厚生労働科学研究委託費

革新的がん医療実用化研究事業

局所進行非扁平上皮非小細胞肺癌に対する シスプラチン＋S-1同時胸部放射線治療と シスプラチン＋ペメトレキセド同時胸部放射線治療の 無作為化第Ⅱ相試験

平成２６年度　委託業務成果報告書

業務主任者　仁保　誠治

平成２７（２０１５）年　３月

本報告書は、厚生労働省の平成26年度厚生労働科学研究委託事業（革新的がん医療実用化研究事業）による委託業務として、独立行政法人国立がん研究センターが実施した平成26年度「局所進行非扁平上皮非小細胞肺癌に対するシスプラチン＋S-1同時胸部放射線治療とシスプラチン＋ペメトレキセド同時胸部放射線治療の無作為化第Ⅱ相試験」の成果を取りまとめたものです。

厚生労働科学研究委託費

革新的がん医療実用化研究事業

局所進行非扁平上皮非小細胞肺癌に対する シスプラチン＋S-1同時胸部放射線治療と シスプラチン＋ペメトレキセド同時胸部放射線治療の 無作為化第Ⅱ相試験

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Ⅰ．委託業務成果報告書（総括）

厚生労働科学研究委託費（革新的がん医療実用化研究事業）
委託業務成果報告

局所進行非扁平上皮非小細胞肺癌に対するシスプラチン＋S-1同時胸部放射線治療とシスプラチン＋ペメトレキセド同時胸部放射線治療の無作為化第Ⅱ相試験

業務主任者　仁保　誠治
独立行政法人国立がん研究センター東病院
呼吸器内科病棟医長

研究要旨

切除不能局所進行非扁平上皮非小細胞肺癌に対する化学放射線治療において、将来の第Ⅲ相試験で検証すべき有望な化学療法レジメンを選択するため、胸部放射線治療と同時に行うS-1+シスプラチン（CDDP）療法とペメトレキセド（PEM）＋CDDP療法の有効性と安全性を検討する多施設共同無作為化第Ⅱ相試験を開始した。平成25年1月から症例登録を開始し、平成27年2月20日現在、49例が登録されている。引き続き症例登録を継続している。

研究分担者

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A．研究目的

切除不能局所進行非扁平上皮非小細胞肺癌に対する有効な化学放射線治療を開発するため、胸部放射線治療と同時に行うS-1＋CDDP併用化学療法とPEM＋CDDP併用化学療法の有効性と安全性を検討する。

B．研究方法

国立がん研究センター東病院、がん研有明病院、静岡がんセンター、九州がんセンター、愛知県がんセンター中央病院、関西医科大学附属枚方病院、横浜市立市民病院、国立がん研究センター中央病院の8施設が参加する多施設共同無作為化第Ⅱ相試験である。プライマリーエンドポイントは2年無増悪生存割合である。目標症例数は70例である。

対象は、切除不能局所進行非扁平上皮癌非小細胞肺癌で、20-74歳、ECOG Performance Status (PS) 0-1、主要臓器機能が保持されており、患者本人の自由意思による文書同意が得られた患者である。

国立がん研究センター東病院内の登録事務局（平成27年2月2日からは横浜市立大学付属市民総合医療センター臨床研究推進センターに移管）で中央登録、ランダム割り付けを行う。割付調整因子は、施設、組織型、性別、病期である。

治療内容は、A群がS-1（80mg/m2/日、14日間）＋CDDP（60mg/m2、第1日）、4週間隔、4コース、同時胸部放射線治療1日2Gy、30回、計60Gy、B群がPEM（500mg/m2、第1日）＋CDDP（75mg/m2、第1日）、3週間隔、4コース、同時胸部放射線治療1日2Gy、30回、計60Gyを行う。

（倫理面への配慮）

参加患者の安全性確保については、適格条件やプロトコール治療の中止変更規準を厳しく設けて

おり、試験参加による不利益は最小化される。また、「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則に従い以下を遵守する。

1) 研究実施計画書のIRB承認が得られた施設のみから患者登録を行う。

2) すべての患者について登録前に充分な説明と理解に基づく自発的同意を本人より文書で得る。

3) データの取り扱い上、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報（プライバシー）保護を厳守する。

4) 研究の第三者的監視：効果安全性評価委員会による第三者的監視を受けることを通じて、科学性と倫理性の確保に努める。

C．研究結果

平成25年1月から症例登録を開始し、平成27年2月20日現在、49例が登録されている。平成26年3月までに施設IRBの承認が得られたのは、国立がん研究センター東病院、がん研有明病院、静岡がんセンター、九州がんセンターの4施設であったが、平成26年6月に愛知県がんセンター中央病院、8月に関西医科大学附属枚方病院、10月に横浜市立市民病院、11月に国立がん研究センター中央病院でIRB承認が得られた。平成25年1月から12月の症例登録数が16例だったのに対し、平成26年1月から12月の症例登録数は27例に増加した。

