厚生労働科学研究費補助金
がん臨床研究事業

再発小細胞肺がんに対する標準的治療法の確立に関する研究

平成22年度　総括研究報告書

研究代表者　後藤　功一

平成23（2011）年　4月

厚生労働科学研究費補助金
がん臨床研究事業

再発小細胞肺がんに対する標準的治療法の確立に関する研究

平成22年度　総括研究報告書

研究代表者　後藤　功一

平成23（2011）年　4月

目　　次

Ⅰ．総括研究報告

厚生労働科学研究費補助金（がん臨床研究事業）
総括研究報告書

再発小細胞肺がんに対する標準的治療法の確立に関する研究

研究代表者　後藤　功一
独立行政法人国立がん研究センター東病院
呼吸器腫瘍科呼吸器内科外来医長

研究要旨

再発小細胞肺がんに対する標準治療の確立を目的に、標準治療と見なされているノギテカン(NGT)療法に対して、我が国で新しく開発されたシスプラチン＋エトポシド＋イリノテカン(PEI)療法の優越性を多施設共同第III相比較試験において検証する。本研究は、平成19年8月にJCOG(Japan Clinical Oncology Group)プロトコール審査委員会の承認を経て、平成19年9月20日より試験を開始した。厚生労働省がん研究助成金17指-2班の参加施設を中心に組織された36施設で施設倫理委員会(IRB)の承認を得て、平成20年1月より本格的に症例登録が始まり、平成23年3月10日現在118例が登録されている。順調に症例集積中であり、今後約1年間で予定通り症例集積が完了することを目指している。

研究分担者

田村友秀	国立がん研究センター中央病院	科長
森　清志	栃木県立がんセンター	部長
岡本浩明	横浜市立市民病院	部長
山本信之	静岡県立静岡がんセンター	部長
横山　晶	新潟県立がんセンター新潟病院	副院長
樋田豊明	愛知県がんセンター中央病院	部長
今村文生	大阪府立成人病センター	部長
平島智徳	大阪府立呼吸器・アレルギー医療センター	部長
中川和彦	近畿大学医学部	教授
武田晃司	大阪市立総合医療センター	部長
木浦勝行	岡山大学大学院医歯薬学総合研究科	准教授
安宅信二	近畿中央胸部疾患センター	部長
里内美弥子	兵庫県立がんセンター	部長
西條長宏	近畿大学医学部	特任教授
瀬戸貴司	九州がんセンター	医師
工藤新三	大阪市立大学大学院医学研究科	准教授
湊　浩一	群馬県立がんセンター	医療局長
澤　祥幸	岐阜市民病院	部長

A. 研究目的

再発小細胞肺がん（初回治療が奏効して、治療終了から90日以上経過して再発を認めたsensitive relapse）を対象にして、現在の標準的治療法と見なされるノギテカン(NGT)療法に対するシスプラチン＋エトポシド＋イリノテカン療法(PEI療法)の優越性を検証することを目的とする。

B. 研究方法

全国36施設の研究グループによる多施設共同

第 III 相比較試験で、エンドポイントは生存期間である。生存期間中央値（MST）を 8 ヶ月から 12 ヶ月に向上させることを見込んでいる。

対象患者は、再発小細胞肺がん（初回治療が奏効して、治療終了から 90 日以上経過して再発を認めた sensitive relapse）であり、小細胞肺がんに対する外科的切除術の既往がなく、初回治療としてプラチナ製剤を含む併用化学療法または放射線化学療法を受けており、75 才以下、ECOG Performance Status（PS）0-2、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。

JCOG データーセンターでの中央登録、無作為化割り付けを行う。なお、割付調整因子は、PS、再発時病期、施設である。

治療内容は、NGT 療法、あるいは PEI 療法を行う。NGT 療法は、ノギテカン 1.0 mg/m^2(day1-5)、3 週間隔、4 コースとする。PEI 療法は、第 1 週目：シスプラチン(25 mg/m^2, day 1)＋エトポシド(60 mg/m^2, day 1-3)、第 2 週目：シスプラチン(25 mg/m^2, day 1)＋イリノテカン(90 mg/m^2, day 1)の 2 週間を 1 コースとして 5 コース(計 10 週）の治療法である。PEI 療法は、1 コース目の第 8 日目より G-CSF を抗癌剤投与日以外に連日投与する。

最終解析は症例集積終了 1 年後、中間解析は 1 回、安全性モニタリングは原則年 2 回。予定症例数は 180 例で集積期間は 4 年を予定している。

(倫理面への配慮)

試験治療の安全性と効果は第 II 相試験で確認済みである。また適切な症例選択規準・治療中止規準の設置により個々の患者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よう配慮した。また、ヘルシンキ宣言や米国ベルモントレポート等の国際的倫理原則および厚生労働省「臨床研究に関する倫理指針」に従い、以下を遵守する。(1)研究実施計画書（プロトコール）の施設 IRB 承認を必須とする。(2)すべての患者に説明文書を用いた十分な説明を行い、考慮の時間を設けた後、自由意思による同意を本人より文書で得る。(3)データの取り扱い上、直接個人が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（プライバシー）保護を厳守する。(4)プロトコール審査委員会、効果・安全性評価委員会、監査委員会を組織し、研究の第三者的監視を行う。

C. 研究結果

平成 18 年に厚生労働省がん研究助成金 17 指-2「呼吸器悪性腫瘍に対する標準的治療確立のための多施設共同研究」班の参加施設を中心とする全国の肺がん臨床研究の主要施設 36 施設で研究グループを組織した。

JCOG プロトコール作成支援機構および審査機構の協力を受け、JCOG 運営委員会において研究コンセプトが承認され、平成 19 年 8 月に JCOG プロトコール審査委員会の承認を経て、平成 19 年 9 月 20 日より本試験を開始した。施設 IRB の承認を得て、平成 20 年 1 月より本格的に症例登録が始まり、平成 23 年 3 月 10 日現在 118 例が登録されている。順調に症例集積中であり、今後約 1 年間で予定通り症例集積が完了することを目指している。なお、平成 22 年 9 月 11 日 JCOG 効果・安全性評価委員会の中間解析審査において本試験の継続が承認されている。

