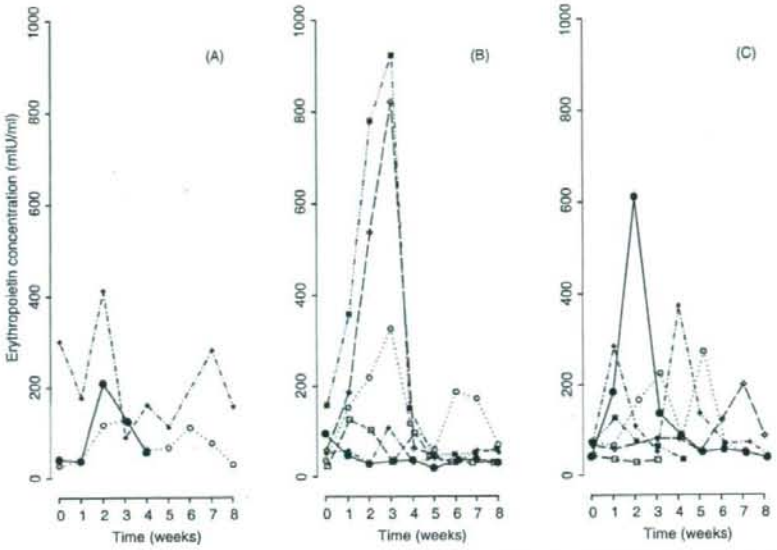

Figure 2. Time-course of trough concentrations of erythropoietin in each dose group. (A) 9000 IU, (B) 18 000 IU, (C) 36 000 IU. Trough concentrations of erythropoietin did not increase with repeated doses of epoetin beta, suggesting that drug accumulation did not occur.

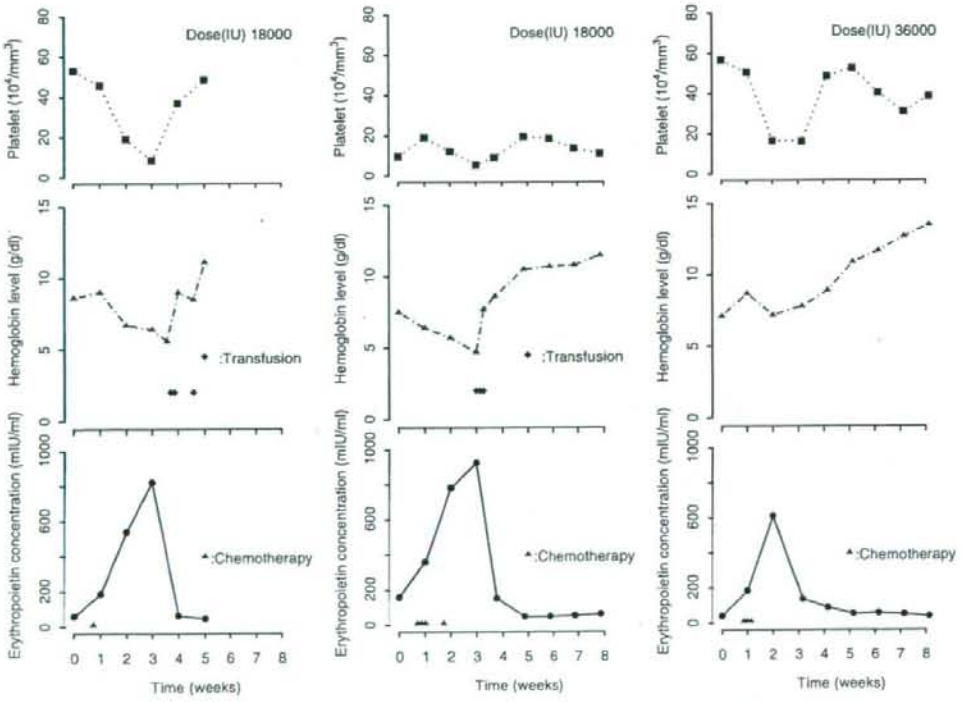

Figure 3. Time-course of trough concentrations of erythropoietin, hemoglobin levels and platelet counts in three patients with extremely high trough concentrations. The elevation of trough concentration is correlated with decrease of platelet counts and Hb levels, which may be associated with bone marrow suppression.

