group D, grade 3 or 4 leucopenia was seen in seven patients (14.6%), anorexia in three patients (6.3%), nausea/vomiting in two patients (4.2%), and hair loss in one patient (2.1%) (Table 4). No episode lasted more than 1 month.

There were no lethal adverse effects in either chemotherapy group.

Mortality

Twenty-six of 87 patients (29.9%) in group A and 14 of 85 (16.5%) in group B died of their tumours, with this difference being significant ($P=0.037$). Nine patients in group A and six in group B died of causes other than cancer, with this difference not significant ($P=0.45$).

The rate of mortality from cancer was 52.1% in group C and 42.6% in group D, with this difference not significant ($P=0.35$). The rate of mortality from other causes was 6.3% in group C and 17.0% in group D, again without significance ($P=0.10$).

DISCUSSION

UFT is an oral fluorinated dihydropyrimidine preparation which combines tegafur, a prodrug of 5-fluorouracil, with uracil, an inhibitor of dihydropyrimidine dehydrogenase, the enzyme which catalyses the metabolism of 5-fluorouracil. One reason for the effectiveness of postoperative adjuvant chemotherapy with UFT in patients with completely resected stage I lung cancer is the action of tegafur. The metabolism of tegafur results in prolongation of active levels of 5-fluorouracil, and its metabolites (GHB and GBL) promote angiogenesis (Yonekura *et al*, 1999; Basaki *et al*, 2001; Tanaka *et al*, 2002). Meta-analysis of several randomised controlled studies has confirmed that UFT is therapeutically useful. The Japan Lung Cancer Research Group (JLCRG) performed Phase III randomised controlled studies of post-operative adjuvant chemotherapy with UFT in patients with stage I adenocarcinoma of the lung, and showed significant improval in survival, with a hazard ratio of 0.71 (95% CI: 0.52–0.98) as compared with surgery alone in this subgroup ($P=0.04$) (Kato *et al*, 2004).

Our study enrolled a wider range of patients than the JLCRG study, including not only adenocarcinoma and completely resected stage I NSCLC, but also stage II and IIIA NSCLC. Survival in patients with stage I disease was significantly better in group B than in group A ($P=0.045$). On analysis by histologic tumour type, survival in patients with adenocarcinoma was slightly but not significantly better in group B ($P=0.065$). In contrast, survival in patients with diploid tumours did not differ between group A and B, probably because of the low patient numbers, which were insufficient for statistical analysis ($n=18$ and 17, respectively). The number of patients with diploid tumour was small as compared with that of patients with aneuploid tumour, and was insufficient for statistical analysis in the present study.

In stage II and III adenocarcinoma, in contrast, no difference in survival was seen either overall, or by ploidy. These results therefore suggest that UFT is effective for the management of stage I lung cancer, consistent with the findings of the WJSG 2nd study and the JLCRG study (Kato *et al*, 2004).

Early studies of DNA ploidy (Granone *et al*, 1993; Salvati *et al*, 1994; Kim *et al*, 1996) reported that aneuploidy is an independent predictor of poor outcome. In contrast, more recent investigations (Fujino *et al*, 1996; Bellotti *et al*, 1997; Reinmuth *et al*, 2000; Pelletier *et al*, 2001) have questioned the value of ploidy as a prognostic factor. Statistical analysis of the prognostic implications of diploidy was precluded in the present study owing to the low number of patients with diploid tumours (stage I, $n=35$; stage II and III, $n=18$).

With regard to the efficacy of the present therapeutic regimen, a meta-analysis of the usefulness of postoperative cisplatin-based adjuvant chemotherapy in NSCLC found good efficacy in stage II and III patients receiving cisplatin-based (320 mg m^{-2} or more) chemotherapy with vinorelbine (Pignon *et al*, 2006). In contrast, the dose of cisplatin in the present study was as low as 160 mg m^{-2} and vindesine was used as a combination drug. These differences

Table 3 Multivariate analysis of outcomes

Factor	Hazard ratio	95% CI	*P*-value
Sex			
Female	1		
Male	1.95	1.11–3.60	0.019
Age (years)			
<60	1		
⩾60	2.24	1.26–4.20	0.0053
Group			
Control	1		
UFT	0.57	0.32–0.97	0.039

Table 4 Toxicity

	UFT						CDDP+VDS+UFT				
	Grade						Grade				
Toxicity ($n=85$)	1	2	3	4	Frequency of G3 or G4 (%)	Toxicity ($n=47$)	1	2	3	4	Frequency of G3 or G4 (%)
Leucopenia	8	2	0	0		Leucopenia	8	11	5	2	14.6
Thrombocytopenia	2	0	0	0		Thrombocytopenia	3	2	0	0	
Anaemia	1	0	0	0		Anaemia	8	6	0	0	
AST	6	0	0	0		GOT	6	3	0	0	
ALT	5	2	0	0		GPT	9	4	0	0	
Anorexia	10	8	1	0	1.2	BUN	5	0	0	0	
Nausea/vomiting	8	1	0	0		Creatinine	2	0	0	0	
Diarrhoea	3	1	0	0		Anorexia	10	14	3	0	6.3
Stomatitis	4	0	0	0		Nausea/vomiting	12	4	2	0	4.2
Pigmentation	6	0	0	0		Diarrhoea	4	1	0	0	
Alopecia	0	1	0	0		Stomatitis	4	0	0	0	
						Alopecia	7	7	1	0	2.1

Abbreviations: BUN, blood urea nitrogen; CDDP, cisplatin; VDS, vindesine sulfate.

are likely associated with the insufficient efficacy seen here. Further, the response rate to UFT in unresectable NSCLC has been reported as only 8% (Keicho *et al*, 1986), and usefulness of postoperative adjuvant chemotherapy has been described for relatively early-stage NSCLC only. The possibility therefore exists that UFT may have insufficient efficacy in stage II/III disease with high malignancy.

In conclusion, although the relation between DNA ploidy pattern and the response to postoperative adjuvant chemotherapy remains unclear, our results suggest that postoperative adjuvant chemotherapy with UFT improves survival and is therapeutically useful in patients with completely resected stage I NSCLC.

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Appendix A

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- Osaka Medical Center for Cancer and Cardiovascular Diseases
- Osaka Prefectural Medical Center for Respiratory and Allergic Diseases
- Kansai Medical University
- Kansai Electric Power Hospital
- Kinki University School of Medicine
- Toneyama National Hospital
- National Kinki Central Hospital for Chest Diseases
- Sumitomo Hospital
- Takarazuka Municipal Hospital
- Kitano Hospital The Tazuke Kofukai Medical Research Institute
- Osaka City General Hospital
- Hyogo College of Medicine