D. 考察

小細胞肺がんは全肺がんの 10-15%を占め、非小細胞肺がんに比べると化学療法や放射線療法の感受性が高く、初回治療に対する奏効率は限局型で 80-100%, 進展型で 60-80%である。しかし、80-90%の小細胞肺がんは再発を来し、5 年生存率は限局型で約 25%、進展型で 0-5%であり、小細胞がん全体の 5 年生存率は 10%未満と不良である。再発後の化学療法に対する反応は悪く、再発から死亡までの MST は 3-4 ヶ月と言われて来た。

近年、再発小細胞肺がんは、初回化学療法が奏効し、治療終了から 60-90 日以上経過して再発を認める sensitive relapse と、初回治療が奏効しない、あるいは奏効しても 60-90 日以内に再発を認める refractory relapse の 2 つに分類されて、臨床研究が行われてきた。これは、この 2 群で化学療法の効果や生存期間に差を認めるためである。例えば、NGT 療法でみると、奏効率、MST は、sensitive relapse では 14-37%、25-37 週、refractory relapse では 6-11%、16-20 週である。

現在までに再発小細胞肺がん(sensitive relapse)を対象とした 3 つの第 III 相試験が報告されている。NGT 療法とシクロホスファミド+アドリアマイシン+ビンクリスチン(CAV)療法を比較した第 III 相試験では、MST:25.0 週対 24.7 週と有意差を認めなかったが、再発に伴う症状の改善では NGT 療法が優れていた。NGT 療法の経口投与法と静脈投与法の比較試験では、奏効率、生存に有意差を認めず、毒性も同程度であった。また、NGT 療法の経口投与と無治療の第 III 相試験では、NGT 療法の有意な MST の延長(26 週対 14

週)を認めた。再発小細胞肺がんに対する標準的化学療法は確立していないが、上記3つの第III相試験の結果に基づいて、世界的にNGT療法が再発小細胞肺がんに対する標準治療とみなされている。そこで、再発小細胞肺がん(sensitive relapse)に対する標準治療の確立を目指して、NGT療法と我々が開発したPEI療法の第III相比較試験を開始した。

E. 結論

再発小細胞肺がんの予後改善を目的とした「再発小細胞肺がんに対する標準的治療法の確立に関する研究」では、「再発小細胞肺癌に対するNGT療法とPEI療法を比較する第III相試験(JCOG0605)」を平成19年9月20日より多施設共同試験として開始し、平成23年3月10日現在118例が登録され、順調に症例集積中である。

F. 健康危険情報

以下の健康危険情報を厚生労働省に報告した。

報告日	平成22年3月31日	平成22年10月1日
AE/AR/ADRの内容	消化管閉塞-結腸	下痢
Grade	4	4
因果関係が疑われる治療法	シスプラチン イリノテカン ロペラミド	シスプラチン イリノテカン エトポシド
因果関係の程度	possible	definite
発生時期	治療開始後30日以内	治療開始後30日以内
転帰	軽快	軽快
死亡の場合、因果関係の程度		

G. 研究発表

1. 論文発表

1. Niho, S., Kubota, K., Yoh, K., Goto, K., Ohmatsu, H., Nihei, K., Ohe, Y., Nishiwaki, Y. Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis. J Thorac Oncol. Inpress, 2011.

2. Suzuki, H., Hirashima, T., Kobayashi, M., Okamoto, N., Tamiya, M., Matsuura, Y., Morishita, N., Uehara, N., Matsui, K., Kawase, I. Prognosis of small-cell lung cancer since the introduction of amrubicin. Med Oncol. Published:online, 2010.

3. Ichinose, Y., Seto, T., Nishiwaki, Y., Kiura, K., Sakai, H., Yokoyama, A., Segawa, Y., Ando, M., Watanabe, K. Phase I study of topotecan and Cisplatin in patients with small cell lung cancer. Jpn J Clin Oncol. 41(2): 197-203, 2011

4. Yamaguchi, K., Shijubo, N., Kodama, T., Mori, K., Sugiura, T., Kuriyama, T., Kawahara, M., Shinkai, T., Iguchi, H., Sakurai, M. Clinical implication of the antidiuretic hormone (ADH) receptor antagonist mozavaptan hydrochloride in patients with ectopic ADH syndrome. Jpn J Clin Oncol. 41: 148-152, 2011.

5. Okamoto, I., Munakata, M., Miyazaki, M., Satoh, T., Takahata, T., Takamatsu, Y., Muto, O., Koike, K., Ishitani, K., Mukaiyama, T., Sakata, Y., Nakagawa, K., Tamura, K. Disturbance of the Growth Hormone-Insulin-like Growth Factor-1 Axis Associated with Poor Performance Status in Patients with Solid Tumors. Jpn J Clin Oncol. 40(3): 222-226, 2010

6. Yoh, K., Kenmotsu, H., Yamaguchi, Y., Kubota, K., Ohmatsu, H., Goto, K., Niho, S., Ohe, Y., Saijo, N., Nishiwaki, Y. Severe interstitial lung disease associated with amrubicin treatment. J Thorac Oncol. 5(9): 1435-1438, 2010.

7. Kobayashi, M., Matsui, K., Iwamoto, Y., Ebi, N., Oizumi, S., Takeda, K., Sawa, T., Shibata, K., Saka, H., Imamura, F., Seki, N., Saito, H., Goto, I., Nakagawa, K.; West Japan Oncology Group. Phase II study of sequential triplet chemotherapy, irinotecan and cisplatin followed by amrubicin, in patients with extensive-stage small cell lung cancer: West Japan Thoracic Oncology Group Study 0301. J Thorac Oncol. 5(7): 1075-1080, 2010

8. Ito, T., Goto, K., Yoh, K., Niho, S., Ohmatsu, H., Kubota, K., Nagai, K., Miyazaki, E., Hypertrophic pulmonary osteoarthropathy as a paraneoplastic manifestation of lung cancer. J Thorac Oncol. 5(7): 976-980, 2010.

