用療法）にゲフィチニブを上乗せする治療法を考案した。しかし、承認後まもなくわが国においてゲフィチニブ投与患者に急性間質性肺障害（ILD）を発症することが明らかになり、また、海外で行われたゲフィチニブとプラチナ製剤を含む抗がん化学療法の同時併用では効果の見られないことが明らかにされた。このことより、当初の治療計画を変更せざるを得なくなった。そこで、第Ⅲ相試験の前に以下の２つの予備試験から実施することにした。

試験１：切除不能ⅢA/ⅢB期のNSCLCで全身状態良好（PS 0,1）、75歳以下を対象としゲフィチニブ250 mg/dayを2週間内服投与した後にHRCTを撮影してILDが発現していないことを確認する。その後にTRT 2 Gy/fr、1日1回を週5日で6週間（総量 60 Gy）併用し、ゲフィチニブは毒性で継続が困難になるか腫瘍が増悪するまで継続することとした。この試験のプライマリーエンドポイントは完遂率とし、60 GyのTRTが終了し、TRT治療日の21日以上ゲフィチニブが併用可能であった症例を完遂例とし、閾値完遂率を75%、期待完遂率90%としてα=0.1、β=0.2とした場合、適格例28例が必要症例数となる。この場合28例中24例が完遂できれば閾値完遂率75%が棄却されるとした。セカンダリーエンドポイントには、奏効率、生存率、無増悪期間、毒性などを含めた。

試験２：切除不能ⅢA/ⅢB期のNSCLC（扁平上皮癌を除く）でPS 0,1、20歳以上70歳以下を対象とし、シスプラチン80mg/m^2 Day 1、ビノレルビン25mg/m^2 Day 1、8を3週間隔で2サイクル投与した後（2サイクル開始後 22日目より）ゲフィチニブ250 mg/dayを2週間内服投与した後ILDの発現のないことを確認してからTRT 2 Gy/frを週5日で6週間（総量 60 Gy）併用する。この試験のプライマリーエンドポイントは、グレード２以上の肺臓炎を認めず治療を完遂で

きた割合とし、その閾値を55%、期待値を90%でα=0.1、β=0.2とした場合、必要症例数を37例で、登録期間、追跡期間をそれぞれ1年6ヶ月とした。
これら2つの予備試験が終了し安全性が確認された場合、シスプラチンとビノレルビン併用化学療法後にゲフィチニブとTRTを併用する試験治療法（ゲフィチニブ群）とシスプラチンとビノレルビン併用化学療法にTRT 60Gyの同時併用療法（標準治療群）の無作為化第Ⅲ相試験を実施する予定にしている。

（倫理面への配慮）
本研究では、まずゲフィチニブと放射線治療との併用試験（試験１）と併用化学療法後にゲフィチニブと放射線治療との併用を行う試験（試験２）でその安全性を十分検討した後にランダム化第Ⅲ相試験（試験３）を開始するよう配慮した。また、適切な症例選択規準、除外規準、治療中止規準を設け、個々の症例の安全性を確保するなど試験参加による不利益を最小限にする。ゲフィチニブによる早期の肺障害例を除外する目的でTRTとの併用開始前2週間のゲフィチニブ単独投与時期を設定し、さらにTRT開始前にHRCTで肺障害例を除くよう配慮した。さらに、ヘルシンキ宣言等の国際的倫理原則に従い、以下の事項を遵守することにしている。(1)研究実施計画書（プロトコール）のＩＲＢ承認の得られた施設のみ症例登録を可能とする。(2)すべ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思による同意を本人より文書で取得する。(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)JCOGとの共同研究とし、臨床試験審査委員会、効果・安全性評価委員会、監査委員会を組織して研究の第３者的監視を行う。さらに、ゲフィチニブによる生存期間の延長は確認されていないなどの新しい情報を逐次患者に説明するよう配慮した。