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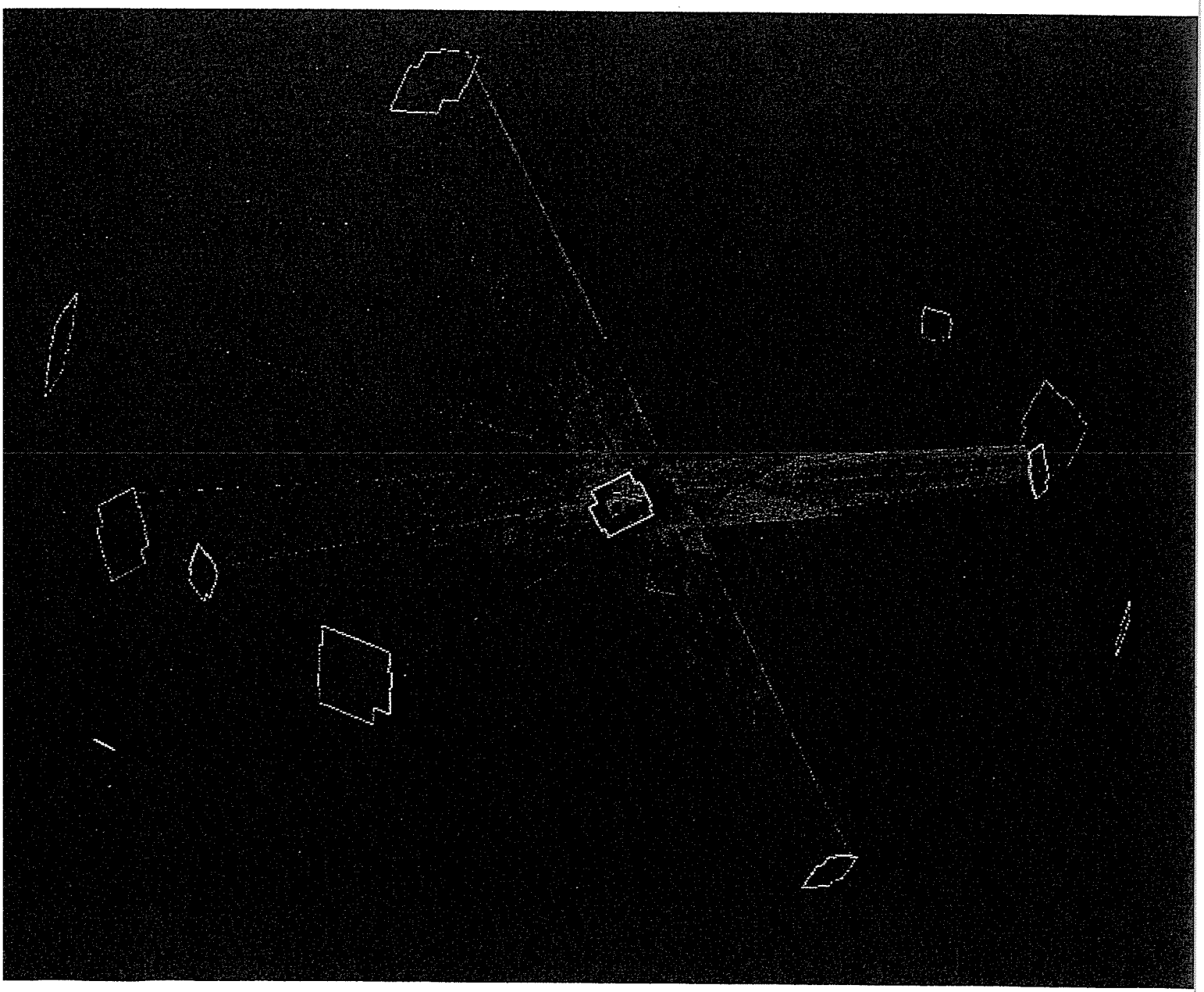
特集 **肺癌治療**

—新たな治療体系確立への展開—

エッセー/対談/トピックス



早期非小細胞肺癌の術後補助化学療法

多田弘人*

要　旨

非小細胞肺癌に対する術後補助化学療法は，長い間その有効性が確立されていなかった．2004 年以降に，新規抗癌剤を用いた補助化学療法で初めて有効であることが証明された．一方，本邦では術後補助化学療法として UFT を用いたところ，有効性が証明されている．今後，分子標的薬剤を用いた補助化学療法の試験が開始予定である．術後補助化学療法は標準治療として確立されており，今後ますます重要性は高くなるものと考えられる．

はじめに

早期非小細胞肺癌の標準治療は，外科手術である．しかしその切除成績は，甲状腺癌，乳癌，胃癌，大腸癌などと比較すると良好とは言えない．主な原因は，術後早い段階で遠隔転移を来すことである．本邦の成績でも，5 年生存率は病理病期 IB で 60.1%，IIA，IIB で 59.9%，42.2%，IIIA では 19.3% であった[1]．これらの成績を向上させるためには，何らかの化学療法を追加する必要がある．そのため，過去多くの補助化学療法が試みられた．その多くは良好な結果をもたらせることがなかったが，つい最近になって補助化学療法の効果が証明されるようになった．そのため，肺癌治療のガイドラインの改定が行われるまでになった．

しかし，エビデンスの作成過程が欧米と本邦では異なるため，ガイドラインが微妙に異なっており解釈に苦しむところである．以下に，今日の本邦で術後補助化学療法が置かれている状況について述べる．

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キーワード：術後補助療法，肺癌，シスプラチン，新規抗癌剤，比較試験

初期の術後補助化学療法

術後補助化学療法が切除単独に対して有効であることが初めて示唆されたのは，Holmes らの比較試験にさかのぼる．II～III期の症例を対象にシクロホスファミド＋ドキソルビシン＋シスプラチン（CAP）という比較的マイルドな化学療法を行うことで，無再発生存で手術単独よりも良好な結果が得られた[2]．これを契機にいろいろな術後補助化学療法の比較試験が行われたが，多くは有効性を証明することはできなかった．そのため，対象とする病期を変更したり，放射線と併用するなど，いろいろな試みがなされた（表1）．その後，CAP よりも強力であるとされているシスプラチン＋エトポシドによる術後補助化学療法も試みられたが[3]，結果的には単一の試験で

表1

A 初期の抗癌剤による術後補助化学療法の比較試験

著者	レジメン	対象 p-stage	n	MST（5年%）	p-value
Holmes[2]	CAP	Ⅱ～Ⅲ	62	NR	positive*
	BCG	Ⅱ～Ⅲ	68	NR	
Lad[15]	RT＋CAP	Ⅰ～Ⅲ	78	20mo	0.04
	RT	Ⅰ～Ⅲ	86	13mo	
Feld[16]	CAP	Ⅰ～Ⅱ	136	NR	NS
	None	Ⅰ～Ⅱ	133	NR	
Niiranen[17]	CAP	Ⅰ～Ⅲ	54	(67%)	0.05
	None	Ⅰ～Ⅲ	56	(56%)	
Ohta[4]	PV	ⅢA	90	31mo	NS
	None	ⅢA	91	37mo	
Keller[3]	RT＋PE	Ⅱ～Ⅲ	246	37.9mo	0.56
	RT	Ⅱ～Ⅲ	242	38.8mo	

B メタアナリシス以降の大規模比較試験

試験	レジメン	対象 p-stage	n	MST（5年%）	ハザード比
ALPI[7]	MVP	Ⅰ～Ⅲ	548	48mo	0.89
	None		540	55mo	
IALT[8]	P＋Any	Ⅰ～Ⅲ	932	(44.5%)	0.86
	None		935	(40.4%)	
CALGB9633[11]	Cb＋Taxol	ⅠB	173	95mo	0.80
	None		171	78mo	
JBR.10[9]	P-Nav	ⅠB～Ⅱ	242	94mo	0.69
	None		240	73mo	
ANITA[10]	P-Nav	ⅠB～Ⅲ	368	66mo	0.79
	None		367	44mo	

C UFT を用いた本邦の試験

著者	レジメン	対象 p-stage	n	MST（5年%）	ハザード比
Wada[12]	PV＋UFT	Ⅰ～Ⅲ	115	(60%)	(p=0.04)
	UFT		108	(64%)	
	None		100	(49%)	
Kato[13]	UFT	ⅠB	498	(88%)	0.71
	None		501	(85%)	
Nakagawa[18]	UFT	Ⅰ	120	(82%)	(p=0.10)
			121	(76%)	

CAP：シクロホスファミド＋ドキソルビシン＋シスプラチン，RT：放射線療法，MST：生存期間中央値，
PV：シスプラチン＋ビンデシン，PE：シスプラチン＋エトポシド，NS：not shown，
MVP：マイトマイシン＋ビンデシン＋シスプラチン，Cb＋Taxol：カルボプラチン＋パクリタキセル，
P-Nav：シスプラチン＋ナベルビン

は有効性を証明することはできなかった．

本邦では，シスプラチン＋ビンデシンという本邦での進行非小細胞肺癌に対する標準療法を用いた術後補助化学療法の比較第Ⅲ相試験が日本臨床腫瘍研究グループ（JCOG）で2本行われたが[4][5]，症例数が少なかったこ

ともあり，いずれも化学療法の有効性を証明するには至らなかった．

現実には，1995 年に BMJ にメタアナリシスとして化学療法薬の投与が切除不能非小細胞肺癌に有効であることが示されるまでは，遠隔転移を有する非小細胞肺癌は化学療法に奏効したものだけが有効であるとされていた．この際に術後補助化学療法に対するメタアナリシスも検討された結果では，シスプラチンを用いた場合 5 年生存で 4％ の生存の向上が見られるが，解析に用いることのできた約 1,300 例の症例数では統計学的に有意差を示すことができなかった[6]．