平成26年2月3日までに登録された20例におけるグレード3-4の有害事象は、好中球減少がA群18%、B群56%、血小板減少がA群0%、B群22%、肝機能障害がA群9%、B群11%、口内炎がA群0%、B群11%、放射線食道炎がA群9%、B群22%であった。グレード3-4の放射線肺臓炎は認められなかった。重篤な有害事象としてB群においてグレード2の気管縦隔瘻が1例報告された。保存的治療で気管縦隔瘻は改善した。化学放射線治療における既知の有害事象であり、研究グループ内で情報を周知し、効果安全性評価委員会に報告した。有害事象の発生の有無を注意深く観察しながら、本試験の症例登録を継続することに問題はないと判断された。

附随研究として「化学放射線治療を施行したⅢ期局所進行非小細胞肺癌におけるCirculating biomarkerによる治療効果・再発モニタリングの検討」の研究計画書を策定し、平成27年1月に国立がん研究センターのIRBに審査を依頼した。

D．考察

非小細胞肺癌（主に腺癌、扁平上皮癌、大細胞癌）は肺癌全体の約85%を占め、約2/3は発見時にすでに切除不能の進行癌であるが、遠隔転移がなく根治的胸部放射線治療が可能であれば、化学療法と併用することで20%ほどの5年生存割合が得られ、治癒の可能性がある。逆に80%以上の患者は再発をきたし、約2/3の患者は遠隔転移をきたす。したがって治療成績の向上のためには、根治的胸部放射線治療と併用可能で、より有効な化学療法レジメンを開発することが不可欠である。

進行非小細胞肺癌を対象とした大規模比較試験の非扁平上皮癌のサブ解析において、PEM+CDDP併用療法はゲムシタビン＋CDDP併用療法より有意に生存期間が延長しており、進行非扁平上皮非小細胞肺癌に対する最強レジメンとされている。海外の第Ⅱ相試験では、PEM＋CDDP併用療法はfull doseで胸部放射線治療と併用可能であることが示されており、局所進行非扁平上皮非小細胞肺癌に対する化学放射線治療で用いられる有望なレジメンとして期待されている。本邦で行われたPEM+CDDP併用療法と同時胸部放射線治療の第1相試験では、full doseでPEM+CDDPと放射線治療が併用可能であったが、18例と小規模な検討であり、日本人における安全性と有効性は充分には評価されていない。

一方、S-1＋CDDP併用療法は本邦で行われた進行非小細胞肺癌を対象とした第Ⅲ相試験において、ドセタキセル＋CDDP併用療法と比較し、全生存期間の非劣性が示された。更に、本邦で行われた胸部放射線治療と同時に行うS-1＋CDDP併用療法の第Ⅱ相試験の長期成績によると、5年生存割合は33%と極めて良好な結果であった。そこで、将来の第Ⅲ相試験の試験アームとして相応しい化学療法レジメンを選択するため、本試験を開始した。

症例登録は順調に推移している。有害事象の内容は過去の局所進行非小細胞肺癌に対する化学放射線治療の報告と同程度であり、許容範囲内と考えられる。

E．結論

「局所進行非扁平上皮非小細胞肺癌に対するシスプラチン＋S-1同時胸部放射線治療とシスプラ

チン＋ペメトレキセド同時胸部放射線治療の無作為化第Ⅱ相試験」では、多施設共同臨床試験を平成25年1月から開始し、平成27年2月20日現在、49例が登録されている。引き続き症例登録を継続している。

F．健康危険情報

厚生労働省に報告した健康危険情報なし。

G．研究発表

1．論文発表

1) Niho S, Nokihara H, Nihei K, Akimoto T, Sumi M, Ito Y, Yoh K, Goto K, Ohmatsu H, Horinouchi H, Yamamoto N, Sekine I, Kubota K, Ohe Y, Tamura T: Dose-escalation study of thoracic radiotherapy in combination with pemetrexed plus cisplatin in Japanese patients with locally advanced nonsquamous non-small cell lung cancer: A post hoc analysis of survival and recurrent sites. Am J Clin Oncol, 2014.

2) Akamatsu H, Mori K, Naito T, Imai H, Ono A, Shukuya T, Taira T, Kenmotsu H, Murakami H, Endo M, Harada H, Takahashi T, Yamamoto N. Progression-free survival at 2 years is a reliable surrogate marker for the 5-year survival rate in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy. BMC Cancer. 2014 Jan 14;14:18.

3) Akamatsu H, Kaira K, Murakami H, Serizawa M, Koh Y, Ono A, Shukuya T, Tsuya A, Nakamura Y, Kenmotsu H, Naito T, Takahashi T, Endo M, Harada H, Nakajima T, Yamamoto N. The impact of clinical outcomes according to EGFR mutation status in patients with locally advanced lung adenocarcinoma who received concurrent chemoradiotherapy. Am J Clin Oncol. 2014 Apr;37(2):144-7.