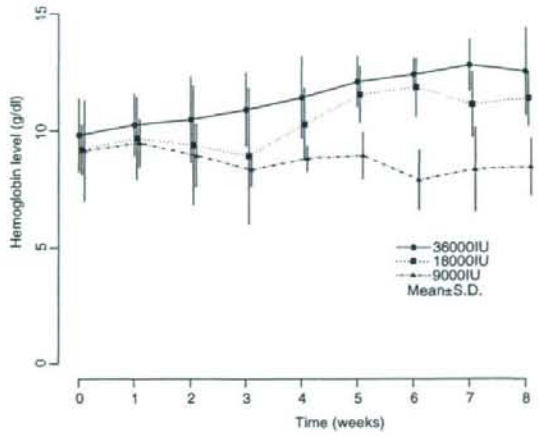

Figure 4. Time-course of mean hemoglobin levels in each dose group. Hemoglobin levels were unchanged at a dose of 9000 IU, but tended to increase at doses of 18 000 and 36 000 IU.

of trough concentrations after once-weekly repeated dose subcutaneous administration in anemic lung cancer patients. The study provides evidence that epoetin beta has almost linear, dose-dependent pharmacokinetics following subcutaneous administration at doses of 9000–36 000 IU in cancer patients.

During the period of once-weekly administrations of epoetin beta, trough concentrations transiently increased after cancer chemotherapy in many patients, but did not appear to continue to increase with repeated administration of epoetin beta. Some patients showed extremely high trough concentrations that were correlated with periods of marked thrombocytopenia. Increases in trough concentrations may be associated with bone marrow suppression, and this finding is in agreement with reports showing that busulfan-induced bone marrow ablation increases serum EPO concentrations (11) and that chemotherapy increases EPO concentrations in patients with leukemia (12,13). Jelkmann reported that elimination of EPO occurs mainly in bone marrow (14). It is conceivable that the function of bone marrow could be damaged by chemotherapeutic agents after chemotherapy. Elimination of EPO could decrease in the damaged bone marrow, thereby the trough levels of EPO could increase.

At 8 weeks, mean changes in hemoglobin levels from baseline were -0.37 ± 1.26, 2.15 ± 1.36 and 2.82 ± 2.17 g/dl for 9000, 18 000 and 36 000 IU, respectively. Hemoglobin levels increased with repeated doses of 18 000 IU or more. A dose-finding study conducted by Sakai et al. (15) in Japanese patients with lung cancer or malignant lymphoma revealed a similar pattern of hemoglobin change (0.04 ± 1.98, 1.04 ± 1.75 and 1.75 ± 2.15 g/dl for 9000, 18 000 and 36 000 IU doses of epoetin beta) and concluded that the recommended dose was 36 000 IU in chemotherapy-induced anemic patients. Taken together, these results suggest that epoetin beta is sufficiently effective for cancer patients with anemia.

In conclusion, subcutaneous administration of epoetin beta at doses of 9000–36 000 IU in cancer patients with anemia yielded pharmacokinetic linearity, with no drug accumulation caused by repeated doses. Epoetin beta administration at 18 000 IU or higher is therefore anticipated to raise hemoglobin levels without compromising safety.