C．研究結果
平成14年本研究班発足時には、切除不能Ⅲ期NSCLCを対象に化学放射線治療（シスプラチンとビノレルビンとTRT同時併用療法）にゲフィチニブを上乗せする治療法を考案した。しかし、方法のところで述べたごとく、ゲフィチニブによるILD,化学療法との併用効果の認められないことなどの理由で試験デザインの変更を余儀なくされた。試験1のプロトコールは平成15年４月に第４版が完成し、６月から施設IRBの承認を得、同年8月より症例の登録が開始された。これまで9例（腺癌７例、その他３例、男性８例）が登録され、このうち2例が不適格例、２例にILDが見られたが、6例が完遂され5例に奏効が得られている。試験２は、平成14年6月にJCOGの臨床試験審査委員会でプロトコールコンセプトの承認を得、平成16年７月に実施計画書の承認を得、平成16年8月より症例の登録が開始された。最初の４例は国立がんセンター中央、および東病院から登録され、2例は現在も治療中であるが重篤な副作用は見られていない。4例の安全性の評価が終了するのは平成17年5月であり、その後に分担研究者の施設（13施設）に拡大して再開することとしている。

D．考察
本研究においては、ゲフィチニブと放射線治療の併用により肺障害が高頻度に出現する可能性が危惧されたために極めて慎重な研究計画となった。種々の検討の結果、ゲフィチニブは腺癌、非喫煙者、女性において有効性が高いこと、扁平上皮癌でILDが多いことが示され、試験２では扁平上皮癌を除くNSCLCに限定することとした。また、2nd-lineのNSCLCにおける、プラセボを対照とした無作為化比較試験（ISEL）でゲフィチニブによる延命効果が見られなかったこと、腫瘍組織のEGFR変異が有効性の予測に有用であることなどが示され、本研究の継続などに問題が投げかけられた。しかし、東洋人の腺癌にEGFRの変異例が多いこと、ISEL試験のサブセット解析において東洋人で有意な延命効果が見られたことから本試験を継続することが承認された。現時点では、試験1、試験2とも登録症例が少なく未だ安全性を確認できるに至っていないが、症例を追加し、平成17年度には第Ⅲ相試験への見通しをつけるよていである。

E．結論
ゲフィチニブとTRTの併用（試験1）は、現時点で重篤な肺障害は見られておらず、完遂の可能性が高いと思われる。シスプラチンとビノレルビンの併用化学療法後にゲフィチニブとTRTを併用する方法（試験２）も未だ4例の登録ではあるが、実施可能であるように思われる。前臨床試験においてEGFR阻害剤と放射線治療の強い相乗効果が認められており、この治療法は切除不能Ⅲ期NSCLCの新しい治療法として有効性が確認されるよう今後の展開に期待したい。種々の問題のため本研究の開始が大幅に遅れたが、これからは新しい有効な治療法の確立に向けて全力を傾注したい。

F．健康危険情報
本研究においては、急性肺障害・間質性肺炎（ILD）発症に特に注意を払うこと、ゲフィチニブ単独でもILDの危険性が約5%、死亡の危険性が約1%ありこれらの症例は、喫煙者、扁平上皮癌、男性、肺線維症など既存の肺病変を有する患者に多いことを患者に説明する。最初の4週間は入院またはそれに準じた管理が必要であること、一旦発症した場合には直ちにステロイドホルモンのパルス療法を行うこと、ゲフィチニブには、そのほか下痢、肝障害、皮膚障害のあることを患者に説明するとともに、担当医は適切な管理を行うよう徹底している。シスプラチン、ビノレルビンの化学療法では強い血液毒性、腎毒性、末梢神経障害、さらに放射線性食道炎などの出現に適切に対処するよう配慮している。

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H. 知的財産権の出願・登録状況（予定を含む。）

1. 特許取得
   特になし
2. 実用新案登録
   なし
3. その他
   特になし

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

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Dose-escalation study of weekly irinotecan and daily carboplatin with concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