9. Igawa, S., Watanabe, R., Ito, I., Murakami, H., Takahashi, T., Nakamura, Y., Tsuya, A., Kaira, K., Naito, T., Endo, M., Yamamoto, N., Kameyam,T. Comparison of Chemotherapy for Unresectable Pulmonary High-grade Non-Small Cell Neuroendocrine

Carcinoma and Small-Cell Lung Cancer. Lung Cancer. 68: 438-445, 2010.

10. Tomita, N., Kodaira, T., Hida, T., Tachibana, H., Nakamura, T., Nakahara, R., Inokuchi, H. The impact of radiation dose and fractionation on outcomes for limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys. 76: 1121-1126, 2010.

11. Horio, Y., Osada, H., Shimizu, J., Ogawa, S., Hida, T., Sekido, Y. Relationship of mRNA expressions of RanBP2 and topoisomerase II isoforms to cytotoxicity of amrubicin in human lung cancer cell lines. Cancer Chemother Pharmacol. 66: 237-243, 2010.

12. Park, JY., Matsuo, K., Suzuki, T., Ito, H., Hosono, S., Kawase, T., Watanabe, M., Oze, I., Hida, T., Yatabe, Y., Mitsudomi, T., Takezaki, T., Tajima, K., Tanaka, H. Impact of smoking on lung cancer risk is stronger in those with the homozygous aldehyde dehydrogenase 2 null allele in a Japanese population. Carcinogenesis. 31: 660-665, 2010.

13. Lara, P., Chamsky, K., Shibata, T., Fukuoka, H., Tamura, T., Crowbey, J., Redmeme, MW., Natale, R., Saijo, N., Gandara, DR. Common arm comparative outcome analysis of phase III trials of cisplatin + irinotecan vs Cisplatin + Etoposeide in extensive disease small cell lung cancer. Cancer. 116(24): 5710-5715, 2010.

14. Kenmotsu, H., Yasunaga, M., Goto, K., Nagano, T., Kuroda, J., Koga, Y., Takahashi, A., Nishiwaki, Y., Matsumura, Y. The antitumor activity of NK012, an SN-38-incorporating micelle, in combination with bevacizumab against lung cancer xenografts. Cancer. 116(19): 4597-4604, 2010

15. Iwasa, T., Okamoto, I., Takezawa, K., Yamanaka, K., Nakahara, T., Kita, A., Koutoku, H., Sasamata, M., Hatashita, E., Yamada, Y., Kuwata, K., Fukuoka, M., Nakagawa, K. Marked anti-tumour activity of the combination of YM155, a novel survivin suppressant, and platinum-based drugs. Br J Cancer. 103(1): 36-42, 2010.

16. Takezawa, K., Okamoto, I., Tsukioka, S., Uchida, J., Kiniwa, M., Fukuoka, M., Nakagawa, K. Identification of thymidylate synthase as a potential therapeutic target for lung cancer. Br J Cancer. 103(3): 354-361, 2010.

17. Sai, K., Saito, Y., Maekawa, K., Kim, S-R., Kaniwa, N., Nishimaki-Mogami, T., Sawada, J., Shirao, K., Hamguchi, T., Yamamoto, N., Kunitoh, H., Yamada, Y., Tamura, T., Yoshida, T., Matsunaga, Y., Ohtsu, A., Saijo, N., Mimani, H. Additive effects of drug transporter genetic polymorphisums on irinotecan pharmacokinetics/pharmacodynamics in Japanese cancer patients. Cancer Chemother Pharmacol. 66: 95-105, 2010.

18. Sai, K., Saito, Y., Tatewaki, N., Hosokawa, M., Kaniwa, N., Nishiwaki-Mogami, T., Naito, M., Sawada, J., Shirao, K., Hamaguchi, T., Yamamoto, N., Kunitoh, H., Tamura, T., Yamada, Y., Ohe, Y., Yoshida, T., Minami, H., Ohtsu, A., Matsumura, Y., Saijo, N., Okuda, H. Association of carboxylesterase 1A genotypes with irinotecan pharmacokinetics in Japanese cancer patients. Br J Clin Pharmacol. 70(2): 222-233, 2010.

19. Saijo, N., Kenmotsu, H. Recent development of molecular targeted drug in lung cancer. Intern Med. 49: 1923-1934, 2010.

H. 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

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Niho, S., Kubota, K., Yoh, K., Goto, K., Ohmatsu, H., Nihei, K., Ohe, Y., Nishiwaki, Y.	Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis.	J Thorac Oncol	Inpress		2011
Suzuki, H., Hirashima, T., Kobayashi, M., Okamoto, N., Tamiya, M., Matsuura, Y., Morishita, N., Uehara, N., Matsui, K., Kawase, I.	Prognosis of small-cell lung cancer since the introduction of amrubicin.	Med Oncol	Published	online	2010
Ichinose, Y., Seto, T., Nishiwaki, Y., Kiura, K., Sakai, H., Yokoyama, A., Segawa, Y., Ando, M., Watanabe, K.	Phase I study of topotecan and Cisplatin in patients with small cell lung cancer.	Jpn J Clin Oncol	41(2)	197-203	2011
Yamaguchi, K., Shijubo, N., Kodama, T., Mori, K., Sugiura, T., Kuriyama, T., Kawahara, M., Shinkai, T., Iguchi, H., Sakurai, M.	Clinical implication of the antidiuretic hormone (ADH) receptor antagonist mozavaptan hydrochloride in patients with ectopic ADH syndrome.	Jpn J Clin Oncol	41	148-152	2011