References

1. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 1999;91:1616–34.
2. Ludwig H. Epoetin in cancer-related anaemia. *Nephrol Dial Transplant* 1999;14[Suppl 2]:85–92.
3. Beguin Y. Prediction of response and other improvements on the limitations of recombinant human erythropoietin therapy in anemic cancer patients. *Haematologica* 2002;87:1209–21.
4. Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *Procrit Study Group J Clin Oncol* 1998;16:3412–25.
5. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz HJ, Nortier JWR. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol* 2003;21:366–73.
6. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 2002;20:4083–107.
7. Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001;19:2875–82.
8. Ozguroglu M, Arun B, Demir G, Demirelli F, Mandel NM, Buyukunal E, et al. Serum erythropoietin level in anemic cancer patients. *Medical Oncology* 2000;17:29–34.
9. Charuruks N, Limpanasithikul W, Voravud N, Sutheesophon K. Erythropoietin level and hematologic parameters in healthy adults. *J Med Assoc Thai* 2000;83:1267–73.
10. Yamazaki C, Watanabe Y, Sakamoto N. Pharmacokinetic study of recombinant human erythropoietin treatment in pre-dialysis end stage renal disease patients. *Japanese J Nephrol* 1993;35:1233–42.
11. Chapel S, Veng-Pedersen P, Hohl RJ, Schmidt RL, Mcguire EM, Widness JA. Changes in erythropoietin pharmacokinetics following busulfan-induced bone marrow ablation in sheep: evidence for bone marrow as a major erythropoietin elimination pathway. *J Pharamcol Exp Ther* 2001;298:820–4.
12. Piroso E, Allan JE, Jaime C. Inappropriate increase in erythropoietin titers during chemotherapy. *Am J Hematol* 1989;32:248–54.
13. Sawabe Y, Kikuno K, Iseki T, Iida S, Tabata Y, Yonemitsu H. Changes in serum erythropoietin and the reticulocyte count during chemotherapy for leukemias. *Eur J Haematol* 1996;57:384–8.
14. Jelkmann W. The enigma of the metabolic fate of circulating erythropoietin (Epo) in view of the pharmacokinetics of the recombinant drugs rhEpo and NESP. *Eur J Haematol* 2002;69:265–74.
15. Sakai H, Ohashi Y, Hirashima K, Saijo N. Japan Erythropoietin Study Group. Once weekly epoetin beta to increase hemoove quality of life in anemic cancer patients receiving chemotherapy. Meeting proceedings of the American Society of *Clinical Oncology* 2004;23:767.

Molecular Biology, Genomics, and Proteomics in Bronchioloalveolar Carcinoma

Marie Wislez, MD,† David G. Beer, PhD,‡ Ignacio Wistuba, MD,* Jacques Cadranel, MD, PhD,* Nagahiro Saijo, MD,§ and Bruce E. Johnson, MD‖*

Abstract: The charge of the Molecular Biology, Genomics, and Proteomics in Bronchioloalveolar Carcinoma Committee was to evaluate the molecular biology, genomic changes, and proteomic findings in patients with bronchioloalveolar carcinoma compared with other types of lung cancer. The literature was reviewed and unpublished information was presented by the committee members at the session. The molecular biology studies have included findings on epidermal growth factor receptor (*EGFR*) mutations, p53 mutations, K-*ras* mutations, and loss of heterozygosity. The genomic changes have mostly focused on the mRNA expression arrays as well as protein studies. The current state of knowledge was reviewed, the missing information was acknowledged, and proposals for future research were identified.

Key Words: Lung neoplasm, Adenocarcinoma, Bronchioloalveolar, Adenocarcinoma, Carcinoma, Non-small cell lung cancer.

(*J Thorac Oncol.* 2006;1: S8–S12)

Little information is available about p53 mutations and p53 protein overexpression detected by immunohistochemistry, microsatellite loss of heterozygosity (LOH), and K-*ras* mutations in adenocarcinoma of the bronchioloalveolar subtype, according to the last World Health Organization (WHO) pathological classification proposed in 1999. However, the frequency of these molecular abnormalities seems to increase during the multistep process of carcinogenesis of peripheral adenocarcinoma going from atypical alveolar hyperplasia adenocarcinoma to bronchioloalveolar carcinoma (BAC) and to invasive adenocarcinoma.

*Service de Pneumologie et de Réanimation Respiratoire, AP-HP, Hôpital Tenon and Laboratoire de Biologie Cellulaire et d'Immunopathologie Pulmonaire, Université Paris VI, Paris, France; †Thoracic/Head and Neck Medical Oncology, The University of Texas–M.D. Anderson Cancer Center, Houston, TX; ‡Thoracic Surgery, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; §National Cancer Center East, Kashiwa, Japan; and ‖Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA.

