Synchronous double primary lung cancers with different response to pemetrexed

Shigeki Umemura[a,b], Hiromichi Yamane[a], Takuya Yano[c], Toshiko Hoshika[c], Yasuhiro Shiote[a,b], Nagio Takigawa[e], Toshimitsu Suwaki[b], Atsuko Shirakawa[d] and Haruhito Kamei[a,b]

We describe the case of a 74-year-old male patient with synchronous double primary lung cancers: adenocarcinoma in the right lower lobe and squamous cell carcinoma in the left upper lobe (LUL). These tumors were difficult to differentiate radiographically from a single metastatic primary cancer, but their eventual diagnoses were triggered by their responses to chemotherapy, which included pemetrexed. After two courses of chemotherapy with pemetrexed and carboplatin, the right lower lobe mass had partially resolved; however, the LUL mass had increased. When S-1 was used as fourth-line chemotherapy, the size of the LUL mass decreased. Pemetrexed is a potentially useful drug for treating nonsquamous cell carcinoma, but may not be appropriate in cases with a coexisting squamous cell carcinoma. Our experience with this interesting case leads us to propose that S-1 monotherapy may provide a treatment option in pemetrexed-refractory cases. ***Anti-Cancer Drugs*** **22:473–476 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2011, **22:**473–476

Keywords: chemotherapy, lung cancer, nonsmall cell, pemetrexed, S-1, second primary, synchronous neoplasms

Departments of [a]Clinical Oncology, [b]Respiratory Medicine, [c]Pharmacology, [d]Pathology, Sumitomo-Besshi Hospital, Niihama and [e]Department of Respiratory Medicine, Okayama University Hospital, Japan

Correspondence to Shigeki Umemura, MD, PhD, Department of Clinical Oncology, Sumitomo-Besshi Hospital, 3-1 Ohji-cho, Niihama 792-8543, Japan
Tel: +81 897 377111; fax: +81 897 377121;
e-mail: ume-fuji@nifty.com

Received 11 December 2010 **Revised form accepted** 14 January 2011

Introduction

It is difficult to clinically distinguish a second primary carcinoma from a metastatic lesion arising from the first tumor [1], especially when emphysema coexists. Here, we report an interesting case of a patient harboring synchronous double primary lung cancers. The tumors were difficult to differentiate radiographically from a single metastatic primary cancer. However, the patient's response to chemotherapy, which included pemetrexed, led to the diagnosis of two histologically distinct tumors. Although most synchronous double primary lung cancers consist of the same cell types, only rarely do cases arise with double primary lung cancers with different histology, such as an adenocarcinoma and a squamous cell carcinoma [2]. Little evidence on drug selection in these cases exists due to the very small numbers of similar cases.

The survival rates of patients with adenocarcinoma have significantly improved recently due to the introduction of more effective treatments, and pemetrexed has proven to be particularly effective in nonsquamous cell lung cancers. It is clear that different histological subtypes of non-small cell lung cancer (NSCLC) show varying response to pemetrexed therapy [3]. Therefore, it is particularly difficult to choose a chemotherapy regimen for cases such as those described above. We reasoned that the responses to chemotherapy in the patient described here, harboring two histologically distinguishable tumor masses, may provide new insights for designing chemotherapeutic protocols for cases with synchronous double primary NSCLCs or single primary NSCLC with a heterogeneous histology.