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Dose-escalation study was performed to evaluate the maximum tolerated dose, recommended dose and toxicity profile of weekly irinotecan with daily carboplatin and concurrent thoracic radiotherapy in patients with locally advanced non-small-cell lung cancer. Thirty-one previously untreated patients with unresectable stage III non-small-cell lung cancer were enrolled in this study. Patients received weekly irinotecan plus carboplatin (20 mg m^{-2} daily for 5 days a week) for 4 weeks and thoracic radiotherapy (60 Gy in 30 fractions). The irinotecan dose was escalated from 30 mg m^{-2} in increments of 10 mg m^{-2}. Four irinotecan dose levels were given and 30 patients were assessable. Their median age was 62 years (range: 52–72 years), 28 had a performance status of 0–1 and two had a performance status of 2, 12 had stage IIIA disease and 18 had IIIB disease. There were 19 squamous cell carcinomas, 10 adenocarcinomas, and one large cell carcinoma. The dose-limiting toxicities were pneumonitis, esophagitis, thrombocytopenia and neutropenia. The maximum tolerated dose of irinotecan was 60 mg m^{-2}, with two patients developing grade 4 pulmonary toxicity and one patient died of pneumonitis (grade 5). The recommended dose of irinotecan was 50 mg m^{-2}. Other grade 3 or 4 toxicities were nausea and vomiting. Three patients achieved complete remission and 15 had partial remission, for an objective response rate of 60.0%. The median survival time was 14.9 months, and the 1- and 2-year survival rates were 51.6% and 34.2%, respectively. The study concluded that the major toxicity of this regimen was pneumonitis. This therapy may be active against unresectable non-small-cell lung cancer and a phase II study is warranted.
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Keywords: non-small cell lung cancer; irinotecan; carboplatin; chemoradiotherapy

In patients with unresectable stage III non-small-cell lung cancer (NSCLC), two or more cycles of cisplatin-based chemotherapy, with or followed by radiation, has been proven to enhance survival (American Society of Clinical Oncology, 1997). Chemotherapy is appropriate for selected patients who have a good performance status. In general, chemotherapy is either given first followed by radiation, or is administered concurrently with radiation. Concurrent chemoradiotherapy regimens employ chemotherapy agents as radiosensitisers. Most studies that have shown a benefit for chemoradiotherapy have used cisplatin- or carboplatin-based combinations (Dillman *et al*, 1990; Le Chevalier *et al*, 1991; Jeremic *et al*, 1995), and both drugs are known to be radiosensitizers (Schaake-Koning *et al*, 1992; Jeremic *et al*, 1996). New active agents, such as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan, have been introduced and clinical trials of these agents for NSCLC have yielded promising data. These agents have been compared with each other in a phase III study performed in patients with advanced NSCLC, and several studies have suggested the radiosensitising properties of these new agents (Tishler *et al*, 1992; Leonard *et al*, 1996; McGinn *et al*, 1996; Okishio *et al*, 1996). However, the phase I and II studies combining these agents with radiotherapy have mostly been preliminary (Choy *et al*, 1994; Greco *et al*, 1996; Gregor, 1997; Mauers *et al*, 1998; Herscher *et al*, 1998). Irinotecan has a mechanism of action targeting the nuclear enzyme topoisomerase I as radiosensitiser *in vitro* (Okishio *et al*, 1996). A response rate of 32% was observed in untreated patients with advanced NSCLC (Fukuoka *et al*, 1992) while a recent phase III study showed that irinotecan in combination with cisplatin achieved a significantly better survival compared with the combination of cisplatin and vindesine in patients with metastatic NSCLC (Fukuoka *et al*, 2000). We have already reported that a phase I/II study of weekly irinotecan with concurrent radiotherapy showed acceptable toxicity (esophagitis, diarrhea, and pneumonitis)(Takeda *et al*, 1999). Carboplatin has also been investigated as a radiosensitizer. Several studies (Groen *et al*, 1995; Kunitoh *et al*, 1997; Atagi *et al*, 2000) of concurrent daily carboplatin and radiotherapy have suggested that this combination is feasible and reasonably effective. Irinotecan and carboplatin have independently shown a synergistic effect with ionizing radiation in preclinical studies (Douple *et al*, 1985; Okishio *et al*, 1996). Based on these findings, we conducted a phase I trial of daily carboplatin and weekly irinotecan with concurrent thoracic radiotherapy for the treatment of locally advanced

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NSCLC in order to find the optimum dose of irinotecan and to estimate the antitumor activity and toxicity profile of this therapy.