大規模比較試験

BMJ の報告のごとく，症例数を多くしないと統計学的有意差を証明できないと考えられることから，ヨーロッパでは大規模比較試験が企画された．イタリアを中心に 1994 年からマイトマイシン/ビンデシン/シスプラチンの 3 剤による化学療法の有効性をみる試験が行われ，2003 年に報告された．1,209 例が登録されたにもかかわらず，ハザード比 0.96 であり，予定どおり 3 コース投与できた割合も 69% で，補助化学療法の有効性を示すことはできなかった[7]．一方シスプラチンとビンカアルカロイドもしくはエトポシドの 2 剤を用いた比較試験が 1995 年からヨーロッパを中心に行われた．こちらは予定症例数を 3,300 例としたが，症例登録が芳しくなく，2000 年に登録が打ち切られ，2004 年に報告された．途中で登録が中止されたにもかかわらず，全体の生存で化学療法群のほうがハザード比 0.83 で，統計学的に $p=0.03$ で有意に良好な結果が得られた[8]．しかし，英国で行われたシスプラチンを用いた比較試験では症例数が 381 例だったためか，術後補助化学療法の効果を証明することはできなかった．

第 3 世代新規抗癌剤を用いた比較試験

1990 年代より，従来のビンデシン，ビンブラスチン，エトポシドよりも単剤で有効性の高い薬剤が幾つか開発された．これらはいずれも進行非小細胞肺癌に対して，シスプラチンやカルボプラチンとの併用で第 2 世代の薬剤よりも高い奏効率と生存率を残すことができた．この中でシスプラチンとビノレルビンを用いて手術単独と比較する試験が，1994 年からカナダを中心に行われた[9]．完全切除された病期 IB～II を対象として 482 人を無作為化割り付けしたところ，シスプラチン＋ビノレルビン群がハザード比は 0.69，5 年生存で 15% の向上が見られ，$p=0.012$ で有意に化学療法群の生存が勝っていた．同様の試験が同じく 1994 年からヨーロッパでも行われ，対象は完全切除された病期 I～IIIA で 840 人が登録された．この結果はカナダの試験結果と非常に似通っており，ハザード比は 0.79，5 年生存で 8.6% 化学療法群が良好であり，統計学的に $p=0.013$ と有意差があった[10]．これらの結果を受け，肺癌の術後補助化学療法は米国の NCCN ガイドラインでも，推奨すべきグレード A とされることになった．ただし，どちらの試験においても 1～2％ の治療関連死亡が観察されていた．

米国でも 1996 年から，進行肺癌に対して米国標準とされているカルボプラチン＋パクリタキセルを用いて，術後病期 IB のみを対象とした術後補助化学療法の比較試験が行われた．当時の臨床腫瘍医は術後化学療法よりも術前化学療法に魅力を感じていたためか，登録は遅々として進まなかった．その中で，当初の予定症例数は 500 例であったが，2000 年にプロトコール改訂が行われて 2 side 検定から 1 side の検定とすることとして，目標症例数を 384 例と縮小することとなった．さらに，2003 年になり中間解析を

することになったが，その時点で有意差が確認されたため 344 例の時点で症例登録が中止され，2004 年の ASCO meeting で公表された．4 年生存で 71% と 59% であり，ハザード比 0.62 で p＝0.028 と有意に化学療法群の生存が勝っており，かつ治療関連死亡も認めなかった．しかし，2006 年の ASCO で観察期間がアップデートされた結果が報告された．ハザード比 0.80 であったが統計学的には p＝0.10 で，カルボプラチン＋パクリタキセルによる補助化学療法の有効性を証明することはできなかった[11]．

UFT を用いた術後補助化学療法

本邦では，UFT を用いた術後補助化学療法の比較試験が数多く行われた．一部では有効性を証明することができなかったが，有効性を証明できたものもある．特に Wada らの報告では，切除単独とシスプラチン＋ビンデシンに UFT を追加する群と UFT 単独との 3 群比較が行われた．3 群の中で最も良好な生存を示したのが UFT 単独群であり，さらにサブセット解析で腺癌のⅠ期症例で有効性が高いことが示唆された[12]．これを受けて，腺癌のⅠ期を対象とした大規模比較試験が試みられた．腺癌完全切除例 1,000 例を対象として，切除単独と UFT 2 年間経口投与との比較試験である．この結果 5 年生存で 2.5% の生存の向上が得られ，ハザード比は 0.70 であった[13]．当時から CT による肺癌発見が増加してきたことを背景に，対象の 3/4 が病期 IA と非常に早期の症例が含まれるようになってきており，全体の生存が非常に良好であったため，生存率の差は少ないがハザード比では大きな差がついていた．この試験を含めて，UFT 単独を用いた 9 つの比較試験（2,003 人）のメタアナリシスが検討され，UFT 投与による死亡のハザード比は 0.74 であり，手術単独と比較して明らかに生存に寄与することが報告された[14]．

今後の課題

欧米では主に病期Ⅱ～Ⅲを対象に第 3 世代抗癌剤とプラチナ製剤の併用療法が標準治療とされているが，本邦では病期 IB を対象に UFT 単独が有効であるとされている．では，本邦でⅡ～Ⅲ期に対してどのような治療が良いのか，また病期 IB におけるプラチナ併用療法は本邦ではどうなのか，についての解答はない．

これらの DNA 障害性の抗癌剤による補助療法の有効性については，手術単独を対照とした比較試験によってある程度の結果が出ている．そのため，同様のレジメンでの比較試験を行うことは陳腐であると考えて，より新しい抗癌剤を用いたレジメンを模索するのか，従来の抗癌剤についてのデータをもう少し集積して確固たる結論を構築するのか，肺癌を専門とする者の考え方がいま問われている．

一方，ゲフィチニブに代表される分子標的薬は，標的分子が明確であることから奏効率の高い集団を抽出することは容易となった．そのためゲフィチニブなどのチロシンキナーゼ阻害薬について，EGFR の遺伝子変異のある肺癌を対象とした比較試験が現在立案中であり，今後数年のうちに結果が得られるものと期待される．

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Post Operative Adjuvant Chemotherapy for Early Stage Non-Small Cell Lung Cancer

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Analysis of *Epidermal Growth Factor Receptor* Gene Mutation in Patients with Non–Small Cell Lung Cancer and Acquired Resistance to Gefitinib

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Abstract

Purpose: Non–small cell lung cancers carrying activating mutations in the gene for the epidermal growth factor receptor (EGFR) are highly sensitive to EGFR-specific tyrosine kinase inhibitors. However, most patients who initially respond subsequently experience disease progression while still on treatment. Part of this "acquired resistance" is attributable to a secondary mutation resulting in threonine to methionine at codon 790 (T790M) of EGFR.

Experimental Design: We sequenced exons 18 to 21 of the *EGFR* gene to look for secondary mutations in tumors with acquired resistance to gefitinib in 14 patients with adenocarcinomas. Subcloning or cycleave PCR was used in addition to normal sequencing to increase the sensitivity of the assay. We also looked for T790M in pretreatment samples from 52 patients who were treated with gefitinib. We also looked for secondary *KRAS* gene mutations because tumors with *KRAS* mutations are generally resistant to tyrosine kinase inhibitors.

Results: Seven of 14 tumors had a secondary T790M mutation. There were no other novel secondary mutations. We detected no T790M mutations in pretreatment specimens from available five tumors among these seven tumors. Patients with T790M tended to be women, never smokers, and carrying deletion mutations, but the T790M was not associated with the duration of gefitinib administration. None of the tumors had an acquired mutation in the *KRAS* gene.

Conclusions: A secondary T790M mutation of *EGFR* accounted for half the tumors with acquired resistance to gefitinib in Japanese patients. Other drug-resistant secondary mutations are uncommon in the *EGFR* gene.