Address for correspondence: Bruce E. Johnson, MD, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, D1234, 44 Binney Street, Boston, MA 02115. E-mail: bruce_johnson@dfci.harvard.edu

Presented at the Consensus Conference on Bronchioloalveolar Cell Carcinoma Palace Hotel, New York, NY, November 4–6, 2004.

ISSN: 1556-0864/06/0109-0008

ATYPICAL ADENOMATOUS HYPERPLASIA

There is an increasing body of evidence to support the concept of atypical adenomatous hyperplasia (AAH) as the precursor of at least a subset of adenocarcinomas.[1] AAH is most frequently detected in lungs from patients bearing lung cancers (9–20%), especially adenocarcinomas (up to 40%) compared with squamous cell carcinomas (11%).[2] Several molecular changes frequently present in lung adenocarcinomas are also present in AAH lesions, and there is further evidence that AAH may represent true preneoplastic lesions.[1] The most important findings are the presence in AAHs of K-*ras* (codon 12) mutations (40%),[3] loss of *LKB1* function (20%),[4] allelic losses in chromosomes 3p (20%), 9p ($p16^{INK4a}$, 10%), 9q (50%), 17q, and 17p (*TP53*, 5%),[5,6] and overexpression of cyclin D1 (70%), p53 (ranging from 10 to 60%),[7] and survivin (50%).[8] Despite the evidence that AAH is a precursor lesion for a subset of lung adenocarcinomas, there is general consensus that the pathogenesis of most adenocarcinomas is still unknown. The findings of relatively infrequent tyrosine kinase domain epidermal growth factor receptor (*EGFR*) mutations in AAH lesions (three out of 40 examined)[9,10] and no *EGFR* mutation[11,12] or relatively low frequency in true BACs of the lung[9] support the concept that genetic abnormalities of *EGFR* are not relevant in the pathogenesis of alveolar types of lung neoplasia. In addition, Tang et al.[13] recently reported that *EGFR* mutation is an early event in the pathogenesis of lung cancer, being identified in histologically normal epithelium of small bronchi and bronchioles adjacent to *EGFR* mutant lung adenocarcinomas in nine out of 21 (43%) patients examined, but in none of the patients without mutation in the tumor. These data further support the notion than AAH lesions are not involved in the pathogenesis of *EGFR* mutant lung adenocarcinomas.

BAC, ADENOCARCINOMA WITH BRONCHIOLOALVEOLAR FEATURES, AND ADENOCARCINOMA OF THE LUNG

The frequency of *EGFR* mutations has also been studied in patients with BAC, adenocarcinoma with BAC features, and adenocarcinomas of the lung. Although responses to EGFR tyrosine kinase inhibitors have been reported to be higher[14] and EGFR mutations were preferentially observed in tumors having BAC features,[12,15] we did not find association with the BAC subtype of adenocarcinoma in 97 cases from

the United States[11] using the criteria stated by the 1999 WHO classification of lung tumors.[16,17]

In addition to the WHO system, Noguchi et al.[18,19] have classified adenocarcinomas into different categories that have different frequencies of genetic changes. Koga et al.[20] reported that p53 mutations were present in approximately 0% of 17 pure BAC, 11% of 27 mixed adenocarcinoma with BAC features, and 48% of 101 invasive adenocarcinomas. Similar to the frequency of mutations, the frequency of p53 protein overexpression detected by immunohistochemistry increased from 6% (2/32 tumors) in pure BAC to 28% (27/133) in BAC with foci of active fibroblastic proliferation (Noguchi type C) and to 40% (14/35) in adenocarcinoma.[21] p53 mutation and protein overexpression were also correlated with the size and invasive component of small peripheral adenocarcinomas (≥5 mm: 41%; <5 mm: 20%).[22,23]

The frequency of allelic losses also increased significantly during malignant progression. According to Noguchi's classification,[18,19] frequencies of allelic losses at chromosomal loci 3p, 17p, 18q, and 22q were significantly lower in BAC with or without alveolar collapse (Noguchi types A and B, respectively) than in BAC with active fibroblastic proliferation (Noguchi type C) in a series of 66 small peripheral adenocarcinomas.[24]