MATERIALS AND METHODS

Patients selection

Patients were eligible for this study if they had histologically or cytologically documented and locally advanced stage III NSCLC that was deemed unresectable. Other eligibility requirements included an age of less than 75 years, an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, no previous chemotherapy or radiotherapy, ability to give written informed consent, as well as adequate pretreatment haematologic function (leukocyte count $\geqslant 4\,000\ \mu l^{-1}$, haemoglobin $\geqslant 9.5$ g dl^{-1}, and platelet count $\geqslant 100{\cdot}000\ \mu l^{-1}$), renal function (a normal serum creatinine concentration), hepatic function (transaminases $\leqslant$ twice the normal range and serum bilirubin level $\leqslant 1.5$ mg dl^{-1}), and pulmonary function ($PaO_2 \geqslant 70$ Torr, %DLco $>60\%$). Patients were excluded if they had contralateral hilar lymph node metastasis, a serious pre-existing disease, or a radiation field that exceeded half of one lung. Patient's informed consent and approval of the institutional ethics committee were mandatory for participation in the trial.

Treatment plan

Irinotecan was administered as a 90-min intravenous infusion once weekly, and carboplatin was given as a 30-min infusion (20 mg m^{-2}) prior to thoracic radiotherapy daily for 5 days each week. Irinotecan and carboplatin were both administered for 4 weeks.

Thoracic radiotherapy started on day 1 and was given to a total dose of 60 Gy in 2.0 Gy fractions, which were delivered five times a week for 6 weeks using a linear accelerator ($\geqslant$4MV). The treatment volumes consisted of original and boost volumes irradiated sequentially. The initial large-field target volume consisted of the primary tumour, mediastinum, and involved hilar of supraclavicular nodes (total dose, 40 Gy), and boost dose of 20 Gy was delivered to a volume that consisted of the primary tumour and involved nodes. A combination of parallel-opposed anterior and posterior and oblique fields was used. The maximal spinal cord dose did not exceed 40 Gy. The target volume of the primary tumour included the complete extent of the visible primary tumour as defined radiographically (by computed tomography) with a minimum 1.5 cm and a maximum 2.5 cm margin around the mass.

The following therapy is optional. If the patient became operable as a result of tumour regression, surgery was done within 1 month of the completion of chemoradiotherapy. If the patient remained inoperable, two cycles of cisplatin with vindesine (cisplatin 80 mg m^{-2} day 1 and vindesine 3 mg m^{-2} on days 1, 8, 15) were given as systemic chemotherapy.

Dose escalation schedule

The starting dose of irinotecan was 30 mg m^{-2} and this was escalated by 10 mg m^{-2} increments in every three patients. There was no interpatient escalation. The next scheduled dose of irinotecan was omitted when grade 3 leukopenia, thrombocytopenia, or grade 2 diarrhea was observed.

Both thoracic radiotherapy and intravenous carboplatin were withheld if grade 3 leukopenia, neutropenia, thrombocytopenia, or grade 4 esophagitis was observed and restarted as soon as possible after recovery to grade 3 esophagitis and grade 2 haematological toxicity.

Dose-limiting toxicity

Dose-limiting toxicity was defined as grade 3 or 4 nonhaematologic toxicity, excluding nausea, vomiting, and alopecia, as neutropenic fever (grade 3 neutropenia and $>38°C$) or as grade 4 haematologic toxicity according to the WHO criteria (World Health Organization, 1979). If irinotecan was omitted two times or more due to any toxicity or radiotherapy and daily carboplatin was postponed for more than one week because of grade 3 haematological toxicity or grade 4 oesophagitis, we decided this was dose-limiting toxicity. If dose-limiting toxicity was observed in one or two out of three patients, an additional three patients were scheduled to be treated at the same dose level, and dose escalation could then continue if the toxicity was only observed in one or two out of six patients. If the dose-limiting toxicity was observed in all three patients or in more than three out of six patients, that dose was defined as the maximum tolerated dose. Recommended dose was defined the previous dose level.