Activating mutations in the gene for the epidermal growth factor receptor (EGFR) are present in a subset of pulmonary adenocarcinomas. Tumors with *EGFR* mutations are highly sensitive to gefitinib and erlotinib, small-molecule EGFR-specific tyrosine kinase inhibitors (1–3). These mutations occur in the tyrosine kinase domain of the *EGFR* gene. Deletion mutations in exon 19 and the substitution of leucine with arginine at codon 858 (L858R) account for ~90% of all these mutations (4). *EGFR* mutations are more prevalent in women, never smokers, patients of Asian ethnicity, and those with adenocarcinoma histology (4). These features are the same as those of patients whose tumors have elevated sensitivity to EGFR-specific tyrosine kinase inhibitors. The response rates of lung cancers with an *EGFR* mutation are as high as 80% (5). Responses are often dramatic, and several reports have shown that patients with *EGFR* mutations survive significantly longer after gefitinib treatment than patients without mutations (6). However, it is also common for patients to show disease progression after presenting with an initial marked response to EGFR-specific tyrosine kinase inhibitors. The mean duration of the initial response is about 3 to 7 months (7, 8).

Recently, it has been reported by two groups that a secondary threonine-to-methionine mutation at codon 790 (T790M) of the *EGFR* gene is related to the acquired resistance to gefitinib and erlotinib (9, 10). Crystal structure modeling has shown that residue T790 is located in the ATP-binding pocket of the catalytic region of EGFR, and it seems to be critical for the binding of erlotinib and gefitinib (9). Substitution of the threonine at codon 790 with a bulkier residue, such as methionine, would result in steric hindrance to the binding of these two drugs. A secondary T790M mutation has been identified in one tumor (9) and in three of six tumors (10) with acquired resistance to gefitinib.

Imatinib is a tyrosine kinase inhibitor specific for BCR-ABL, KIT, and platelet-derived growth factor A, which is used to treat

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chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor. Analogous secondary mutations in the kinase domains of these genes are considered to constitute one of the mechanisms of acquired drug resistance (11–14). The structural similarity between ABL and EGFR tyrosine kinases is fairly high, and the most common mutation related to acquired resistance is a threonine-to-isoleucine mutation at codon 315 (T315I), corresponding to T790M in the *EGFR* gene (15). In CML, 20 to 30 other mutations of the *ABL* gene have been identified as responsible for acquired resistance to imatinib (12, 16–19), so secondary *EGFR* gene mutations other than T790M are possible (Fig. 1).

Secondary mutations of the *ABL* gene have also been detected in pretreatment samples from some CML patients, although the fraction of mutant cells was very low (16, 20). The existence of a similar mechanism is expected for non-small cell lung cancer. Furthermore, we and others have reported that the T790M mutation of the *EGFR* gene exists as a major mutation independently of gefitinib treatment, although instances are very rare (21, 22).

It has also been reported that *KRAS* mutations are associated with a lack of sensitivity to gefitinib and erlotinib (23, 24). Therefore, it is possible that acquired *KRAS* mutations are also associated with acquired resistance.

In this study, we looked for the T790M mutation and other secondary mutations of the *EGFR* gene in tumors from patients who showed disease progression after presenting with an initial response to EGFR-specific tyrosine kinase inhibitor treatment and in tumors before gefitinib treatment. We also looked for *KRAS* mutations in the same tumors.

Materials and Methods

Patients. Patients with non-small cell lung cancer who initially responded but subsequently experienced disease progression while on gefitinib treatment were defined as having "acquired resistance." A detailed definition of the effectiveness of gefitinib treatment was described in our previous study (25). Briefly, gefitinib treatment is judged to be effective when tumors show a decrease of at least a 30% in tumor diameter in imaging studies or when elevated carcinoembryonic antigen levels decrease to a level less than half the baseline level.

Fourteen tumor samples and 10 corresponding pretreatment tumor samples from eligible patients were obtained according to this definition at the time of diagnosis or treatment. The selection of patients depended only on whether a second tumor sample collected at the time of progression could be obtained. Appropriate approval from the institutional review board and the patients' written informed consent were obtained. Patient characteristics and details of the samples are shown in Table 1. All patients had adenocarcinomas, and the median duration of gefitinib treatment was 367 days (range, 69-921 days). We also analyzed the samples of 52 patients who had been treated with gefitinib for recurrent disease after they had undergone pulmonary resection. This cohort was part of our previous study, and their clinical details are described elsewhere (25).

Subcloning mutational analysis of the EGFR *gene.* Genomic DNA and total RNA (if possible) were extracted from each sample (Table 1). Exons 18 to 21 of the *EGFR* tyrosine kinase domain were amplified using PCR or reverse transcription-PCR (RT-PCR) methods. PCR for genomic DNA was done using AmpliTaq Gold (Applied Biosystems, Foster City, CA) and the following primers: exon 18, 5′-GAGGTGACCC-TTGTCTCTGTGT-3′ (forward) and 5′-CCCAAACACTCAGTGAAACAAA-3′ (reverse); exon 19, 5′-TGCCAGTTAACGTCTTCCTTCT-3′ (forward) and 5′-ATGTGGAGATGAGCAGGGTCTA-3′ (reverse); exon 20, 5′-TGAAACTC-AAGATCGCATTCAT-3′ (forward) and 5′-CATGGCAAACTCTTGCTATCC-3′

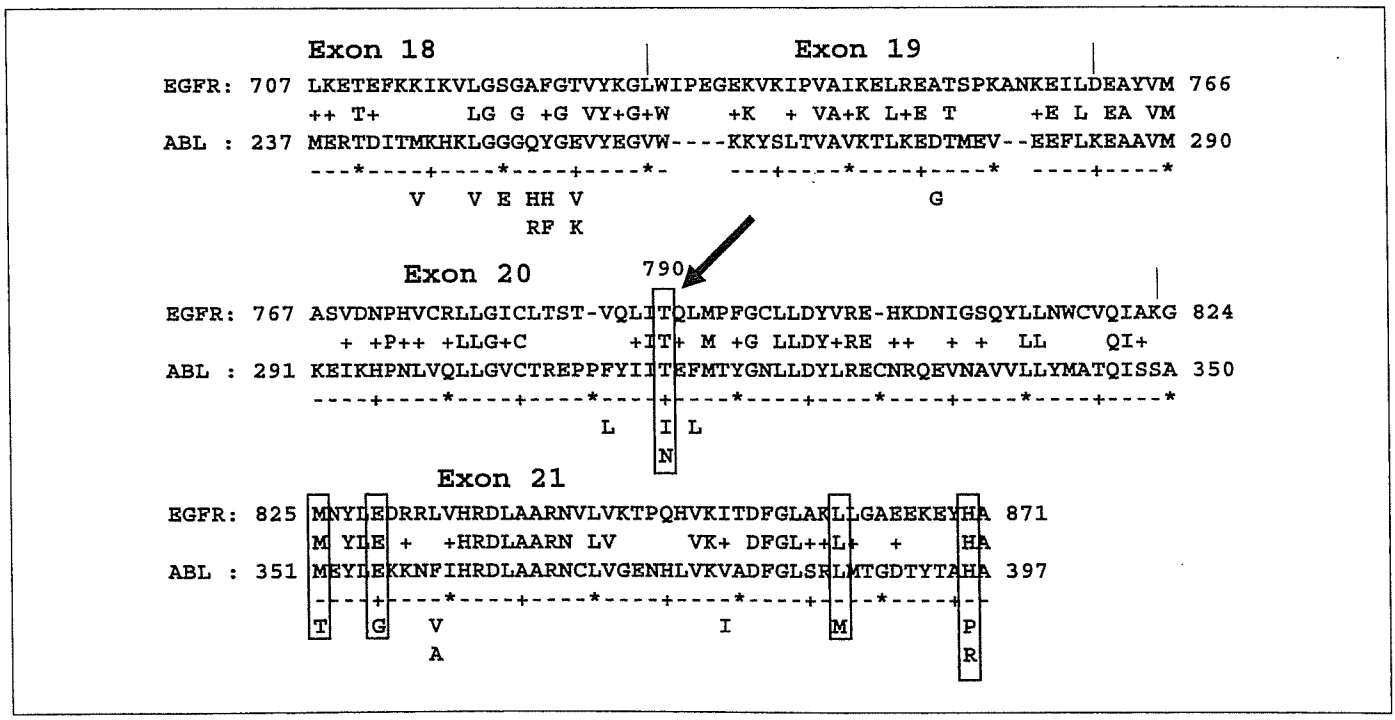

Fig. 1. Structural similarity between EGFR tyrosine kinase and ABL. This amino acid alignment was obtained using basic local alignment search tool, and both sequences were obtained from Genbank (accession nos.: EGFR, NM 005228; ABL, NM 005157). Top line, EGFR; bottom line, ABL. Vertical lines, boundaries between exons. Numbers at each end, codon numbers. Capital letters under the alignment, amino acid changes in ABL that have been reported as acquired imatinib resistance mutations. Square frames, qualifying codons as common codons in EGFR and ABL and as acquired resistance mutant codons in ABL. Arrow, location of codon 790 of EGFR and codon 315 of ABL.