Okamoto, I., Munakata, M., Miyazaki, M., Satoh, T., Takahata, T., Takamatsu, Y., Muto, O., Koike, K., Ishitani, K., Mukaiyama, T., Sakata, Y., Nakagawa, K., Tamura, K.	Disturbance of the Growth Hormone-Insulin-like Growth Factor-1 Axis Associated with Poor Performance Status in Patients with Solid Tumors.	Jpn J Clin Oncol	40(3)	222-226	2010
Yoh, K., Kenmotsu, H., Yamaguchi, Y., Kubota, K., Ohmatsu, H., Goto, K., Niho, S., Ohe, Y., Saijo, N., Nishiwaki, Y.	Severe interstitial lung disease associated with amrubicin treatment.	J Thorac Oncol	5(9)	1435-1438	2010
Kobayashi, M., Matsui, K., Iwamoto, Y., Ebi, N., Oizumi, S., Takeda, K., Sawa, T., Shibata, K., Saka, H., Imamura, F., Seki, N., Saito, H., Goto, I., Nakagawa, K.; West Japan Oncology Group.	Phase II study of sequential triplet chemotherapy, irinotecan and cisplatin followed by amrubicin, in patients with extensive-stage small cell lung cancer: West Japan Thoracic Oncology Group Study 0301.	J Thorac Oncol	5(7)	1075-1080	2010
Ito, T., Goto, K., Yoh, K., Niho, S., Ohmatsu, H., Kubota, K., Nagai, K., Miyazaki, E.,	Hypertrophic pulmonary osteoarthropathy as a paraneoplastic manifestation of lung cancer.	J Thorac Oncol	5(7)	976-980	2010
Igawa, S., Watanabe, R., Ito, I., Murakami, H., Takahashi, T., Nakamura,Y., Tsuya, A., Kaira, K., Naito, T., Endo, M., Yamamoto, N., Kameyam,T.	Comparison of Chemotherapy for Unresectable Pulmonary High-grade Non-Small Cell Neuroendocrine Carcinoma and Small-Cell Lung Cancer.	Lung Cancer	68	438-445	2010

Tomita, N., Kodaira, T., Hida, T., Tachibana, H., Nakamura, T., Nakahara, R., Inokuchi, H.	The impact of radiation dose and fractionation on outcomes for limited-stage small-cell lung cancer.	Int J Radiat Oncol Biol Phys	76	1121-1126	2010
Horio, Y., Osada, H., Shimizu, J., Ogawa, S., Hida, T., Sekido, Y.	Relationship of mRNA expressions of RanBP2 and topoisomerase II isoforms to cytotoxicity of amrubicin in human lung cancer cell lines.	Cancer Chemother Pharmacol	66	237-243	2010
Park, JY., Matsuo, K., Suzuki, T., Ito, H., Hosono, S., Kawase, T., Watanabe, M., Oze, I., Hida, T., Yatabe, Y., Mitsudomi, T., Takezaki, T., Tajima, K., Tanaka, H.	Impact of smoking on lung cancer risk is stronger in those with the homozygous aldehyde dehydrogenase 2 null allele in a Japanese population.	Carcinogenesis	31	660-665	2010
Lara, P., Chamsky, K., Shibata, T., Fukuoka, H., Tamura, T., Crowbey, J., Redmeme, MW., Natale, R., Saijo, N., Gandara, DR.	Common arm comparative outcome analysis of phase III trials of cisplatin + irinotecan vs Cisplatin + Etoposeide in extensive disease small cell lung cancer.	Cancer	116(24)	5710-5715	2010
Kenmotsu, H., Yasunaga, M., Goto, K., Nagano, T., Kuroda, J., Koga, Y., Takahashi, A., Nishiwaki, Y., Matsumura, Y.	The antitumor activity of NK012, an SN-38-incorporating micelle, in combination with bevacizumab against lung cancer xenografts.	Cancer	116(19)	4597-4604	2010

Iwasa, T., Okamoto, I., Takezawa, K., Yamanaka, K., Nakahara, T., Kita, A., Koutoku, H., Sasamata, M., Hatashita, E., Yamada, Y., Kuwata, K., Fukuoka, M., Nakagawa, K.	Marked anti-tumour activity of the combination of YM155, a novel survivin suppressant, and platinum-based drugs.	Br J Cancer	103(1)	36-42	2010
Takezawa, K., Okamoto, I., Tsukioka, S., Uchida, J., Kiniwa, M., Fukuoka, M., Nakagawa, K.	Identification of thymidylate synthase as a potential therapeutic target for lung cancer.	Br J Cancer	103(3)	354-361	2010
Sai, K., Saito, Y., Maekawa, K., Kim, S-R., Kaniwa,N., Nishimaki-Mogami, T., Sawada, J., Shirao, K., Hamguchi, T., Yamamoto, N., Kunitoh, H., Yamada, Y., Tamura, T., Yoshida, T., Matsunaga, Y., Ohtsu, A., Saijo, N., Mimani, H.	Additive effects of drug transporter genetic polymorphisums on irinotecan pharmacokinetics/pharmacodynamics in Japanese cancer patients.	Cancer Chemother Pharmacol	66	95-105	2010
Sai, K., Saito, Y., Tatewaki, N., Hosokawa, M., Kaniwa, N., Nishiwaki-Mogami, T., Naito, M., Sawada, J., Shirao, K., Hamaguchi, T., Yamamoto, N., Kunitoh, H., Tamura, T., Yamada, Y., Ohe, Y., Yoshida, T., Minami, H., Ohtsu, A., Matsumura, Y., Saijo, N., Okuda, H.	Association of carboxylesterase 1A genotypes with irinotecan pharmacokinetics in Japanese cancer patients.	Br J Clin Pharmacol	70(2)	222-233	2010
Saijo, N., Kenmotsu, H.	Recent development of molecular targeted drug in lung cancer.	Intern Med	49	1923-1934	2010