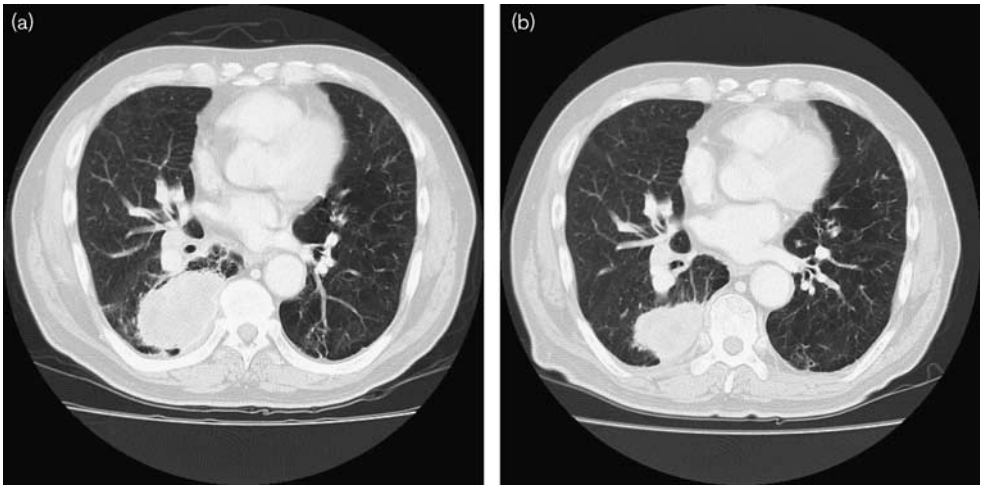
Case report

A 74-year-old male patient was admitted to our hospital because of a productive cough lasting 1 month. He had a smoking history of 56 pack-years. X-ray and computed tomography of the chest showed an oval mass in the right lower lobe (RLL, Fig. 1a), a round mass in the left upper lobe (LUL, Fig. 2a), a mediastinal lymph node swelling, and bilateral emphysema. The RLL mass was much larger than the LUL mass. Therefore, the RLL mass was considered as the major primary tumor, and the LUL mass was initially considered as a metastatic lesion. Transbronchial biopsy and subsequent sequence analysis of the right lower bronchus showed a poorly differentiated adenocarcinoma (Fig. 3) lacking detectable epidermal growth factor receptor (EGFR) mutations. A mediastinal lymph node was also enlarged, suggesting that radical treatment would not be beneficial.

Therefore, the patient was treated with two cycles of first-line chemotherapy tailored for the main primary RLL tumor: pemetrexed (500 mg/m^2, day 1, every 3 weeks) and carboplatin (area under the curve 5, day 1, every 3 weeks). After two cycles, the sizes of the RLL

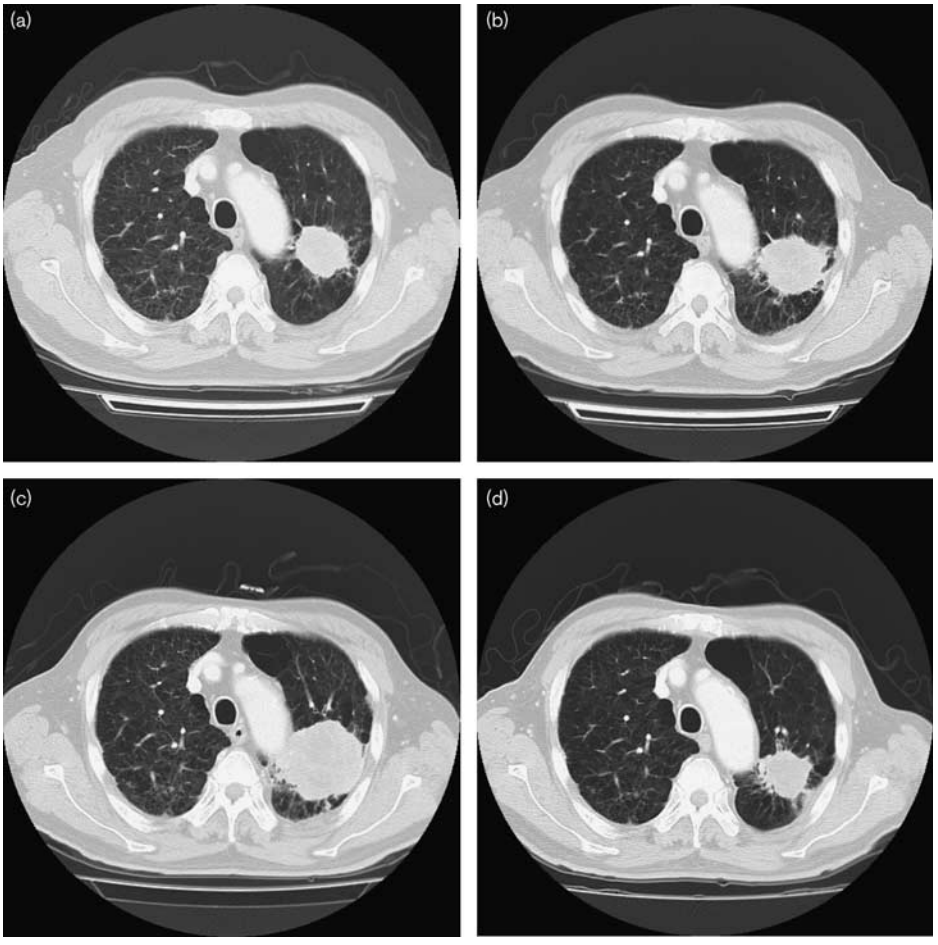
0959-4973 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e328344a964