Table 1. Patient characteristics and results of sequencing analysis

Patient no.	Sex	Smoking status	Prior treatment	Gefitinib response	Gefitinib treatment days	Analyzed specimen (state)	Nucleic acid	Activating mutation	T790M mutation	T790M (pre-gefitinib samples)
1	F	NS	S	E	642	LN (Fr)	RNA	Δ2	+	—
2	M	FS	S	E	368	PE (Al)	RNA	Δ3	–	—
3	M	NS	S	E	116	PE (Al)	RNA	Δ1	–	—
4	F	FS	CT	E	599	PE (CL)	RNA	Δ1	–	NA
5	F	NS	CRT	E	921	LU (Al)	RNA	Δ1	+	NA
6	F	NS	None	E	181	PE (Al)	RNA	Δ1	+	—
7	F	FS	CT	E	346	BO (Al)	RNA	Δ1	+	—
8	F	NS	S→CRT	E	623	LN (Al)	RNA	L858R	–	NA
9	M	FS	S	E	915	BR (Fr)	DNA	L858R*	–	—
10	M	FS	S→CRT	NE	69	PE (Al)	DNA	L858R	–	—
11	F	FS	None	E	560	LU (Fr)	RNA	L858R*	+	NA
12	F	NS	CT	E	239	PE (Al)	RNA	Δ1	+	—
13	F	NS	S	E	367	PE (Al)	RNA	L858R	–	—
14	F	NS	CRT	E	235	LN (Al)	RNA	Δ1	+	—

NOTE: Patients 1, 4, and 13 received gefitinib therapy twice. Pretreatment samples from patients 4, 5, 8, and 11 were not available. Patient 10 was defined as not evaluable according to our definition. However, this patient showed a 46% decrease in carcinoembryonic antigen and a marked reduction in pleural effusion on initial treatment before subsequent progression. Therefore, we regarded this case as eligible for this study.

Abbreviations: Al, alcohol fixed; BO, bone metastasis; BR, brain metastasis; CL, cell line; CRT, chemoradiotherapy; CT, chemotherapy; del, deletion; E, effective; F, female; Fr, frozen; FS, former smoker; ins, insertion; LN, lymph node; LU, lung tumor; M, male; NA, not available; NE, not evaluable; NS, never smoker; PE, pleural effusion; RT, radiotherapy; S, surgery; Δ1, del E746-A750; Δ2, del L747-P753 insS; Δ3, del L747-A750 insP.

*Patients 9 and 11 had another point mutation (L833V in patient 9 and R776H in patient 11).

(reverse); and exon 21, 5′-GAGCTTCTTCCCATGATGATCT-3′ (forward) and 5′-GAAAATGCTGGCTGACCTAAAG-3′ (reverse). The PCR conditions were as follows: 1 cycle of 95°C for 11 minutes, 45 cycles of 95°C for 30 seconds, 60°C for 30 seconds, and 72°C for 40 seconds followed by 1 cycle of 72°C for 4 minutes.

RT-PCR for RNA was done with primers 5′-AGCTTGTGGAGCCTCTTACACC-3′ (forward 1) and 5′-TAAAATTGATTCCAATGCCATCC-3′ (reverse 1) in a one-step RT-PCR setup using Qiagen OneStep RT-PCR kits (Qiagen, Valencia, CA) as described previously (26). RT-PCR conditions were as follows: 1 cycle of 50°C for 30 minutes and 95°C for 15 minutes, 40 cycles of 94°C for 50 seconds, 62°C for 50 seconds, and 72°C for 1 minute followed by 1 cycle of 72°C for 10 minutes.

The PCR products were subcloned using TOPO TA Cloning kits (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Each clone was then directly amplified with the same primers using AmpliTaq Gold and cycle sequenced using BigDye Terminator v3.1/1.1 cycle sequencing kits (Applied Biosystems). Subcloning PCR conditions were as follows: 1 cycle of 95°C for 11 minutes, 45 cycles of 95°C for 50 seconds, 62°C for 50 seconds, and 72°C for 70 seconds followed by 1 cycle of 72°C for 4 minutes.

The sequencing reaction products were electrophoresed using an ABI PRISM 3100 system (Applied Biosystems). Both forward and reverse sequences were analyzed with basic local alignment search tool, and the chromatograms were analyzed by manual review.

Cycleave real-time PCR assay. Details of the cycleave real-time PCR assay have been described previously (27). Briefly, genomic DNA was extracted, and exon 20 of the *EGFR* gene was amplified by real-time quantitative PCR assay on a SmartCycler (TaKaRa, Gifu, Japan) using Cycleave PCR Core kits (TaKaRa) with a T790M-specific cycling probe and a wild-type cycling probe. As few as ~5% of tumor cell molecules could be detected in this assay.

Mutational analysis of the KRAS *gene.* A RT-PCR direct sequence assay was done for RNA, and a cycleave real-time PCR assay was done for DNA. *KRAS* primers for PCR were 5′-GGCCTGCTGAAAATGACTGA-3′ (forward 1) and 5′-TCTTGCTAAGTCCTGAGCCTGTT-3′ (reverse 3). Codon 12 cycling probes and a wild-type cycling probe were used in cycleave real-time PCR assays. Direct sequencing was used to identify codon 12, 13, and 61 mutations.

Results

Detection of secondary mutations in the EGFR *gene or the* KRAS *gene.* For the analysis of secondary mutations, we first amplified exons 18 to 21 of the *EGFR* gene, which include the region homologous to the region of the *ABL* gene that contains all the secondary mutations thus far reported to be responsible for imatinib resistance in CML. All 14 tumors with acquired resistance had activating mutations of the *EGFR* gene, either deletion mutations, including codons 746 to 750 (nine patients), or L858R (five patients). Seven tumors had a secondary T790M mutation (Table 1; Fig. 2).

When we sequenced corresponding tumor samples that had been obtained before gefitinib treatment, the same activating mutations were always present, whereas T790M was not detected in any of the available pretreatment samples (samples for patients 4, 5, 8, and 11 were not available).

Mutant bands for T790M in the sample from patient 7 were as strong as the wild-type bands, and the mutant bands were stronger than the wild-type bands in patient 12 (Fig. 2). However, in most cases, the T790M mutant bands were weaker than the wild-type bands.