2．学会発表

1) 倉田宝保　化学放射線療法：シンポジウム（口頭）第54回日本呼吸器学会学術講演会 2014年4月25-27日

2) 山口正史、稲益英子、吉田月久、豊川剛二、白石祥理、豊澤亮、竹中朋祐、平井文彦、瀬戸貴司、竹之山光広、一瀬 幸人　非小細胞肺癌に対する術前導入化学療法または化学放射線療法後の肺全摘術の安全性の検討（ポスター）　第31回日本呼吸器外科学会　2014年5月29-30日

3) Kosuke Tanaka, Tomoyo Oguri, Tatsuya Yoshida, Jangchul Park, Junichi Shimizu, Yoshitsugu Horio, Takeshi Kodaira, Toyoaki Hida, Kosuke Tanaka. The impact of EGFR mutation on definitive concurrent chemoradiation therapy for inoperable stage III lung adenocarcinoma（ポスター）ASCO2014　2014年5月30-6月3日

4) Takenaka T, Inamasu E, Yoshida T, Toyokawa G, Nozaki K, Hirai F, Yamaguchi M, Seto T, Takenoyama M, Ichinose Y. Concurrent chemoradiotherapy for patients with post-operative recurrence of surgically resected non-small cell lung cancer（口頭）第60回国際外科学会日本支部総会 2014年6月14

5) 山口正史、稲益英子、豊川剛二、吉田月久、白石祥理、竹中朋祐、平井文彦、瀬戸貴司、竹之山光広、一瀬幸人．ワークショップ「Locally advanced non-small cell lung cancer: Role of surgery as combined modality treatment / 局所進行期：局所進行期肺がんの治療における外科治療の役割」臨床病期III期の局所進行非小細胞肺癌に対するS-1/Cisplatinによる化学放射線同時併用導入療法後の切除の経験（口頭）第12回日本臨床腫瘍学会学術集会　2014年7月17日－19日

6) 角南久仁子、四方田真紀子、高木雄亮、細見幸生、中原善朗、大熊裕介、下川恒生、長又誠、井口万里、岡本浩明、岡村樹、渋谷昌彦. Phase 2 study of short-term vitamin supplementation prior to cisplatin-pemetrexed therapy for non-small cell

lung cancer / 非小細胞肺癌に対してのシスプラチン・ペメトレキセド療法に先行する短期間ビタミン補充法の第II相試験　第12回日本臨床腫瘍学会学術集会　2014年7月17日-19日

7) Seiji Niho, Shigeki Umemura, Koichi Goto, Hironobu Ohmatsu, Masamichi Toshima, Atsushi Motegi, Satoko Arahira, Masakatsu Onozawa, Tetsuo Akimoto, Yuichiro Ohe. Proton therapy with concurrent chemotherapy for non-small cell lung cancer: our experiences and future direction. (口頭) 第12回日本臨床腫瘍学会総会学術集会 2014/7/19

8) 四方田真紀子, 高木雄亮、細見幸生、角南久仁子、中原善朗、大熊裕介、下川恒生、長又誠、井口万里、岡本浩明、岡村樹、渋谷昌彦. シスプラチン・ペメトレキセド療法に先行する短期間ビタミン補充法の第II相試験（ポスター）第52回日本癌治療学会学術集会　2014年8月28日-30日

9) 下川恒生、高木雄亮、細見幸生、角南久仁子、中原善朗、大熊裕介、四方田真紀子、長又誠、井口万里、岡本浩明、 岡村樹、澁谷昌彦. シスプラチン・ペメトレキセド療法に先行する短期間ビタミン補充法の前向き試験（口頭）第55回日本肺癌学会学術集会　2014年11月14日-16日

H. 知的財産等の出願・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

Ⅱ．　学会等発表実績

学 会 等 発 表 実 績

委託業務題目「局所進行非扁平上皮非小細胞肺癌に対するシスプラチン＋S-1同時胸部放射線治療とシスプラチン＋ペメトレキセド同時胸部放射線治療の無作為化第Ⅱ相試験」

１．学会等における口頭・ポスター発表

発表した成果	発表者氏名	発表した場所 （学会等名）	発表した時期	国内・外の別
化学放射線療法:シンポジウム（口頭）	倉田宝保	第54回日本呼吸器学会学術講演会	2014年4月25-27日	国内
非小細胞肺癌に対する術前導入化学療法または化学放射線療法後の肺全摘術の安全性の検討（ポスター）	山口 正史 稲益 英子 吉田 月久 豊川 剛二 白石 祥理 豊澤 亮 竹中 朋祐 平井 文彦 瀬戸 貴司 竹之山 光広 一瀬 幸人	第31回日本呼吸器外科学会	2014年5月29-30日	国内
The impact of EGFR mutation on definitive concurrent chemoradiation therapy for inoperable stage III lung adenocarcinoma（ポスター）	Tanaka K, Oguri T, Yoshida T, Park J, Shimizu J, Horio Y, Kodaira T, Hida T	ASCO2014	2014年5月30-6月3日	国外
Concurrent chemoradiotherapy for patients with post-operative recurrence of surgically resected non-small cell lung cancer（口頭）	Takenaka T, Inamasu E, Yoshida T, Toyokawa G, Nozaki K, Hirai F, Yamaguchi M Seto T, Takenoyama M, Ichinose Y	第60回国際外科学会日本支部総会	2014年6月14日	国内