Response and toxicity evaluation

Responses were evaluated according to the World Health Organization (WHO) criteria and toxicity was assessed prior to any further non-protocol therapy according to the WHO criteria (World Health Organization, 1979). Pulmonary toxicity was recorded as Grade 0–5 according to late Radiation Therapy Oncology Group (RTOG) criteria (Robert *et al*, 1999) as follows: 0, none; 1, asymptomatic or mild symptoms, slight radiographic appearances; 2, moderate symptomatic fibrosis or pneumonitis, low-grade fever, patchy radiographic appearances; 3, severe symptomatic fibrosis or pneumonitis, dense radiographic changes; 4, severe respiratory insufficiency, continuous oxygen, assisted ventilation; and 5, fatal. All reported responses and toxicities were confirmed by independent extramural review. Survival was measured from the initiation of chemoradiotherapy to death, and survival curves were estimated using the Kaplan–Meier method (Kaplan and Meier, 1958).

RESULTS

Patient characteristics

Between May 1996 and July 1998, 31 patients with histologically or cytologically confirmed stage III NSCLC were enrolled in this dose escalation study. Their clinical characteristics are summarised in Table 1. Four dose levels of irinotecan were administered (Table 2), and 30 patients were assessable for toxicity and efficacy. The

Table 1 Patient characteristics

No. of patients enrolled	31
Evaluability	
Not evaluable	1[a]
Response and toxicity	30
Age; median (range) years	62 (52–72)
Performance status (ECOG)	
0	10 (33%)
1	18 (60%)
2	2 (7%)
Sex	
Male	24 (80%)
Female	6 (20%)
Histology	
Squamous cell carcinoma	19 (63%)
Adenocarcinoma	10 (33%)
Large cell carcinoma	1 (3%)
Stage	
IIIA	12 (40%)
IIIB	18 (60%)

Abbreviation: ECOG, Eastern Cooperative Oncology Group. [a]A brain metastasis was discovered on day 7 of treatment, and this patient was removed from the study.

Table 2 Dose levels of irinotecan, dose actually delivered and dose intensity

Irinotecan (mg m^{-2}) dose level	No. of evaluable patients	Administration of irinotecan		DI (mg m^{-2} per week) (% of ADDI)	Administration of carboplatin		DI (mg m^{-2} per day) (% of ADDI)	Treatment of radiotherapy	
30	14	complete	10	27.3	complete	13	19.0	complete	12
		one dose missed	3[a,b,c]	(91.1%)	6 doses	1[b]	(95.0%)	28 Gy	1[b]
		two doses missed	1[b]					12 Gy	1[b]
40	6	complete	5	38.3	complete	5	19.8	complete	6
		one dose missed	1[d]	(95.8%)	19 doses	1[e]	(99.2%)		
50	7	complete	6	48.2	complete	6	19.9	complete	6
		one dose missed	1[a]	(96.4%)	19 doses	1[e]	(99.3%)	52 Gy	1[a]
60	3	complete	2	55	complete	3	20.0	complete	1
		one dose missed	1[a]	(91.7%)			(100%)	50 Gy	2

Abbreviation: DI, dose-intensity, ADDI, actually delivered dose intensity. [a]Myelosuppression, [b]disease progression, [c]skin rash, [d]diarrhoea, [e]mistake.

remaining one patient who enrolled into irinotecan dose level of 50 mg m^{-2} was ineligible because brain metastasis was confirmed after enrollment. For these 30 patients, the median age was 62 years (range: 52–72 years). The performance status was 0–1 in 28 patients, while it was 2 in two patients. Twelve patients were in stage IIIA and 18 were in stage IIIB. Their tumours included 19 squamous cell carcinomas, 10 adenocarcinomas, and one large cell carcinoma.

Actual doses of chemotherapy and radiotherapy

The planned individual drug doses, the actual delivered doses and dose intensity are listed in Table 2. Fourteen patients were treated with 30 mg m^{-2} of irinotecan. Although six patients should have been the maximum number in one step in our protocol, we added eight patients in first step to carry out this protocol safely because grade 4 pulmonary toxicity was observed in one patient, in the former study (Takeda *et al*, 1999) of weekly irinotecan combined with concurrent thoracic radiation therapy we experienced the treatment related death of pneumonitis and the Monitoring Committee of this protocol decided to add more patients in initial step. Administration of irinotecan was withheld due to neutropenia in three patients, disease progression in two patients, and diarrhea and localized erythema in one patient. Three patients did not complete the intravenous carboplatin schedule, one due to disease progression and the other due to a mistake about administration times. Dose intensities of irinotecan and carboplatin are listed in Table 2. The percentage of actually delivered dose-intensity of irinotecan and carboplatine was range from 91.1% to 100%. Twenty-five out of the 30 patients (83.3%) completed their radiotherapy as scheduled. The reason for not completing radiotherapy was disease progression in two patients and thrombocytopenia in one patient. Also, the first patient who received 60 mg m^{-2} of irinotecan suffered treatment-related death from pneumonitis and thrombocytopenia, so the other two patients treated at this dose level discontinued radiotherapy after 50 Gy.