Ⅲ. 研究成果の刊行物・別刷

研究代表者	後藤　功一	国立がん研究センター東病院
研究分担者	田村　友秀	国立がん研究センター中央病院
	森　　清志	栃木県立がんセンター
	岡本　浩明	横浜市立市民病院
	山本　信之	静岡県立静岡がんセンター
	横山　　晶	新潟県立がんセンター新潟病院
	樋田　豊明	愛知県がんセンター中央病院
	今村　文生	大阪府立成人病センター
	平島　智徳	大阪府立呼吸器･アレルギー医療センター
	中川　和彦	近畿大学医学部
	武田　晃司	大阪市立総合医療センター
	木浦　勝行	岡山大学大学院医歯薬学総合研究科
	安宅　信二	近畿中央胸部疾患センター
	里内美弥子	兵庫県立がんセンター
	西條　長宏	近畿大学医学部
	瀬戸　貴司	九州がんセンター
	工藤　新三	大阪市立大学大学院医学研究科
	湊　　浩一	群馬県立がんセンター
	澤　　祥幸	岐阜市民病院

Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis

Seiji Niho, MD, Kaoru Kubota, MD,* Kiyotaka Yoh, MD,* Koichi Goto, MD,* Hironobu Ohmatsu, MD,* Keiji Nihei, MD,† Yuichiro Ohe, MD,* and Yutaka Nishiwaki, MD**

Background: Pericardial effusion is defined as M1a in the Union Internationale Contre le Cancer seventh tumor, node, metastasis edition for lung cancer. The clinical course of small cell lung cancer (SCLC) with pericardial effusion but without distant metastasis (M1a) has not been adequately investigated.

Methods: The medical records of patients with SCLC treated at the National Cancer Center Hospital East between July 1992 and December 2007 were reviewed. During this period, 766 patients were newly diagnosed as having SCLC. Thirty-three of the 416 patients with limited disease (LD) SCLC (8%) had pericardial effusion. Seventy-nine patients with LD-SCLC (19%) had ipsilateral pleural effusion or dissemination. Of these, 16 patients had both pericardial and ipsilateral pleural effusion. We divided the 96 M1a patients into two subgroups: group A ($n = 33$) included patients with pericardial effusion, and group B ($n = 63$) included patients with ipsilateral pleural effusion or disseminated pleural nodules but without pericardial effusion.

Results: The median survival time among the patients with LD-M1a was 13.4 months (95% confidence interval: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively. The survival of the patients with LD-M1a was intermediate between those of the patients with LD-M0 and patients with extensive disease M1b ($p < 0.0001$). The overall survival period was not statistically different between groups A and B ($p = 0.5182$). Nineteen patients in group A received chemoradiotherapy, but only two patients survived for more than 2 years (2- and 5-year survival rate: 11% both). Twenty-six patients in group B received chemoradiotherapy, and four patients survived for more than 5 years (5-year survival rate: 18%).

Conclusions: Long-term survival was achieved among patients with SCLC with pericardial effusion but without distant metastasis who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in patients with SCLC with ipsilateral pleural effusion but without pericardial effusion or distant metastasis.

Divisions of *Thoracic Oncology and †Radiation Oncology, National Cancer Center Hospital East, Chiba, Japan.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Seiji Niho, MD, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan. E-mail: siniho@east.ncc.go.jp

ISSN: 1556-0864/11/0604-0796

Key Words: Small cell lung cancer, Limited disease, Pericardial effusion.

(*J Thorac Oncol.* 2011;6: 796–800)

Lung cancer is the leading cause of cancer-related deaths worldwide. Small cell lung cancer (SCLC) accounts for approximately 15% of all forms of lung cancer. Compared with non-SCLC, SCLC grows rapidly, quickly disseminates to the regional lymph nodes and distant sites, and is sensitive to chemotherapy with a response rate of 70 to 80%. The Veterans Administration Lung Study Group proposed a clinical two-stage system for SCLC that distinguishes limited disease (LD) and extensive disease (ED). LD is defined as being limited to one hemithorax, including mediastinal, contralateral hilar, and ipsilateral supraclavicular lymph nodes, whereas ED represents tumor spread beyond these regions.[1] The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). Conversely, ED-SCLC is treated with chemotherapy alone. The original definition of LD was a tumor volume that could be encompassed by a reasonable radiotherapy plan. According to the International Association for the Study of Lung Cancer (IASLC)'s consensus report, however, the classification of LD-SCLC includes bilateral hilar or supraclavicular nodal involvement and ipsilateral pleural effusion, regardless of whether the cytological findings are positive or negative.[2] Pericardial effusion has not been defined precisely.

In 2007, the IASLC proposed a new tumor, node, metastasis (TNM) classification for lung cancer,[3–6] and the Union Internationale Contre le Cancer (UICC) seventh TNM edition has been available since 2009. According to the UICC seventh TNM edition, malignant pleural or pericardial effusion and tumor with pleural nodules are defined as M1a, leading to stage IV. An analysis of 12,620 patients with SCLC in the IASLC database demonstrated that patients who have ipsilateral pleural effusion without extrathoracic metastases (M1a) have a survival that is intermediate between stages I and III without effusion and stage IV. Nevertheless, no information regarding the presence of pericardial effusion is available in the IASLC database.[7]

Our previous retrospective analysis also demonstrated that the survival of patients with LD-SCLC with ipsilateral pleural effusion was intermediate between those of patients with LD without ipsilateral pleural effusion and patients with

ED, and long-term survival was achieved by patients with LD-SCLC who successfully underwent definitive TRT after their ipsilateral pleural effusion had disappeared after induction chemotherapy.[8] In this retrospective study, we investigated the clinical course and overall survival among patients with LD-SCLC with pericardial effusion, compared with those among patients with ED-SCLC or LD-SCLC with or without ipsilateral pleural effusion.

PATIENTS AND METHODS

In this study, LD-SCLC was defined as disease limited to one hemithorax, including mediastinal, contralateral hilar, and supraclavicular lymph nodes, ipsilateral pleural effusion, and pericardial effusion; ED-SCLC was defined as tumor spread beyond these manifestations.

We retrospectively reviewed the medical records of patients with lung cancer treated at the National Cancer Center Hospital East between July 1992 and December 2007.