ワークショップ「Locally advanced non-small cell lung cancer: Role of surgery as combined modality treatment / 局所進行期：局所進行期肺がんの治療における外科治療の役割」臨床病期III期の局所進行非小細胞肺癌に対するS-1/Cisplatinによる化学放射線同時併用導入療法後の切除の経験（口頭）	山口正史 稲益英子 豊川剛二 吉田月久 白石祥理 竹中朋祐 平井文彦 瀬戸貴司 竹之山光広 一瀬幸人	第12回日本臨床腫瘍学会学術集会	2014年7月17-19日	国内
Phase 2 study of short-term vitamin supplementation prior to cisplatin-pemetrexed therapy for non-small cell lung cancer / 非小細胞肺癌に対してのシスプラチン・ペメトレキセド療法に先行する短期間ビタミン補充法の第II相試験（口頭）	角南 久仁子 四方田 真紀子 高木 雄亮 細見 幸生 中原 善朗 大熊 裕介 下川 恒生 長又 誠 井口 万里 岡本 浩明 岡村 樹 渋谷 昌彦	第12回日本臨床腫瘍学会学術集会	2014年7月17-19日	国内
Proton therapy with concurrent chemotherapy for non-small cell lung cancer: our experiences and future direction. （口頭）	Niho S, Umemura S, Goto K, Ohmatsu H, Toshima M, Motegi A, Arahira S, Onozawa M, Akimoto T, Ohe Y	第12回日本臨床腫瘍学会学術集会	2014年7月17-19日	国内
シスプラチン・ペメトレキセド療法に先行する短期間ビタミン補充法の第II相試験（ポスター）	四方田 真紀子 高木 雄亮 細見 幸生 角南 久仁子 中原 善朗 大熊 裕介 下川 恒生 長又 誠 井口 万里 岡本 浩明 岡村 樹 渋谷 昌彦	第52回日本癌治療学会学術集会	2014年8月28-30日	国内
統計家から見るエビデンス（口頭）	山中竹春	第55回日本肺癌学会学術集会	2014年11月14日-16日	国内

シスプラチン・ペメトレキセド療法に先行する短期間ビタミン補充法の前向き試験(口頭)	下川恒生 高木雄亮 細見幸生 角南久仁子 中原　善朗 大熊裕介 四方田真紀子 長又誠 井口万里 岡本浩明 岡村樹 澁谷昌彦	第55回日本肺癌学会学術集会	2014年11月14日-16日	国内

学 会 等 発 表 実 績

委託業務題目「局所進行非扁平上皮非小細胞肺癌に対するシスプラチン＋S-1同時胸部放射線治療とシスプラチン＋ペメトレキセド同時胸部放射線治療の無作為化第Ⅱ相試験」

２．学会誌・雑誌等における論文掲載

掲載した論文	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Dose-escalation study of thoracic radiotherapy in combination with pemetrexed plus cisplatin in Japanese patients with locally advanced nonsquamous non-small cell lung cancer: A post hoc analysis of survival and recurrent sites.	Niho S, Nokihara H, Nihei K, Akimoto T, Sumi M, Ito Y, Yoh K, Goto K, Ohmatsu H, Horinouchi H, Yamamoto N, Sekine I, Kubota K, Ohe Y, Tamura T	Am J Clin Oncol	2014年	国外
Progression-free survival at 2 years is a reliable surrogate marker for the 5-year survival rate in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy	Akamatsu H, Mori K, Naito T, Imai H, Ono A, Shukuya T, Taira T, Kenmotsu H, Murakami H, Endo M, Harada H, Takahashi T, Yamamoto N	BMC Cancer	2014年1月	国外
The impact of clinical outcomes according to EGFR mutation status in patients with locally advanced lung adenocarcinoma who received concurrent chemoradiotherapy.	Akamatsu H, Kaira K, Murakami H, Serizawa M, Koh Y, Ono A, Shukuya T, Tsuya A, Nakamura Y, Kenmotsu H, Naito T, Takahashi T, Endo M, Harada H, Nakajima T, Yamamoto N	Am J Clin Oncol	2014年4月	国外

Ⅲ. 研究成果の刊行物・別刷り

Dose-Escalation Study of Thoracic Radiotherapy in Combination With Pemetrexed Plus Cisplatin in Japanese Patients With Locally Advanced Nonsquamous Non–Small Cell Lung Cancer

A Post Hoc Analysis of Survival and Recurrent Sites

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Objectives: We performed a post hoc analysis of progression-free survival (PFS), overall survival (OS), and recurrent sites in patients with locally advanced nonsquamous non–small cell lung cancer who were enrolled in a phase I trial of combination chemotherapy consisting of pemetrexed plus cisplatin with concurrent thoracic radiotherapy.

Methods: Patients received pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) on day 1 every 3 weeks for 3 cycles plus concurrent thoracic radiotherapy consisting of 60 Gy (n = 6) or 66 Gy (n = 12); 4 to 6 weeks thereafter, patients received consolidation treatment with pemetrexed (500 mg/m^2) every 3 weeks for up to 3 cycles. We reviewed the medial records to collect data on progression, recurrent sites, late toxicity, and survival.