Fig. 1



Computed tomographic scan showing (a) a large oval mass in the right lower lobe (b) reduced size of mass after two cycles of pemetrexed and carboplatin.

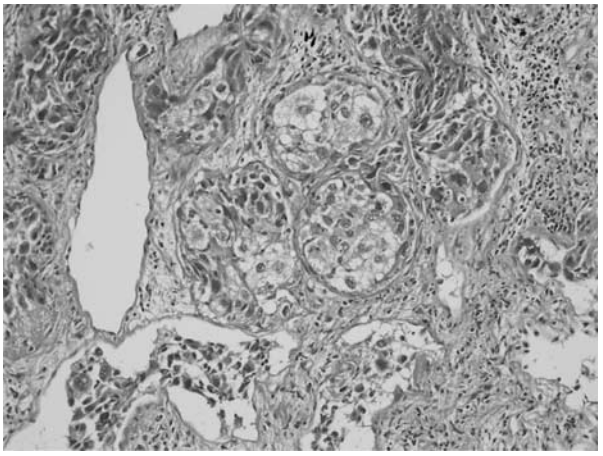
Fig. 2



Computed tomographic scan showing (a) a round mass in the left upper lobe; (b) increased size of mass after two cycles of pemetrexed and carboplatin; (c) more increased size of mass before treating with S-1 monotherapy; (d) reduced size of mass showing partial response after four cycles of S-1.

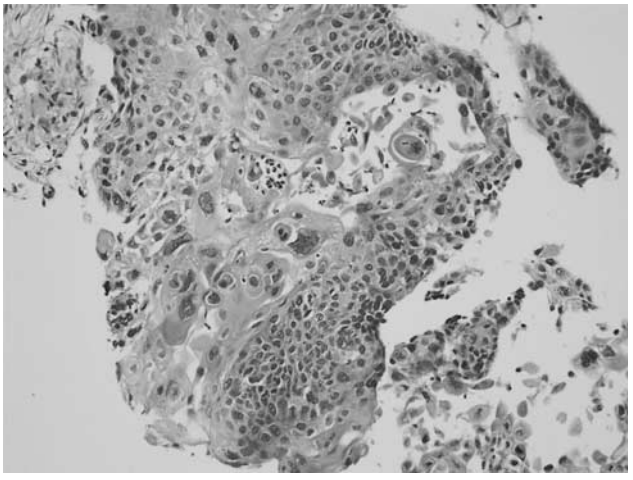
mass (Fig. 1b) and mediastinal lymph node were markedly reduced, indicating a partial response; however, the size of the LUL mass increased (Fig. 2b). Considering the specificity of this protocol, the LUL mass was suspected to differ histologically from the RLL mass. Next, we performed transbronchial biopsy and sequence analysis of the LUL mass, which showed a squamous cell carcinoma (Fig. 4) lacking detectable EGFR mutations. The patient next received one cycle of second-line chemotherapy: gemcitabine (1000 mg/m^2, days 1 and 8, every 3 weeks) and carboplatin (area under the curve 5, day 1, every 3 weeks), and after that, one cycle of third-line chemotherapy: docetaxel (60 mg/m^2, day 1, every 3 weeks). The LUL mass was refractory to both regimens (Fig. 2c), and the patient's respiratory status deteriorated, making oxygen administration on exertion necessary. He was then treated with fourth-line chemotherapy: S-1 (80 mg/m^2, days 1–14, every 3 weeks). After four cycles, the size of the LUL mass decreased, indicating a partial response (Fig. 2d). His respiration improved to the point at which he could walk without oxygen administration. Full names and mechanisms of action of the chemotherapeutic agents used are listed in Table 1.