Two tumors had another point mutation as well as L858R (L833V in patient 9 and R776H in patient 11). L833 corresponds to F359 of ABL, where a secondary mutation to valine or alanine has been reported in CML (Fig. 1; ref. 12). However, the pretreatment sample of patient 9 revealed that L833V existed before treatment in the same ratio as the L858R band. The ratios of L833V and L858R bands were unchanged

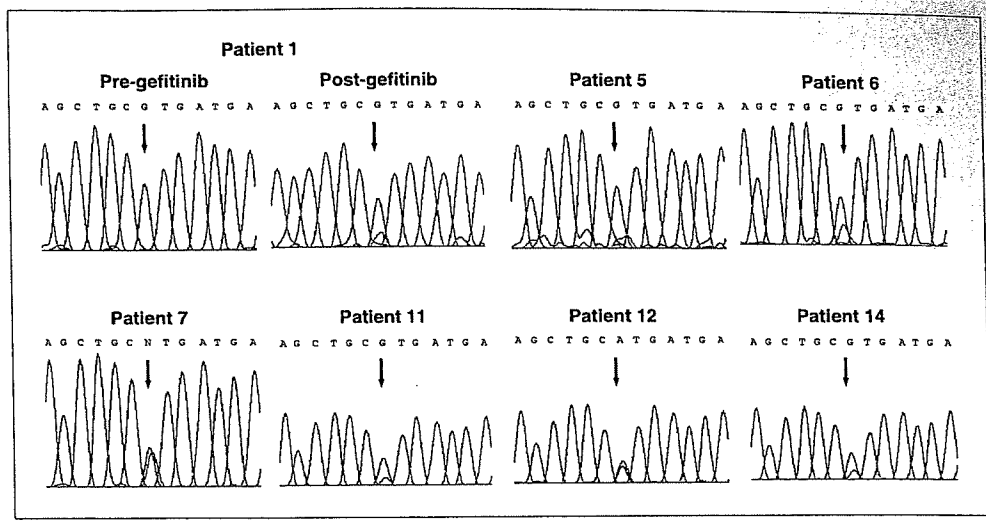

Fig. 2. Sequencing chromatograms for *EGFR* exon 20. SecondaryT790M mutations were observed in seven patients. Antisense strands of each chromatogram. Arrows, small peaks of the C→T substitution at nucleotide 2,369 (G→A on the antisense strand), which results in the T790M mutation. This substitution was observed only in posttreatment samples. T790M mutant bands were clearly detected on sequencing chromatograms, except in that of patient 5; in this patient, it was unclear because of artifacts.

before and after gefitinib treatment. Although the T790M mutant band was weaker than the L858R mutant band in patient 11, the intensity of the R776H mutant band was the same as that of the L858R mutant band and both mutations were heterozygous. We considered these point mutations to be primary mutations and not associated with "acquired" resistance.

To increase the sensitivity for the detection of T790M and other possible secondary mutations in the tyrosine kinase domain, each PCR product was subcloned and multiple subclones were amplified and sequenced directly. All the T790M mutations found by sequencing the noncloned PCR products were confirmed by this subcloning method, but no new T790M mutations were detected even when >50 clones were analyzed in samples from patients 2 and 3 (Table 2). Furthermore, we detected no secondary mutations in exons 18 to 21 other than T790M.

The T790M mutations were either present in clones with activating (or sensitizing) mutations or in other clones without activating mutations (Table 2). In three tumors (of patients 1, 5, and 14), T790M was present only in clones with activating mutations, whereas in the remaining four tumors (patients 6, 7, 11, and 12), T790M was present in both clones with and without activating mutations. No tumor carried the T790M mutation only in the wild-type clones. However, four of five T790M mutations were in clones without activating mutations in the tumor of patient 6.

We also looked for mutations in codon 12 (and codons 13 and 61 in RNA samples) in the *KRAS* gene. However, none of the samples from the tumors studied had *KRAS* mutations.

Relationship between T790M mutation and clinical and genetic features. T790M mutations were more frequent in women (women, 7 of 10; men, 0 of 4), who had never smoked (never smoker, 5 of 8; previous smoker, 2 of 6), and with deletion mutations (deletion, 6 of 9; L858R, 1 of 5). There was no difference in the incidence of T790M in the presence or absence of prior chemotherapy (with, 4 of 8; without, 3 of 6; Table 1).

We also compared the duration of gefitinib treatment, which is considered to correlate roughly with the time to progression, with the presence or absence of T790M. However, the median treatment times were almost identical (tumors with T790M, 346 days; tumors without T790M, 368 days; Fig. 3).

Analysis of corresponding tumor tissues before gefitinib treatment in patient 1. To determine whether rare T790M

Table 2. Analysis of acquired mutation using the subcloning method

Patient no.	Activating mutation	Total clones	Activating mutant clones		Wild-type clones	
			With T790M	Without T790M	With T790M	Without T790M
1	Δ2	21	8	10	0	3
2	Δ3	54	0	52	0	2
3	Δ1	51	0	50	0	1
4	Δ1	21	0	13	0	8
5	Δ1	51	3	39	0	9
6	Δ1	47	1	17	4	25
7	Δ1	20	4	5	1	10
8	L858R	18	0	14	0	4
9	L858R	20	0	14	0	6
10	L858R	20	0	5	0	15
11	L858R	21	5	10	1	5
12	Δ1	23	11	9	1	2
13	L858R	21	0	8	0	13
14	Δ1	19	7	8	0	4

mutant clones existed before gefitinib treatment, we analyzed the corresponding tumor tissues of patient 1, whose tissue after gefitinib treatment had a secondary T790M mutation. Tumor tissue was obtained at the time of operation. PCR products from the tumor before gefitinib treatment were subcloned, and 103 subclones were amplified and sequenced directly. However, at this sensitivity, we detected no clone carrying the T790M mutation. Among 103 clones, 92 (89%) had activating deletion mutations, suggesting that the mutant allele was amplified before gefitinib treatment. The incidence of clones with deletional mutations was similar (18 of 21, 85%) in a cervical lymph node taken after gefitinib resistance had developed.

To further explore of possible association of T790M with metastatic spread, we looked for the T790M mutation in hilar and mediastinal lymph nodes with metastases dissected at the time of surgery. Genomic DNA was extracted from lymph nodes from four stations (aortopulmonary, ascending aorta, main bronchus, and intrapulmonary) and analyzed using cycleave real-time PCR. However, we detected no T790M mutations.

Analysis of tumors for T790M before gefitinib treatment in 52 patients who were treated with gefitinib. The possible presence of T790M at a low frequency in tumors before gefitinib treatment might affect the tumor response or the time to progression after gefitinib treatment. In a previous study, we sequenced exons 18 to 23 of the *EGFR* genes of 52 patients who had been treated with gefitinib for recurrent disease after they had undergone pulmonary resection. None of them had the T790M mutation. Here, we used a cycleave real-time PCR assay, which is more accurate analysis than normal sequence, to investigate whether rare T790M mutant cells were present. However, we detected no T790M mutations in these 52 tumors.

Discussion

We studied 14 tumors with acquired resistance to gefitinib for secondary mutations occurring in the *EGFR* tyrosine kinase domain. Seven of the 14 tumors had a secondary T790M mutation, an incidence consistent with those of previous studies (9, 10). Whereas clones with activating mutations (deletion or L858R) might well have been eliminated by selection pressure during gefitinib treatment, those clones were always present in tumors that developed acquired resistance. In most cases, clones with the T790M mutation were not predominant.

The T790M mutations occur more frequently in women who had never smoked and who had a deletion-type mutation. Time to progression did not differ between tumors that acquired secondary T790M mutations and those that did not. However, these tendencies require careful interpretation because of the number of samples was small.

In a previous report, Kobayashi et al. (9) showed that the T790M mutation was observed with either wild-type or deletion mutation sequences, whereas Pao et al. (10) showed that both the T790M and L858R mutations were in the same allele. Our data showed that three samples had the T790M mutation only in the clones with activating mutation and four samples had the T790M mutation in the clones with and without activating mutation, whereas the most of T790M mutation was in the clones with activating mutation, except for

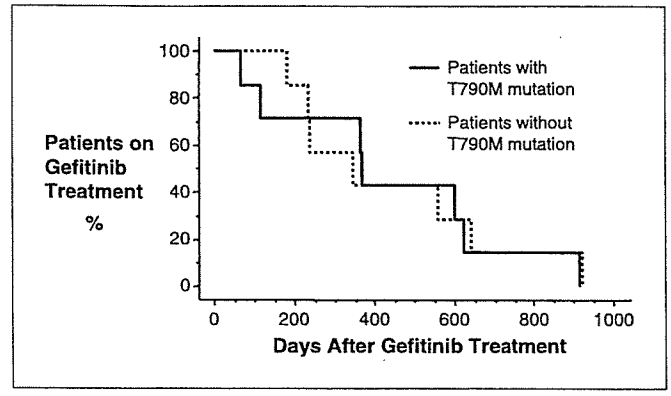

Fig. 3. Effect of the T790M mutation on the length of gefitinib treatment. The length of gefitinib treatment was considered to be roughly related to time to progression. Median treatment times were almost identical in both the presence and absence of the T790M mutation.

the samples of patient 6. It is possible that this could result from a PCR error or DNA repair error at the subcloning step. Bell et al. (28) have reported that artifactual PCR-generated allelic separation occurred with probability of ~30% in their analysis. However, it is also possible that the T790M mutation occurs in both alleles or that tumor heterogeneity exists.