Results: No late radiation morbidity was observed. Thirteen patients (72%) exhibited disease progression: 8 patients had distant metastases, 8 patients had local recurrence (within the radiation field [n = 6], outside the radiation field [n = 2], and both [n = 1]), and 3 patients had local recurrence plus distant metastases. The median PFS was 10.5 months (95% confidence interval [CI], 8.8-12.3), and the 3-year PFS rate was 28% (95% CI, 7.0-48.6). Ten of the 18 patients died of lung cancer. The median follow-up time for the censored cases was 42.8 months (range, 38.1 to 52.9 mo). The median OS was 27.3 months (95% CI, 13.1-41.6), and the 3-year OS rate was 50% (95% CI, 26.9-73.1).

Conclusions: The median PFS and OS in our study were comparable to those of historical chemoradiotherapy controls.

Key Words: cisplatin, pemetrexed, thoracic radiotherapy, overall survival, progression-free survival

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Platinum-based chemotherapy and concomitant thoracic radiotherapy (TRT) are the standard of care for patients with unresectable locally advanced non–small cell lung cancer (NSCLC). Third-generation anticancer agents, such as paclitaxel, docetaxel, gemcitabine (GEM), and irinotecan cause intolerable esophagitis and/or pneumonitis, if they are concurrently administered with TRT. Therefore, these agents are usually administered weekly at a low dose when used for chemoradiotherapy.[1–4]

Pemetrexed (PEM) is an inhibitor of thymidylate synthase and other folate-dependent enzymes, including dihydrofolate reductase and glycinamide ribonucleotide formyl transferase. PEM plus cisplatin (CDDP) has enabled a statistically superior overall survival (OS) period in chemonaive patients with advanced nonsquamous NSCLC compared with GEM plus CDDP.[5,6] Nowadays, combination chemotherapy consisting of CDDP plus PEM is a standard regimen for patients with advanced nonsquamous NSCLC. In addition, PEM reportedly has a radiosensitizing potential when evaluated in vitro.[7] The tolerability of full-dose chemotherapy consisting of CDDP plus PEM combined with TRT has been confirmed in several phase I/II studies conducted in western countries.[8–13] We conducted a dose-escalation study of TRT used in combination with PEM plus CDDP followed by PEM consolidation therapy in Japanese patients with locally advanced nonsquamous NSCLC. The dose-escalation study was funded by Eli Lilly Japan (K.K.). Concurrent TRT at a total dose of 66 Gy combined with PEM plus CDDP was found to be feasible in the Japanese population.[14] The objectives of the dose-escalation study included the determination of the recommended TRT dose, safety, and response. Here, we report the results of a post hoc analysis of progression-free survival (PFS), OS, recurrent sites, late toxicity, and poststudy treatment in those patients who were enrolled in the above-mentioned dose-escalation study.

PATIENTS AND METHODS

Patient Population and Study Treatment

The design and results of the dose-escalation study have been published previously.[14] Briefly, eligible patients had

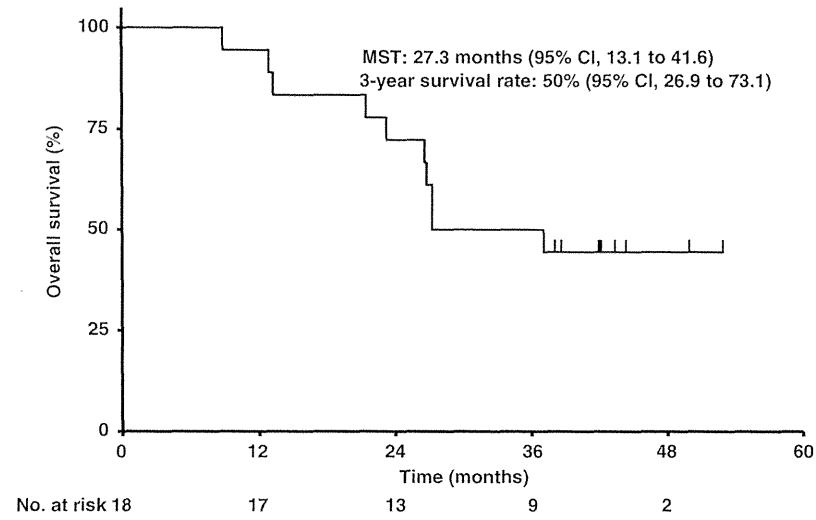

FIGURE 1. Overall survival curve for 18 eligible patients. CI indicates confidence interval; MST, median survival time.