Fig. 3



Poorly differentiated adenocarcinoma diagnosed by transbronchial biopsy of the right lower lobe mass (hematoxylin and eosin stain, × 200).

Fig. 4



Squamous cell carcinoma diagnosed by transbronchial biopsy of the left upper lobe mass (hematoxylin and eosin stain, × 200).

Table 1 Names and mechanisms of action of the chemotherapeutic agents used

Drug	Mechanisms of action
Carboplatin	Reacting with DNA, forming cross-links, which inhibits DNA replication and transcription
Pemetrexed	Inhibiting three enzymes used in purine and pyrimidine synthesis-thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase
Gemcitabine	Gemcitabine triphosphate competes with deoxycytidine triphosphate as an inhibitor of DNA polymerase
Docetaxel	Promoting microtubule polymerization and inhibiting tubulin depolymerization, resulting in the inability of cells to replicate
S-1 (composed of tegafur (FT), 5-chloro-2,4-dihydroxypyridine [gimestat (CDHP)], and oteracil potassium (oxo) in a molar ratio of 1 : 0.4 : 1)	
FT	Inhibiting thymidylate synthetase, leading to inhibition of DNA and RNA synthesis and cell death
CDHP	Inhibiting the activity of dihydropyrimidine dehydrogenase, thereby maintaining prolonged blood and tumor 5-fluorouracil concentrations
Oxo	Preventing phosphorylation of 5-fluorouracil by inhibiting the effect of orotate phosphoribosyl transferase, reducing the gastrointestinal toxicity of fluorouracil

CDHP, 5-chloro-2,4-dihydroxypyridine; FT, tegafur; Oxo, potassium oxonate.

Discussion

Radiological differentiation of synchronous double primary lung cancers from a single lung cancer with intrapulmonary metastasis can be difficult, especially when emphysema coexists, as in the case reported here [1]. The incidence of multiple primary lung carcinomas has been reported to range from 1 to 7%. Ferguson *et al.* [2] showed that 67.9% of synchronous double primary lung cancers consist of the same cell types, suggesting a common etiology for most synchronous tumors. Squamous cell cancer accounts for approximately 60% of synchronous secondary primary lung cancers, and in approximately 60% of these cases, the tumors are histologically indistinguishable [4].

Cases such as those reported here are rare and, hence, it has not been possible to establish a basis for drug selection. In fact, physicians have selected the regimen based on their own preferences. In our case, there were three lesions: large RLL and LUL masses and a mediastinal lymph node metastasis, which was considered to be related to the main RLL mass. Initially, the large major RLL mass was thought to have the largest impact on prognosis. Therefore, we selected a first-line chemotherapy regimen to address the main RLL mass, regardless of whether the LUL mass was histologically different.

Recently, the survival rate of patients with adenocarcinoma has greatly improved because of the implementation of more effective treatment. It is clear that different histological subtypes of NSCLC have had differential improvements [3,5]. The growth regulation of NSCLCs is highly cell type specific. EGFR levels and activation of signaling mediators were significantly different between adenocarcinoma and squamous cell carcinoma [6]. Furthermore, one of the targets of pemetrexed, thymidylate synthase expression, was significantly higher in squamous cell carcinoma compared with adenocarcinoma [7,8]. Two large randomized phase III studies and one comprehensive review [9–11] showed a significant and consistent treatment-by-histology interaction with pemetrexed. Unlike docetaxel or gemcitabine, the treatment advantage for pemetrexed in patients with nonsquamous histology is reproducible and valid [11]. Pemetrexed may be preferable to other agents for patients with nonsquamous NSCLC; hence, we selected pemetrexed and carboplatin for the first-line treatment.