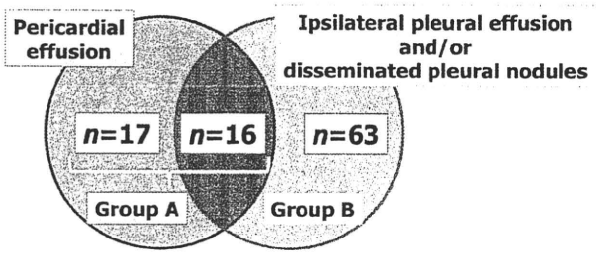

FIGURE 1. Patients with small cell lung cancer with M1a. Group A included patients with pericardial effusion, and group B included patients with ipsilateral pleural effusion or disseminated pleural nodules, but without pericardial effusion.

During this period, 766 patients were newly diagnosed as having SCLC. Four hundred sixteen patients were diagnosed as having LD-SCLC and 350 were diagnosed as having ED-SCLC using conventional staging procedures, including a medical history and physical examination, chest radiography, computed tomography (CT) scan of the chest, CT scan or ultrasound of the abdomen, bone scan, and CT scan or magnetic resonance imaging of the brain. Thirty-three of the 416 patients with LD-SCLC (8%, 95% confidence interval [CI]: 6–11%) had pericardial effusion and were included in this study. Seventy-nine of the 416 patients with LD-SCLC (19%, 95% CI: 15–23%) had ipsilateral pleural effusion or dissemination. Four patients had a disseminated mass without pleural effusion detected using CT scan. Sixteen patients with LD-SCLC had both pericardial and ipsilateral pleural effusion. Therefore, 63 patients with LD-SCLC had ipsilateral pleural effusion or dissemination without pericardial effusion. We divided the 96 M1a patients into two subgroups: group A included patients with pericardial effusion, and group B included patients without pericardial effusion. Group B patients had ipsilateral pleural effusion or disseminated pleural nodules (Figure 1).

The overall survival time was defined as the interval between the start of treatment and death or the final follow-up visit. The median overall survival time was estimated using the Kaplan-Meier analysis method.[9] Survival data were compared among the groups using a log-rank test. This study was approved by an institutional review board.

RESULTS

The patient characteristics are listed in Table 1. Eighty-three percent of the patients were male, and 81% had a performance status of 0 or 1. Fifty-four percent of the patients

TABLE 1. Patient Characteristics

	ED-SCLC (M1b)	LD-SCLC with Pericardial Effusion (M1a) (Group A)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B)	LD-SCLC (M0)
No. of patients	350	33	63	320
Sex				
Male	291	29	50	262
Female	59	4	13	58
Age (yr)				
Median	66	67	68	66
Range	28–85	37–82	46–83	22–87
Performance status				
0	22	0	4	108
1	224	25	47	190
2	63	6	9	15
3–4	41	2	3	7
Treatment delivered				
Chemotherapy	316	14	36	50
Chemoradiotherapy	25	19	26	224
Surgery + chemotherapy	0	0	0	33
Surgery alone	0	0	0	10
Best supportive care	9	0	1	3

LD, limited disease; SCLC, small cell lung cancer; ED, extensive disease.

TABLE 2. Timing of Thoracic Radiotherapy in Patients with M1a Small Cell Lung Cancer

Timing of Thoracic Radiotherapy	LD-SCLC with Pericardial Effusion (M1a) (Group A, n = 19)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B, n = 26)
Concurrently with the first course of chemotherapy	0	3
Concurrently with the second course of chemotherapy	0	4
Concurrently with the third course of chemotherapy	8	5
Concurrently with the fourth course of chemotherapy	4	0
Sequentially after chemotherapy	7	14

LD, limited disease; SCLC, small cell lung cancer.

received chemotherapy, and 38% received chemoradiotherapy. Six percent of the patients underwent surgical resection with or without adjuvant chemotherapy. Among the 96 patients with LD-M1a, all but one patient received chemotherapy (n = 50) or chemoradiotherapy (n = 45). Three patients underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. Four, 13, and four patients underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Twenty-one patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Among the group A patients, 12 patients underwent TRT concurrently with the third or fourth course of chemotherapy, and seven patients underwent TRT sequentially after chemotherapy. TRT was conducted if the pericardial effusion disappeared after induction chemotherapy. Among the group B patients, 12 patients underwent TRT concurrently with chemotherapy, and 14 patients underwent TRT sequentially (Table 2). Thirteen patients received prophylactic cranial irradiation of 25 Gy (seven patients in group A and six patients in group B).

Figure 2 shows the survival of all 766 patients with SCLC belonging to category M. The survival of patients with LD-M1a was intermediate between those of patients with LD-M0 and ED-M1b ($p < 0.0001$). Six hundred eighty-two patients have died. The median follow-up time was 65.8 months, ranging from 3.2 to 160.1 months. The median survival time among the patients with LD-M1a was 13.4 months (95% CI: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively.

Survival analyses for the subgroup of patients with LD-M1a (n = 96) are shown in Figures 3, 4 and Table 3. Overall survival was not statistically different between groups A and B (p = 0.5182). All 14 patients who received chemotherapy in group A died within 3 years. One patient in group B who received chemotherapy as an initial treatment survived for more than 5 years, but this patient received chemoradiotherapy as a second-line treatment after a local

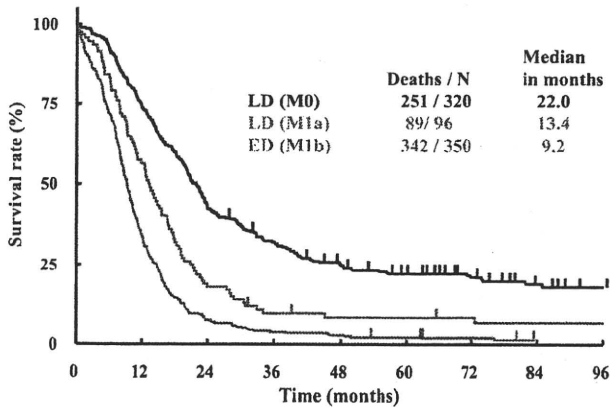

FIGURE 2. Overall survival among all 766 patients with M-category small cell lung cancer. LD, limited disease; ED, extensive disease.