nonsquamous NSCLC with unresectable stage IIIA or IIIB disease. The clinical stage was diagnosed according to the 6th edition of the TNM Classification of Malignant Tumors. Patients received PEM (500 mg/m^2) plus CDDP (75 mg/m^2) on day 1 every 3 weeks for 3 cycles. The first 6 patients were given TRT at a total dose of 60 Gy concurrently, and the next 12 patients were given TRT at a total dose of 66 Gy concurrently. TRT was initiated by anteroposterior opposed fields up to 40 Gy/20 fractions, including elective nodal irradiation to the mediastinum. A booster dose was added to the primary lesion and metastatic lymph nodes by oblique fields at a total dose of 60 or 66 Gy. Treatment planning was based on computed tomography (CT) simulation. The primary lesion and metastatic lymph nodes were defined as gross tumor volume. Subclinical lymph node regions were included as clinical target volume for elective nodal irradiation. The planning target volume was defined as clinical target volume plus appropriate margins (horizontal 0.1 to 1 cm; vertical 1 to 2 cm) in expectation of some setup errors and respiratory motion. Four to 6 weeks after the completion of the chemoradiotherapy, PEM (500 mg/m^2) was administered on day 1 every 3 weeks for up to 3 cycles as a consolidation chemotherapy. Safety was assessed until 30 days after the completion of the protocol treatment in the dose-escalation study. After the 30-day follow-up period, physical examinations, toxicity assessments, chest x-rays, and blood tests were conducted every 1 to 3 months, as necessary, as part of our standard clinical practice. For instance, if tumor progression was clinically suspected based on the patient's symptoms, physical examination, chest x-ray, and/or elevation of serum tumor markers, a CT scan of the chest and abdomen, magnetic resonance imaging or CT scan of the brain, bone scan, and/or positron emission tomography were performed.

Study Design and Statistical Analysis

The endpoint of the dose-escalation study did not include the PFS or OS. Response and safety were assessed until 30 days after the completion of the protocol treatment. We retrospectively reviewed the medical records of patients who were enrolled in the dose-escalation study to collect data on progression, recurrent sites, late toxicity, poststudy treatment, and survival.

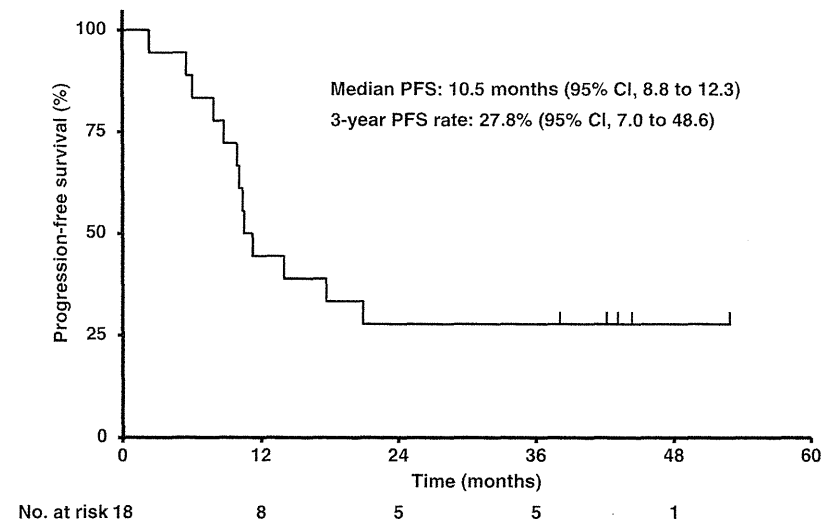

FIGURE 2. Progression-free survival (PFS) curve for 18 eligible patients. CI indicates confidence interval.

The OS was defined as the interval between the start of chemoradiotherapy and death or the final follow-up visit. The PFS was defined as the interval between the start of chemoradiotherapy and the first documented evidence of disease progression or death, whichever occurred first. The time-to-event distributions were estimated using the Kaplan-Meier method. The present study was approved by an institutional review board.

RESULTS

Recurrent Sites and Late Toxicity

Between November 2008 and December 2010, a total of 20 patients were enrolled in the dose-escalation study, and 18 patients received the protocol treatment. Thirteen patients (72%) had disease progression and recurrence: 8 patients had distant metastases, 8 patients had local recurrence (within the radiation field [n=6], outside the radiation field [n=2], and both [n=1]), and 3 patients had local recurrence plus distant metastases. Distant metastases included the brain (n=3), adrenal gland (n=2), bone (n=2), liver (n=2), and lung (n=2). The sites of distant metastasis overlapped in some cases.

As we reported previously, 8 patients developed grade 2 or 3 pneumonitis (1 patient developed grade 3 and 7 patients developed grade 2). Five patients required steroid therapy, leading to an improvement in the radiation pneumonitis.[14] None of the patients experienced a recurrence of pneumonitis after the follow-up period of the dose-escalation study. No late radiation morbidity was observed.

PFS and OS

The median PFS was 10.5 months (95% confidence interval [CI], 8.8-12.3 mo), and the 2- and 3-year PFS rates were both 27.8% (95% CI, 7.0%-48.6%). Ten of the 18 patients died of lung cancer. The median follow-up time for the censored cases was 42.8 months (range, 38.1 to 52.9 mo). The median OS was 27.3 months (95% CI, 13.1-41.6 mo), and the 3-year OS rate was 50% (95% CI, 26.9%-73.1%) (Figs. 1, 2).