Haematologic toxicity

Thirty patients were assessable for haematologic toxicity, and the results summarised in Table 3. Haematologic toxicities were mild. The only grade 4 leukopenia and neutropenia were seen in one patient (grade 4 neutropenia) given 30 mg m^{-2} of irinotecan. G-CSF was administered to five of 14 patients on 30 mg m^{-2} of irinotecan, three of six on 40 mg m^{-2}, four of seven on 50 mg m^{-2}, and all three on 60 mg m^{-2} dose of irinotecan. Grade 4 thrombocytopenia occurred in two patients (one at the 50 mg m^{-2} and one at 60 mg m^{-2} doses of irinotecan) and this was dose-limiting toxicity. These two patients required platelet transfusions.

Table 3 Haematologic toxicity

Irinotecan dose level (mg m^{-2})	No. of patients	Toxicity (WHO grade)					
		Haemoglobin		Neutrophils		Platelets	
		3	4	3	4	3	4
30	14	1	0	2	1	1	0
40	6	1	0	2	0	0	0
50	7	0	0	2	0	0	1
60	3	0	0	3	0	0	1

Nonhaematologic toxicity

The nonhaematologic toxicities are summarised in Table 4. One patient suffered from grade 3 esophagitis at an irinotecan dose of 40 mg m^{-2}, and two patients had grade 3 nausea with vomiting at 30 mg m^{-2} of irinotecan. No patient suffered from either grade 3 or 4 diarrhea. Grade 4 pneumonitis was observed in two patients treated with 60 mg m^{-2} of irinotecan, as well as in one patient each at both 30 mg m^{-2} and 40 mg m^{-2}. Grade 5 pneumonitis was observed in one patient with 60 mg m^{-2} of irinotecan. Grade 4–5 pneumonitis was dose-limiting toxicity and was observed in all three patients at the 60 mg m^{-2} of irinotecan dose. Therefore we decided that this dose was defined as the maximum tolerated dose. Of these five patients who had grade 4–5 pneumonitis, all were treated with steroids and three required mechanical ventilation. Four patients eventually recovered, however one patient given 60 mg m^{-2} of irinotecan suffered treatment-related death. Pneumonitis seemed to be a principal toxicity of this combined modality.

Response

The response to treatment is summarised in Table 5. Three patients achieved complete remission and 15 patients achieved partial remission, for an overall objective response rate of 60.0% (95% confidence interval 41.4–78.6%). Among the 18 responders, five patients underwent surgical resection of their residual disease and five received systemic chemotherapy with cisplatin and vindesine. Among the 11 patients with stable disease, four also received systemic chemotherapy.

Survival and duration of response

The overall median survival time (MST) was 14.9 months, while the 1-year and 2-year survival rates were 51.6% and 34.2%, respectively. In the responding patients (i.e., those who achieved either complete