In CML, 20 to 30 mutations in the *ABL* gene are responsible for acquired resistance to imatinib. Many types of mutations have been detected, and there are four distinguishable clusters (P-loop, T315, M351, and A-loop; ref. 29). Furthermore, secondary mutations in the ABL kinase domain are found in 50% to 90% of patients (29), many more than in patients with non-small cell lung cancer. We detected no novel mutations in the *EGFR* gene other than T790M. Two tumors had another point mutations together with L858R, L833V, or R776H. We considered these point mutations to be primary mutations and not associated with acquired resistance. However, these conclusions were based only on sequencing and subcloning methods, and we have no evidence of the functional effects of these mutations. There may be differences in the mechanisms of acquired resistance between non-small cell lung cancer and CML.

We previously reported that, in a series of 397 unselected patients with non-small cell lung cancer who had undergone surgery, 2 female patients with no history of smoking had L858R plus T790M mutations (21). Because these patients were not treated with gefitinib, T790M might well have conferred a growth advantage. These tumors were aggressive and later developed recurrent disease. One was treated with gefitinib but was refractory to treatment. A similar case was reported by another group (22). Inspired by this observation and because the secondary mutations related to imatinib resistance in CML were detected at low frequencies (0.01-0.9%) in pretreatment samples (16, 20), we attempted to detect minor clones with the T790M mutation in samples before gefitinib treatment. However, we could not detect the T790M mutation by assays that can detect mutant cells if there is about 1% to 5% at least. It remains unclear whether a more sensitive method would have detected rare clones with the T790M mutation in our samples.

Why tumors with T790M mutant cells acquire resistance to gefitinib despite the fact that mutant band for the T790M

mutation was almost always weaker than wild-type band remains unclear. It is possible that cells with the T790M mutation preexist at a very low frequency and gradually increase during gefitinib treatment by clonal selection as in cases of CML (16). It is also possible that amplification of the activating mutant allele occurs in resistant tumors and parts of them have the T790M mutation. Another possibility is that multiple coexisting mechanisms, including the T790M mutation, cause acquired resistance cooperatively or independently. A recent study suggested that increased internalization of ligand-bound EGFR is one of the mechanisms underlying acquired gefitinib resistance (30). It is also likely that *EGFR* gene amplification (31) by alteration of downstream molecules, such as AKT (32), might play a role in the acquisition of resistance to gefitinib.

Mutations in *KRAS* are associated with a lack of sensitivity to gefitinib and erlotinib (23). We looked for *KRAS* mutations because of the possibility that acquired *KRAS* mutations are associated with acquired resistance. There were no *KRAS* mutations in any tumor. The same finding has been reported in a previous study (10), suggesting that *KRAS* mutations are not associated with acquired resistance.

In conclusion, half of tumors with acquired resistance to gefitinib had secondary T790M mutations. No novel mutations in the *EGFR* gene were present in contrast to CML.

Acknowledgments

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AN EXTREMELY SOLID VARIANT OF ADENOID CYSTIC CARCINOMA ARISING IN THE LOWER TRACHEA

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Summary

A 54-year-old Japanese man consulted our hospital because he was diagnosed as having pneumoconiosis on a medical check up. Bronchoscopic examination showed a buldging endobronchial polypoid lesion in the right. main stem bronchus and partial polypectomy was performed. Histological examination showed that the tumor was composed of large solid sheets of medium sized tumor cells with moderate nuclear pleomorphism and lacked the characteristic cribriform or cylindromatous pattern. Small tubules or cystic spaces, which contained pale eosinophilic fluid or hyalinized stromas, were present within tumor sheets. Immunohistochemically, S-100 and smooth muscle actin were positive for tubular or peritubular areas. So a provisional pathologic diagnosis for polypectomy specimen was salivary gland-like carcinoma of low grade malignancy. The tumor was surgically resected. In a peripheral small area corresponding to 0.1% of tumor, a few cribriform nests containing basophilic mucoid materials were recognized. Taken together, the pathologic diagnosis was an extremely solid variant of adenoid cystic carcinoma arising in the lower trachea.

Key words : Adenoid cystic carcinoma, Solid variant, Trachea

Introduction

Adenoid cystic carcinoma (ACC) is the most common salivary gland-like tumor occurring in the lower respiratory tract and usually arises in the lower trachea, main stem bronchi or lobar bronchi[1)]. ACC is classified into tubular, cribriform and solid histological subtype[2-4)] and the presence of characteristic cribriform or cylindromatous growth pattern serves to confirm the correct pathologic diagnosis for ACC[5)]. However, there are a few circumstances that may induce difficulties in the pathologic diagnosis by the lack of the distinctive cribriform or cylindromatous growth pattern. In the present case, we encounted ACC showing an extremely solid growth pattern with cribriform nests rarely seen in less than 0.1% of tumorous area and without cylindromatous pattern. We had great difficulty in establishing a pathologic diagnosis by preoperative polypectomy specimen that showed tumorous

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large solid cell sheets that entirely lacked cribriform or cylindromatous pattern histologically. We herein report a rare case of extremely solid variant of ACC arising in the lower trachea and discuss the differential pathologic diagnosis and the key to making an accurate diagnosis.

Case Report

A 54-year-old Japanese man consulted our hospital after he was diagnosed as having pneumoconiosis on a medical check up. On bronchoscopic examination, polypoid tumor at the anterior wall of right main bronchus adjacent to carina was incidentally revealed. Endoscopically, the tumor presented as a buldging endobronchial polypoid lesion with a smooth surface (Fig.1). Bronchoscopic partial polypectomy was performed and a provisional pathologic diagnosis was made as salivary gland-like carcinoma of low-grade malignancy. Clinically, metastases were not found in any other organs or lymph nodes. Laboratory tests including serum CEA, NSE and CYFRA were in the normal range. The tumor was completely resected at Osaka City General Hospital.

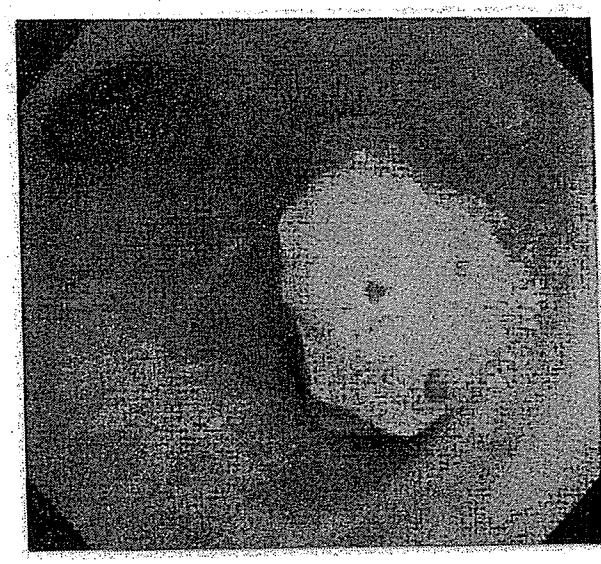

Fig. 1. Bronchial endoscopy showing a buldging endobronchial polypoid lesion with a smooth surface arising in the right main bronchus adjacent to the carina.