Poststudy Treatment

Of the 13 patients who progressed after the protocol treatment, 8 patients received cytotoxic chemotherapy, 5 patients received epidermal growth factor receptor tyrosine kinase inhibitor, and 3 patients received both treatments. Two patients received only best supportive care including whole brain irradiation. One patient underwent salvage surgery. This patient was a 54-year-old man who had a 4.6 cm mass invading the mediastinum, in the right upper lobe of the lung. The mediastinal (#4R) and hilar (#10R and 11s) lymph nodes were swollen. A transbronchial biopsy revealed NSCLC, not otherwise specified, and transbronchial aspiration cytology revealed an adenocarcinoma, because many malignant cell clusters with papillary structure were observed. We diagnosed this patient as having an adenocarcinoma of the lung with clinical T4N2M0 and stage IIIB. He entered this clinical trial and received 3 cycles of CDDP plus PEM and concurrent TRT of 66 Gy followed by 2 cycles of consolidation chemotherapy with PEM. A partial response was achieved; however, 1 year and 2 months after the start of the chemoradiotherapy, the right hilar mass had increased in size. No other recurrent lesions were observed. He underwent salvage surgery consisting of a right pneumonectomy. The pathologic diagnosis was moderately to poorly differentiated squamous cell carcinoma of the lung. One year and 5 months after the salvage surgery, he developed a right supraclavicular lymph node metastasis

TABLE 1. Efficacy Outcomes From Clinical Trials Evaluating Combination Chemotherapy of Cisplatin Plus Pemetrexed Concurrent With Thoracic Radiotherapy in Patients With Locally Advanced Non-Small Cell Lung Cancer

References	No. Patients	Concurrent Chemoradiotherapy	Consolidation Chemotherapy	Dose of Thoracic Radiotherapy (Gy)	Patients With Squamous Histology (%)	Median PFS (95% CI) (mo)	2 y PFS Rate (%)	Median OS (95% CI) (mo)	2 y OS Rate (95% CI) (%)
Brade et al[10]	39	CDDP 20 mg/m^2 (days 1-5) + PEM 500 mg/m^2, q3w, 2 cycles	CDDP 75 mg/m^2 (day 1) + PEM 500 mg/m^2 (day 1), q3w, 2 cycles	60-66	26	11.8 (9.8-21.9)	NA	19.7	NA
Choy et al[8]	52	CDDP 75 mg/m^2 (day 1) + PEM 500 mg/m^2 (day 1), q3w, 3 cycles	PEM 500 mg/m^2, q3w, 3 cycles	64-68	21	13.1 (8.3-NA)	NA	27.0 (23.2-NA)	58.4 (42.6-71.3)
This study	18	CDDP 75 mg/m^2 (day 1) + PEM 500 mg/m^2 (day 1), q3w, 3 cycles	PEM 500 mg/m^2, q3w, 3 cycles	60-66	0	10.5 (8.8-12.3)	27.8	27.3 (13.1-41.6)	72.2 (51.4-93.0)

CDDP indicates cisplatin; CI, confidence interval; NA, not available; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival.

without any other recurrent lesions. The initial TRT field did not include this region. To date, the patient has received radiotherapy to the right supraclavicular lymph node.

DISCUSSION

Combination chemotherapy consisting of CDDP plus PEM is one of the standard chemotherapy regimens for advanced nonsquamous NSCLC.[6] Our study and previous clinical trials demonstrated that full-dose chemotherapy consisting of CDDP plus PEM could be administered concurrently with TRT.[8–11] Therefore, combination chemotherapy consisting of CDDP plus PEM and concurrent TRT has been considered promising. However, the median PFS was 10.5 months in our study, which is comparable to historical controls for chemoradiotherapy in patients with advanced NSCLC.[1,2] Other phase II studies of CDDP plus PEM and concurrent TRT revealed a median PFS of 12 to 13 months (Table 1).[8,10] These studies included patients with a squamous cell histology (21% to 26%). In contrast, the 2-year OS rate was 72% in our study, which is numerically better than that in the previous studies. Patient accrual for a global phase III study comparing CDDP plus PEM versus CDDP plus etoposide in combination with TRT for locally advanced nonsquamous NSCLC has been completed. However, an official announcement of the results of the global study has not yet been made.

A subset analysis of 3 large-scale randomized studies demonstrated that nonsquamous patients treated with PEM-based therapy experienced a longer survival period than squamous patients.[5,6,15] Since then, PEM has not been recommended for the treatment of squamous cell carcinoma of the lung. In contrast, an exploratory analysis of OS in a randomized phase II study of PEM, carboplatin, and TRT with or without cetuximab revealed no significant difference in OS between the squamous and nonsquamous patients.[16] The eligibility criteria for our study were restricted to a nonsquamous histology; however, pathologic examination of the salvage surgery specimen revealed a squamous cell carcinoma of the lung in 1 patient. Thus, a completely accurate pathologic diagnosis is difficult based only on cytology or small biopsy samples.