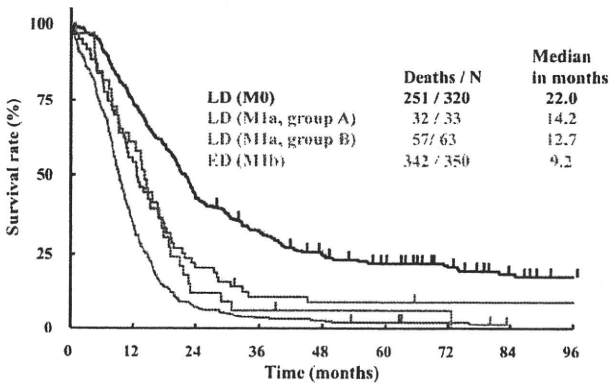

FIGURE 3. Overall survival among patients with M-category small cell lung cancer, subgroups A and B. LD, limited disease; ED, extensive disease.

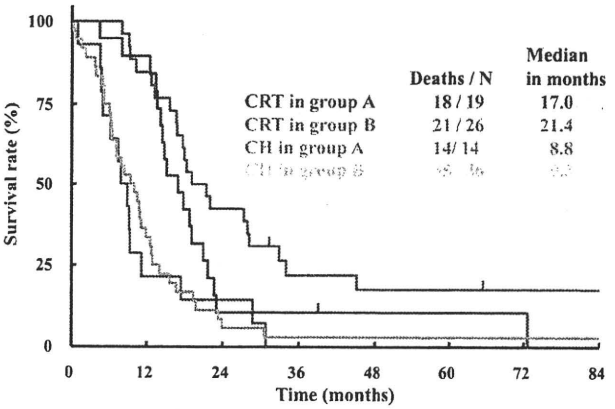

FIGURE 4. Overall survival among M1a patients with small cell lung cancer according to subgroups A, B, and initial treatment delivered. CRT, chemoradiotherapy; CH, chemotherapy.

TABLE 3. Survival Data

Subgroup	No. of Patients	Median Survival Time (mo) (95% CI)	1-yr Survival Rate (%)	2-yr Survival Rate (%)	3-yr Survival Rate (%)	5-yr Survival Rate (%)
ED (M1b)	350	9.2 (8.5–10.0)	34	7	3	2
LD (M0)	320	22.0 (20.0–23.5)	74	43	33	22
LD with pericardial effusion (group A)	33	14.2 (9.1–17.5)	61	12	6	6
Receiving CRT	19	17.0 (13.6–21.0)	89	11	11	11
Receiving Chemotherapy	14	8.8 (4.7–11.1)	21	14	0	0
LD with ipsilateral pleural effusion but without pericardial effusion (group B)	63	12.7 (10.2–16.7)	54	21	11	9
Receiving CRT	26	21.4 (16.7–28.2)	85	42	22	18
Receiving chemotherapy	36	9.3 (6.3–11.8)	33	6	3	3

CI, confidence interval; ED, extensive disease; LD, limited disease; CRT, chemoradiotherapy.

TABLE 4. Six Patients with M1a Small Cell Lung Cancer who Survived for More Than 5 yr

Age (yr)	Sex	Group	Initial Treatment	Survival Time (mo)	State
64	M	A	Chemoradiotherapy	72.6	Dead
70	F	B	Chemoradiotherapy	146.5	Alive
53	M	B	Chemotherapy[a]	140.4	Alive
73	F	B	Chemoradiotherapy	138.0	Alive
72	M	B	Chemoradiotherapy	117.0	Alive
68	M	B	Chemoradiotherapy	65.5	Alive

[a] This patient received chemoradiotherapy as a second-line treatment after a local recurrence. Therefore, all six patients received chemoradiotherapy and achieved long-term survival for more than 5 yr.

M, male; F, female.

recurrence. Four of the 26 patients who received chemoradiotherapy in group B survived for more than 5 years (Table 4). Conversely, only 2 of the 19 patients who received chemoradiotherapy in group A survived for more than 2 years. One patient developed a local recurrence at 4 years and 10 months after the initiation of first-line chemoradiotherapy and died of lung cancer 14 months later. The remaining patient also developed a local recurrence at 2 years and 9 months after the initiation of first-line chemoradiotherapy and received second-line chemotherapy. This patient was still alive at the time of the data cutoff.

DISCUSSION

This retrospective analysis demonstrated that the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) was intermediate between those of M0 and M1b patients. It is suitable that patients with ipsilateral pleural effusion or pericardial effusion belong to M1a category in the UICC seventh TNM edition. No statistically significant difference in the overall survival between M1a patients with pericardial effusion (group A) and those with ipsilateral pleural effusion but without pericardial effusion (group B) was observed. Among the patients who successfully underwent chemoradiotherapy, the patients in group B had 2-, 3-, and 5-year survival rates of 42%, 22%, and 18%, respectively, whereas the patients in group A had a 2-year survival rate of only 11%. Our previous retrospective analyses demonstrated that the median survival time of patients with cytologically positive and cytologically negative pleural effusion were 9.3 and 12.7 months, respectively. Furthermore, all 11 patients with cytologically positive pleural effusion died within 3 years.[8] Long-term survival for more than 5 years was achieved only by patients with cytologically negative pleural effusion. We speculate that an inflammatory process, such as atelectasis, causes ipsilateral pleural effusion in some patients. Conversely, most pericardial effusion is believed to be malignant. Therefore, long-term survival was seldom achieved by patients with pericardial effusion, even if they received chemoradiotherapy.

Recently, the applicability of the UICC seventh TNM edition for SCLC was investigated using the California Cancer Registry database. This database included 108 and 1518 M1a patients with pericardial effusion and pleural dissemination, respectively. No significant difference in overall survival was observed among patients with pleural or pericardial effusion (median survival time: 7 versus 7 months, 2-year survival rate: 16.7% versus 9.7%, respectively).[10] These data were comparable with our results. Nevertheless, no information regarding the treatment performed for the M1a patients was included in the previous article.