Pathologic Findings

I. Polypectomy specimen: Polypectomy specimen showed that the tumor was composed of large solid sheets with occasional cystic spaces (Fig.2). Large solid cell sheets consisted of medium sized tumor cells with moderate nuclear pleomorphism and inconspicuous nucleoli. Numerous small tubules in variously sized and large cystic spaces, which contained pale eosinophilic fluid or hyalinized stroma, were recognized within the sheets (Fig.3). Vacuolated cells or spindle cells were sometimes seen. Mitoses ranged from 6 to 7 per 10 high-power fields. There were no hemorrhagic or necrotic areas. The tumor lacked the characteristic cribriform or cylindromatous pattern of conventional ACC and had little stroma other than intraluminal hyalinized structures. Immunohistochemically most tumor

Fig. 2. Large solid tumor cell sheets with occasional cystic spaces.

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呼吸器 common disease の診療

肺癌のすべて

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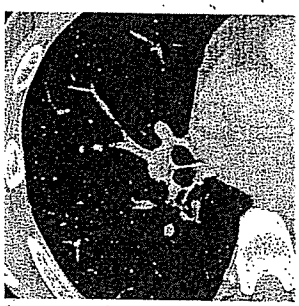

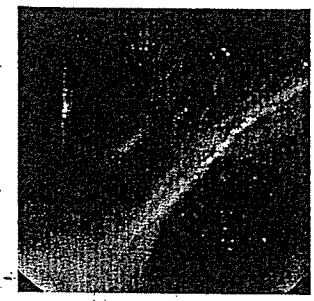

common disease

文光堂

解説

2. 術前治療

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●Key Words
neoadjuvant chemotherapy, induction chemotherapy, non-small cell lung cancer, mediastinal lymph-adenopathy

はじめに

非小細胞肺癌の切除成績を向上させるには，局所効果を向上させることと遠隔転移を抑制することが必要である．そのために，術前後の放射線療法や術後化学療法が各種試みられた．しかし，術前後の放射線治療はむしろ有害事象を招くだけで生存に寄与することはないとされている．また，化学療法も2002年までは比較試験によってその効果を証明することができなかった[1]．

そこで，化学療法をより効果的に行う手段として術前治療が注目されるようになった．手術前であるため，投与時期がより早く，また全身状態が良好であることから化学療法の効果がいっそう強く発揮されるものと考えられた．しかし，治療方法としては手術がもっとも根治性が高いものであることや術前治療を行うことによる合併症の増加も予想されるために，対象は手術だけでは治癒率の低い局所進行肺癌から始められた．臨床的に縦隔リンパ節転移が認められる場合には，手術単独では5年生存率で10%未満であると報告されており[2～4]，縦隔リンパ節転移陽性の集団を対象とすることが多い．

Ⅰ．局所進行肺癌（stage ⅢA-ⅢB）

1．初期の術前化学療法（表1）

1980年代に，stage ⅢA-ⅢBを対象として術前の化学療法のfeasibility studyが数多くなされた．一部では化学療法に放射線治療を追加することも行われた．

1990年代になり，BurkesらやMartiniらは手術適応が困難であると考えられる縦隔リンパ節転移陽性症例を対象にしてMVPを用いた術前治療を報告した[5,6]．奏効率は64～77%と高く切除率も56～(
であり，MSTで19ヵ月という結果が得られた．
の結果は，縦隔リンパ節転移陽性症例は切除対象
除くべきであるという中で発表されたものであっ
め，世界的に大きなインパクトを与えた．その後，
くの施設で術前化学療法が行われたがいずれも第
試験であり，臨床試験の目的としては安全性と効
みることが目的であった[7～9]．

2．術前化学療法の比較試験（表2）

術前化学療法を行うことの意義を観察するため
術単独との比較試験は必須であると考えられる
年代に米国とスペイン[10～12]から三つの比較試験
告された．ⅢA期を対象としN2を多く含む集団
術前化学療法をする群としない群に無作為に割り
て比較をしたものである．それぞれの試験におい
除単独の成績に隔たりは大きいが，いずれも術前
療法施行群が良好な予後を示したため，どの試験
間解析の段階でearly stoppingになった．

本邦でもJCOGで，術前化学療法を行うか否
比較試験が縦隔鏡検査でリンパ節転移が陽性であ
とが判明した症例を対象に行われた．症例登録が
ないために途中で試験の中断を余儀なくされたが
の解析結果では両群間に全く差を認めなかった[13]
れは，症例数が少なかったために有用性を検証て
かった可能性は否定できないが，本邦の外科医の
治療に対する考え方を揺るがしたといえよう．

化学療法は一般的に早期症例の方が効果を得や
すいと考えられている．そのため，Depierre
ⅠB-ⅢAまでの症例を対象に術前化学療法に続
切除をするものと手術単独を比較した[14]．結果に
効率は64%と高く，全体では予後に差を認めな

【表1】術前化学療法

source	stage	n	chemotherapy	response rate	resection rate	MST (survival)
Burkes [5]	ⅢAN2 ⅢBN2	39	MVP×2～3	64%	56%	19mo. 26%：3yr
Martini [6]	ⅢAN2	136	MVP×2～3	77%	65%	19mo. 28%：3yr
Darwish [7]	ⅢAN2	46	PE×2～3	82%	72%	24.5mo. 53%：2yr
Elias [8]	ⅢAN2	34	PFL×3	65%	82%	18mo.
Sugarbaker [9]	ⅢAN2	74	PVb×2-ope-RT	88%≧NC	62%	NR 23%：3yr

【表2】術前化学療法の比較試験

author	treatment	stage	n	CR＋PR	MST (mo.)	p-value
Pass [10]	PE-ope-PE ope-PE	ⅢA, N2	13 14	62%	29 16	0.095
Rosell [11]	MIP-ope-RT ope-RT	ⅢA	30 30	60%	26 8	<0.001
Roth [12]	CEP-ope-CEP ope	ⅢA	26 32	35%	64 11	<0.018
Nagai [13]	MVP-ope ope	ⅢA, N2	30 30	28%	17 16	0.52
Depierre [14]	MIP-ope-MIP-(RT) ope-(RT)	ⅠB-ⅢA	179 176	64%	36 26	0.11
Pisters [16]	CbTaxol-ope ope	ⅠB-Ⅱ	168 167	41%	47 40	0.32

たが，c-n0-1のサブセットでは術前化学療法施行群の方が良好であった．Pistersらは，stage ⅠB-Ⅱを対象に2コースのCBDCA＋paclitaxelを行った後手術を行う2相試験を行った[15]．56%の症例でPRが得られ，86%で完全切除が行われた．これらの結果を受けて，より早期の症例を対象とした切除単独と術前治療後の切除との比較試験が各国で企画され進行中である．

米国ではCBDCA＋paclitaxelを術前に3コース行う群と切除単独の比較試験が行われていたが（S-9900）[16]，術後化学療法が有効であると報告が相次いだために症例集積の途中で試験は中断された．その中間解析が2005年のASCOで報告された．臨床病期ⅠB-Ⅱを対象に，術前にCBDCA＋paclitaxelを3コース行ってから手術するか，いきなり手術を行うかの比較3相試験である．1999年から2004年までに354例が登録され，168例が化学療法群で167例が切除単独群であった．奏効率は41%で切除率はおのおの94%と89%であった．前治療により腫瘍の遺残を認めなかったものが10%にみられた．MSTは47ヵ月と40ヵ月で術前化学療法の方が予後良好の傾向ではあるが統計学的有意差は認められなかった．今後の経過観察の結果が期待される．しかし，術後補助療法の成績と比較して非常に優れているとは考えがたい．米国では，術前化学療法と術後化学療法の比較試験が検討されているが，いまだ開始はされていない．

Ⅱ. 術前放射線化学療法

1. Pancoast肺癌

Pancoast症候群は，本来Horner症候群，腕神経叢症状，胸痛を3徴とする腫瘍をいう．一方，Pancoast肺癌は第2肋骨よりも上方の肺尖部に発生し，胸壁浸潤をきたしているものをいい，superior sulcus tumorともいわれる．1960年代に，放射線治療を行った後に切除することにより成績が向上することが報告され[17]，その後放射線治療後に手術を行うことが標準的であると考えられるようになった．近年ではCDDP＋VP-16に放射線治療45Gyを照射した後手術を行う多施設共同試験が行われ，pathological CRが32%にみられMST 33ヵ月，5年生存率41%