No late radiation morbidity was observed in this study; however, 8 of the 18 patients (44%) experienced grade 2 or 3 radiation pneumonitis. Five patients required steroid therapy. In general, pneumonitis sometimes recurs during the tapering of steroids. Fortunately, the recurrence of pneumonitis was not observed in this study. At least, a phase II study on CDDP, PEM, and TRT is warranted to evaluate the safety of this regimen in Japanese patients, as drug-induced pneumonitis, such as that caused by gefitinib and erlotinib, is more frequently observed in Japanese patients than in non-Japanese patients. A randomized phase II study comparing CDDP plus PEM and CDDP plus S-1 in combination with TRT for locally advanced nonsquamous NSCLC is ongoing in Japan (UMIN000009914).

In conclusion, the PFS and OS in our study were comparable to those in historical controls for chemoradiotherapy in patients with locally advanced NSCLC. No late radiation morbidity was observed.

REFERENCES

1. Segawa Y, Kiura K, Takigawa N, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. *J Clin Oncol.* 2011;28:3299–3306.
2. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol.* 2010;28:3739–3745.
3. Vokes EE, Herndon JE II, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol.* 2007;25:1698–1704.
4. Vokes EE, Herndon JE II, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B Study 9431. *J Clin Oncol.* 2002;20:4191–4198.
5. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist.* 2009;14:253–263.
6. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26:3543–3551.
7. Bischof M, Weber KJ, Blatter J, et al. Interaction of pemetrexed disodium (ALIMTA, multitargeted antifolate) and irradiation in vitro. *Int J Radiat Oncol Biol Phys.* 2002;52:1381–1388.
8. Choy H, Schwartzberg LS, Dakhil SR, et al. Phase 2 study of pemetrexed plus carboplatin, or pemetrexed plus cisplatin with concurrent radiation therapy followed by pemetrexed consolidation in patients with favorable-prognosis inoperable stage IIIA/B non-small-cell lung cancer. *J Thorac Oncol.* 2013;81:1308–1316.
9. Brade A, Bezjak A, MacRae R, et al. Phase I trial of radiation with concurrent and consolidation pemetrexed and cisplatin in patients with unresectable stage IIIA/B non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011;79:1395–1401.
10. Brade A, Bezjak A, MacRae R, et al. A phase II study of concurrent pemetrexed/cisplatin/radiation for unresectable stage IIIA/b non-small cell lung cancer. *J Clin Oncol.* 2010;28:536s, abstr 7087.
11. Cardenal F, Arnaiz MD, Moran T, et al. Phase I study of concurrent chemoradiation with pemetrexed and cisplatin followed by consolidation pemetrexed for patients with unresectable stage III non-small cell lung cancer. *Lung Cancer.* 2011;74:69–74.
12. Gadgeel SM, Ruckdeschel JC, Patel BB, et al. Phase II study of pemetrexed and cisplatin, with chest radiotherapy followed by docetaxel in patients with stage III non-small cell lung cancer. *J Thorac Oncol.* 2011;6:927–933.
13. Li BS, Gong HY, Huang W, et al. Phase I study of pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced non-small cell lung cancer. *Am J Clin Oncol.* 2012;35:115–119.
14. Niho S, Kubota K, Nihei K, et al. Dose-escalation study of thoracic radiotherapy in combination with pemetrexed plus cisplatin followed by pemetrexed consolidation therapy in Japanese patients with locally advanced nonsquamous non-small-cell lung cancer. *Clin Lung Cancer.* 2013;14:62–69.
15. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet.* 2009;374:1432–1440.
16. Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol.* 2011;29:3120–3125.

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BMC Cancer

RESEARCH ARTICLE Open Access

Progression-free survival at 2 years is a reliable surrogate marker for the 5-year survival rate in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy

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Abstract

Background: In locally advanced Non-Small-Cell Lung Cancer (LA-NSCLC) patients treated with chemoradiotherapy (CRT), optimal surrogate endpoint for cure has not been fully investigated.

Methods: The clinical records of LA-NSCLC patients treated with concurrent CRT at Shizuoka Cancer Center between Sep. 2002 and Dec. 2009 were reviewed. The primary outcome of this study was to evaluate the surrogacy of overall response rate (ORR) and progression-free survival (PFS) rate at 3-month intervals (from 9 to 30 months after the initiation of treatment) for the 5-year survival rate. Landmark analyses were performed to assess the association of these outcomes with the 5-year survival rate.

Results: One hundred and fifty-nine patients were eligible for this study. The median follow-up time for censored patients was 57 months. The ORR was 72%, median PFS was 12 months, and median survival time was 39 months. Kaplan-Meier curve of progression-free survival and hazard ratio of landmark analysis at each time point suggest that most progression occurred within 2 years. With regard to 5-year survival rate, patients with complete response, or partial response had a rate of 45%. Five-year survival rates of patients who were progression free at each time point (3-months intervals from 9 to 30 months) were 53%, 69%, 75%, 82%, 84%, 89%, 90%, and 90%, respectively. The rate gradually increased in accordance with progression-free interval extended, and finally reached a plateau at 24 months.

Conclusions: Progression-free survival at 2 years could be a reliable surrogate marker for the 5-year survival rate in LA-NSCLC patients treated with concurrent CRT.

Keywords: Locally advanced non-small cell lung cancer, Chemoradiotherapy, Surrogate endpoint, Overall response rate, Progression-free survival

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