Recent studies suggest that analysis of the three-dimensional dose distribution gives useful data for the prediction of pulmonary toxicity (Martel *et al*, 1994; Marks *et al*, 1997; Graham, 1997). We could not calculate radiotherapy volume data since three-dimensional (3D) radiation therapy were not available with our study. So we calculated radiation portal size by two-dimensional treatment planning data. Radiation portal size was range from 105 m^2 to 322 m^2 (mean $\pm$ SD; 179.7 $\pm$ 48.0 m^2). For five patients with grade 4 or 5 pulmonary toxicity, radiation field size was range from 168 m^2 to 304 m^2 (mean $\pm$ SD; 208.8 $\pm$ 54.4 m^2). There was no significant relationship between radiation field size and pulmonary toxicity. It is very difficult to interpret the toxicity without more information about radiation volume data. This study thinks it is also worth reporting the premorbid lung function data, so we collected the individual data of pulmonary function tests (PFTs) before radiotherapy. Premorbid lung function data (including spirometry, volume measurements, and diffusion capacity) as follows (mean $\pm$ SD): the per cent predicted vital capacity (%VC) 89.4 $\pm$ 19.2%; the forced expiratory volume in 1 sec (FEV1) 1.88 $\pm$ 0.58 L; the per cent predicted diffusion capacity to carbon monoxide (%DLCO) 90.1 $\pm$ 21.7%. For five patients with grade 4 or 5 pulmonary toxicity, lung function data as follows (mean $\pm$ SD): %VC 93.6 $\pm$ 15.9%; FEV1.0 1.91 $\pm$ 0.67L; %DLCO 78.0 $\pm$ 23.5%. There was no relationship between PFT parameters and pulmonary toxicities. According these limited information, we suggest that pulmonary toxicity may be drug related rather than field size or baseline PFTs. In our study, radiation volume was not estimated, so we have to plan further study to reveal whether a dose and radiation volume are related to the occurrence of pulmonary toxicity.

The efficacy of combined-modality therapy for inoperable stage III NSCLC is reported to vary and the reason for this is unclear, although differences between the eligibility criteria used in various studies may account for the different outcomes (Mattson *et al*, 1988; Morton *et al*, 1991; Sause *et al*, 1995). In the present study, the maximum tolerated dose of irinotecan was 60 mg m^{-2}. Pneumonitis, esophagitis, thrombocytopenia and neutropenia were the dose-limiting toxicities and pneumonitis was the principal toxicity of this regimen, whereas myelosuppression was mild. The overall response rate was 60.0%, while in patients given 50 and 40 mg m^{-2} of irinotecan, the response rate was 57.1 and 100%, respectively. At an irinotecan dose of 40 or 50 mg m^{-2}, pneumonitis was manageable and haematologic toxicity was mild. Based on our findings we therefore decided that 50 mg m^{-2} of irinotecan was the recommended dose. Although these data are still preliminary, the median survival time was 14.9 months and the 1- and 2-year survival rates were 51.6 and 34.2%, respectively, which were reasonably good. When comparing these results with similar combined modality studies, the MST and survival rates are most encouraging. And the MST of 21.9 months and 24.3 months in patients who underwent surgery or had adjuvant chemotherapy was better than that in patients who had no additional treatment. It is because that optional treatment was done in responding patients or stable patients. It should be discussed whether in responding patients additional treatment is necessary.

In conclusion, irinotecan combined with daily carboplatin for 4 weeks and concurrent thoracic radiotherapy appears to be feasible and improve the survival of patients with unresectable locally advanced NSCLC. MTD and recommended dose of irinotecan were 60 mg m^{-2} and 50 mg m^{-2}, respectively. Principal toxicity of this combined modality was pneumonitis. A phase II study of this combination is warranted.

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Table 4 Nonhaematologic toxicity

Irinotecan dose level (mg m^{-2})	No. of patients	Toxicity (WHO grade)						(RTOG grade)		
		Esophagitis		Diarrhoea		Nausea/ Vomiting		Pneumonitis		
		3	4	3	4	3	4	3	4	5
30	14	0	0	0	0	2	0	2	1	0
40	6	1	0	0	0	0	0	0	1	0
50	7	0	0	0	0	0	0	0	0	0
60	3	0	0	0	0	0	0	0	2	1

Table 5 Response to treatment

Irinotecan dose level (mg m^{-2})	No. of patients	Response				Response rate (%)
		CR	PR	SD	PD	
30	14	1	5	7	1	42.8
40	6	0	6	0	0	100.0
50	7	1	3	3	0	57.1
60	3	1	1	1	0	66.7
Overall	30	3	15	11	1	60.0 (41.4–78.6)[a]

CR=complete remission; PR=partial remission; SD=stable disease; PD=progressive disease; [a]95% confidence interval.

or partial remission), the median duration of response was 11.0 months. In the patients who had either surgery or adjuvant chemotherapy, the MST was 21.9 months (range: 7.8 to 33.0 months) and 24.3 months (range: 5.4 to 32.4 months), respectively. In the other patients, the MST was 10.6 months (range: 1.1 to 36.9 months). The overall survival of all the patients is plotted in Figure 1.