However, in the case reported here, pemetrexed and the carboplatin regimen were not effective for treating the LUL mass, and its progression adversely affected the patient's respiratory status. Thus, a chemotherapeutic regimen including pemetrexed may not be appropriate for such a case having synchronous double primary lung cancers with nonsquamous NSCLC and squamous histologies, even when the primary nonsquamous cell carcinoma predominates. Furthermore, in the case of a single primary nonsquamous cell NSCLC combined with a squamous cell carcinoma, pemetrexed may not be recommended. If we choose pemetrexed for treating nonsquamous NSCLC with a squamous cell component, adding another chemotherapeutic agent for broadening the antitumor spectrum may be beneficial. Several nonplatinum pemetrexed-containing regimens including drugs such as gemcitabine and vinorelbine have been studied among chemotherapy-naïve patients with NSCLC [12–14]. The antimetabolic agent, S-1, inhibits thymidylate synthase by a different mechanism than pemetrexed. A pooled analysis of S-1 trials showed that a combination of cisplatin and S-1 may not act differently according to the histological type [8]. This case showed that S-1 monotherapy may be effective even in pemetrexed-refractory cases. Therefore, chemotherapy including S-1 may become one of the treatment options in pemetrexed-refractory cases.

In conclusion, we note that a chemotherapy regimen for patients with synchronous double NSCLCs with different histologies has not been well established and, therefore, it is particularly difficult to make informed treatment decisions. This situation may improve if oncologists recognize that it is fundamentally important to obtain adequate tissue samples of both tumors for histological confirmation at the time of initial diagnosis. However, it is also essential to consider the histological subtype, extent of disease, and molecular markers to prudently choose a chemotherapy regimen.

Acknowledgement

This study did not receive any funding.

References

1 Aziz TM, Saad RA, Glasser J, Jilaihawi AN, Prakash D. The management of second primary lung cancers. A single centre experience in 15 years. *Eur J Cardiothorac Surg* 2002; **21**:527–533.
2 Ferguson MK, DeMeester TR, DesLauriers J, Little AG, Piraux M, Golomb H. Diagnosis and management of synchronous lung cancers. *J Thorac Cardiovasc Surg* 1985; **89**:378–385.
3 Neal JW. Histology matters: individualizing treatment in non-small cell lung cancer. *Oncologist* 2010; **15**:3–5.
4 Detterbeck FC, Jones DR, Kernstine KH, Naunheim KS; American College of Physicians. Lung cancer. Special treatment issues. *Chest* 2003; **123**:244S–258S.
5 West H, Harpole D, Travis W. Histologic considerations for individualized systemic therapy approaches for the management of non-small cell lung cancer. *Chest* 2009; **136**:1112–1118.
6 López-Malpartida AV, Ludeña MD, Varela G, García Pichel J. Differential ErbB receptor expression and intracellular signaling activity in lung adenocarcinomas and squamous cell carcinomas. *Lung Cancer* 2009; **65**:25–33.
7 Ceppi P, Volante M, Saviozzi S, Rapa I, Novello S, Cambieri A, *et al.* Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. *Cancer* 2006; **107**:1589–1596.
8 Yamamoto N, Yamanaka T, Ichinose Y, Kubota K, Sakai H, Gemma A, *et al.* Pooled analysis of S-1 trials in non-small cell lung cancer according to histological type. *Anticancer Res* 2010; **30**:2985–2990.
9 Scagliotti GV, Parikh P, Von Pawel J, Biesma B, Vansteenkiste J, Manegold C, *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.
10 Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, Von Pawel J, *et al.* Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; **22**:1589–1597.
11 Scagliotti G, Hanna N, Fossella F, Sugarman K, Blatter J, Peterson P, *et al.* The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist* 2009; **14**:253–263.
12 Monnerat C, Le Chevalier T. Review of the pemetrexed and gemcitabine combination in patients with advanced-stage non-small cell lung cancer. *Ann Oncol* 2006; **17**:v86–v90.
13 Ma CX, Nair S, Thomas S, Mandrekar SJ, Nikcevich DA, Rowland KM, *et al.* Randomized phase II trial of three schedules of pemetrexed and gemcitabine as front-line therapy for advanced non-small-cell lung cancer. *J Clin Oncol* 2005; **23**:5929–5937.
14 Clarke SJ, Boyer MJ, Millward M, Underhill C, Moylan E, Yip D, *et al.* A phase I/II study of pemetrexed and vinorelbine in patients with non-small cell lung cancer. *Lung Cancer* 2005; **49**:401–412.