Our retrospective analysis has several limitations. First, the number of M1a patients with pericardial effusion was only 33, because only 8% of the patients with LD-SCLC exhibited pericardial effusion. Second, we did not conduct a cytological examination of the pericardial effusion. Pericardial puncture or drainage is usually performed in patients with cardiac tamponade. None of the patients in group A had cardiac tamponade; therefore, a pericardial puncture was technically difficult. Third, examination period was more than 15 years, from 1992 to 2007. Irinotecan, active for SCLC, has been commonly used from 2000 in Japan. Patients in this study were treated with a potential range of different chemotherapeutic agents during the period, which was not controlled.

Only 2 of 19 patients (11%) who received chemoradiotherapy in group A survived for more than 3 years. Con-

versely, all 14 patients who did not receive chemoradiotherapy in group A died within 3 years. TRT probably improves local control and achieves long-term survival in some patients. Definitive TRT is recommended in M1a patients with SCLC, if ipsilateral pleural or pericardial effusion has disappeared after induction chemotherapy.

In conclusion, the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) is intermediate between those of M0 and M1b patients. No statistically significant difference in the overall survival of M1a patients with pericardial effusion and those with ipsilateral pleural effusion but without pericardial effusion was observed. Long-term survival was achieved among M1a patients with pericardial effusion who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in M1a patients with ipsilateral pleural effusion but without pericardial effusion.

ACKNOWLEDGMENTS

Supported, in part, by a grant from the Ministry of Health, Labor, and Welfare for the third term Comprehensive Strategy for Cancer Control and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare, Japan.

REFERENCES

1. Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep 3* 1973;4:31–42.
2. Stahel RA, Ginsberg R, Havemann K, et al. Staging and prognostic factors in small cell lung cancer: a consensus report. *Lung Cancer* 1989;5:119–126.
3. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–714.
4. Postmus PE, Brambilla E, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2007;2:686–693.
5. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:593–602.
6. Rusch VW, Crowley J, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:603–612.
7. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol* 2007;2:1067–1077.
8. Niho S, Kubota K, Yoh K, et al. Clinical outcome of chemoradiation therapy in patients with limited-disease small cell lung cancer with ipsilateral pleural effusion. *J Thorac Oncol* 2008;3:723–727.
9. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
10. Ignatius Ou SH, Zell JA. The applicability of the proposed IASLC staging revisions to small cell lung cancer (SCLC) with comparison to the current UICC 6th TNM Edition. *J Thorac Oncol* 2009;4:300–310.

Med Oncol
DOI 10.1007/s12032-010-9623-z

ORIGINAL PAPER

Prognosis of small-cell lung cancer since the introduction of amrubicin

Hidekazu Suzuki · Tomonori Hirashima · Masashi Kobayashi · Shinji Sasada · Norio Okamoto · Motohiro Tamiya · Yuka Matsuura · Naoko Morishita · Nobuko Uehara · Kaoru Matsui · Ichiro Kawase

Received: 8 June 2010 / Accepted: 5 July 2010

Abstract Several studies have demonstrated the effectiveness of amrubicin (AMR) in small-cell lung cancer (SCLC). This study aimed to assess the change in the prognosis of SCLC before and after the commercial availability of AMR. We retrospectively analyzed data from 243 patients with newly diagnosed SCLC. Patients diagnosed before the start of the sale of AMR (January 1997–May 2002) constituted Group A, and patients diagnosed after its introduction (December 2002–December 2006), constituted Group B. The overall survival and demographic factors of the 2 groups were compared. Similar comparisons were also performed on subsets. Median survival time (MST) was 313 days for Group A and 388 days for Group B ($P = 0.031$). Group B with limited disease (LD) demonstrated a significantly longer median survival time (321 vs. 506 days; $P = 0.022$) than Group A, whereas no significant difference was noted between the groups of patients with extensive disease (ED) (296 vs. 280 days; $P = 0.895$). In the subset of refractory relapse of LD, the MST was clearly longer in Group B than in Group A (220 vs. 321 days; $P < 0.001$). Multivariate analysis for LD patients indicated that performance status (hazard ratio 2.072; $P = 0.003$) and commercial availability of AMR (0.596; $P = 0.022$) are significant factors. The present study has demonstrated prolonged survival times for LD patients since the start of the sale of AMR. The use of AMR in ED patients requires further investigations.

Keywords Amrubicin · Limited disease · Prognosis · Refractory relapse · Retrospective study · Small-cell lung cancer

Introduction

Lung cancer ranks high among the causes of cancer death in developed countries. Small-cell lung cancer (SCLC) accounts for approximately 13% of all lung cancers [1], and 5-year survival rates of SCLC remain low. The first-line therapy is cisplatin (CDDP) + etoposide (ETP) + concurrent radiotherapy in the case of the limited disease (LD) type of SCLC [2]; CDDP + ETP or CDDP + irinotecan (CPT) in the case of the extensive disease (ED) type of SCLC [3]. This disease recurs in the vast majority of patients.

Many agents have been tried in second-line treatments, although results have shown limited effectiveness. At present, topotecan (TOP) is widely used as a second-line chemotherapy in European and North American countries. However, TOP as second-line chemotherapy is not satisfactory, as it resulted in a response rate of 7% and an MST of 25.9 weeks [4]. The response rate was 26% in a Japanese phase II study in which TOP was used for patients with recurrent SCLC [5].

As a new agent for SCLC, amrubicin (AMR) became commercially available in Japan in December 2002, earlier than in the rest of the world. AMR is an anthracycline derivative and seems to exert its anti-tumor effect primarily by acting on DNA topoisomerase II to stabilize a cleavable complex [6].

H. Suzuki (✉) · T. Hirashima · M. Kobayashi · S. Sasada · N. Okamoto · M. Tamiya · Y. Matsuura · N. Morishita · N. Uehara · K. Matsui · I. Kawase
Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 3-7-1 Habikino Habikino-shi, Osaka 583-8588, Japan
e-mail: suzukih@opho.jp

Published online: 15 July 2010