Pattern of failure

The sites of initial relapse are shown in Table 6. There were 22 sites of relapse in 29 patients who had partial remission or stable disease. The primary tumour inside the radiation field was the site of initial relapse in eight patients (seven without and one with distant metastasis), while distant metastasis was in ten patients and pleural effusion in four patients. Of five patients who underwent surgery, three patients had no relapse, one died of another disease, and one had pulmonary metastasis.

DISCUSSION

Our present study showed that the combination of daily low-dose carboplatin and weekly irinotecan with concurrent thoracic radiotherapy is feasible. All three patients who received 60 mg m^{-2} of irinotecan developed grade 4–5 pneumonitis, although grade 4–5 pneumonitis was not observed at the 50 mg m^{-2} dose. In our former study of a phase I/II study (Takeda *et al*, 1999) of weekly irinotecan alone and concurrent thoracic radiotherapy in patients with stage III NSCLC, radiation therapy (2 Gy daily to a total dose of 60 Gy) was performed concurrently with administration of irinotecan done once weekly for 6 weeks. Twenty-seven patients were enrolled at three irinotecan dose levels (30, 45 and 60 mg m^{-2}). In that phase I study, grade 4 pneumonitis occurred in one patient at a dose of 60 mg m^{-2}, while in the phase II study using 45 mg m^{-2}, one out of 10 patients developed severe toxicity (grade 4 pneumonitis plus grade 3 diarrhea) and died. In our study, the irinotecan administration period was reduced from 6 to 4 weeks because in our former study (Takeda *et al*, 1999) the number of patients increased who experienced the skip of the 5th and/or 6th administration of irinotecan. On the former study we added the daily carboplatin as another radiosensitiser.

Development of pulmonary toxicity is generally thought to be related to radiation dose, method of fractionation, and volume of the lung irradiated (Ginsberg *et al*, 1993). In patients receiving combined chemoradiotherapy, other confounding factors, such as the type of chemotherapeutic agent, also may play an important role in determining the risk of this toxicity. New chemotherapeutic agents, such as paclitaxel, have also been reported to show pulmonary toxicity (Choy *et al*, 1998). Therefore, the mechanism of pneumonitis seemed to be an interaction between all three parts of the treatment.

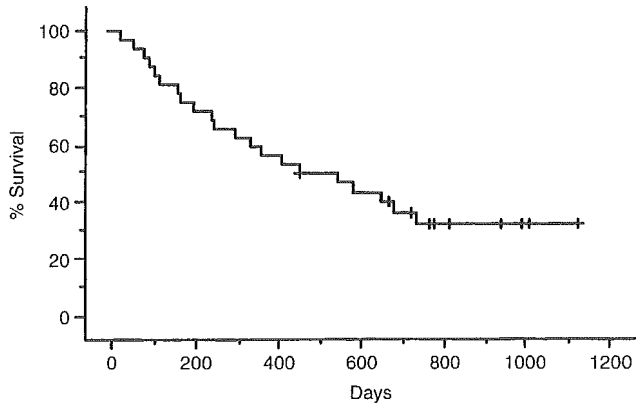

Figure 1 Overall survival. The estimated 1- and 2-year survival rate were 51.6 and 34.2%, and the median survival time was 14.9 months.

Table 6 Initial relapse sites

Initial relapse site	Patients (*n*)	%
Inside radiation field	8	27
Primary tumour site	7[b]	23
Mediastinal lymph node	1	3
Outside radiation field	14	47
Pleural effusion	4	13
Bone	3	10
Lung	2[b]	7
Supraclavicular lymph node	1	7
Liver	1	3
Skin	1	3
Spinal cord	1	3
Response continued	5	17
Unknown[a]	3	10

[a]Patients died without disease progression, including one who had treatment-related death, two who died of other diseases. [b]One patient had two (primary, lung) simultaneous initial relapse sites.

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