The frequency and type of K-*ras* mutation in BAC are related to the cytological features (mucinous versus nonmucinous). This raises the question of whether the mucinous form might represent a biological entity separate from the nonmucinous form. Small series of tumors (all <50) from patients with adenocarcinoma of the lung show that the K-*ras* mutation is present in 73 to 100% of the mucinous types and that the type of the mutation was usually G to A (codon 12), whereas it was seen in 10 to 43% in the nonmucinous types, usually in G to T transversions.[25–27] Mutations at codon 12 of the K-*ras* oncogene were found in 39% of 41 AAH, 42% of 18 adenocarcinomas, and none of five lung neoplasms that were not adenocarcinomas. Of the patients with both an AAH and a synchronous adenocarcinoma, more than half did not have the mutation in both the AAH and the synchronous lung adenocarcinoma, suggesting that peripheral adenocarcinomas arise not always from AAH but sometimes directly from a background of field cancerization.[27]

Adenocarcinomas with BAC features are also characterized by an intense inflammatory reaction especially containing alveolar neutrophils and macrophages. Increased numbers of tumor-infiltrating neutrophils are linked to poorer outcomes in these patients.[28] Tumor environment drives local neutrophil recruitment and activation via C-X-C chemokine release such as interleukin-8 and epithelial cell–derived neutrophil activating protein 78 but also prolongs alveolar neutrophil survival through the production of soluble antiapoptotic factors (granulocyte–macrophage colony–stimulating factor and granulocyte colony–stimulating factor).[29,30] The mechanisms by which neutrophils influence the prognosis of adenocarcinoma with BAC features could be multiple. It has been postulated that the persistence of neutrophil alveolitis would result in persistent release of proinflammatory mediators such as cytokines, proteases, and reactive oxygen and nitrogen species that can damage DNA and activate oncogenes.[31,32] Among these factors released by neutrophils, hepatocyte growth factor seems to be particularly involved in the progression of these types of tumors, especially through its mitogenic and scattering properties, favoring c-Met expressing tumor-cell migration along the alveolar basal membrane.[33] Lastly, neutrophils might be involved in luminal tumor spread by promoting tumor-cell shedding (M. Wislez, AACR 2004), described pathologically as the presence of micropapillary clusters that are also involved in the mechanism of aerogenous progression.[34]

GENOMIC AND PROTEOMIC STUDIES OF BAC

As mentioned before, BAC is thought to arise from AAH and is potentially an intermediate to invasive adenocarcinoma. Extensive analyses of BAC using gene-expression profiling and proteomic-based studies have not yet been performed and are only available for limited numbers of these cancers. These types of studies may have the potential to define similarity or differences in the observed types of adenocarcinoma of the lung. Of particular interest is the potential regulatory pathway involved in the lepidic growth patterns of BAC, which is different from most other adenocarcinomas of the lung. The observation that some adenocarcinomas can exhibit regions of BAC provides complexity and has resulted in multiple pathological-based classifications.[14,16–19] Genomic studies have the potential to define the similarities as well as key differences between BAC, adenocarcinomas with BAC features, and adenocarcinomas of the lung.

Recent studies examining individual genes have hinted at differences between BAC and adenocarcinomas. The tumor suppressor in the lung cancer-1 gene encodes an adhesion molecule and is frequently associated with LOH at that locus in non–small-cell lung cancer. Both normal lung cells and BAC retain expression of tumor suppressor in lung cancer-1, whereas 63% of adenocarcinomas demonstrated decreased expression detected by immunohistochemistry.[35] BACs have very low p53 DNA mutation frequencies compared with adenocarcinomas of the lung.[20] LOH at the 3p FHIT loci was observed in 43% of BAC, and 12th codon K-*ras* mutations are detected in the mucinous form of BAC.[36] A comparative LOH study between 14 BAC and 20 stage I lung adenocarcinomas using nine chromosomal regions revealed that the most frequently affected chromosomal regions in BAC were 8q and 17p.[37] In adenocarcinomas of the lung, LOH at 1p, 3p, 7q, and 18q was more frequent than in BAC, and fractional allele loss was greater in adenocarcinomas of the lung than BAC.

Using immunocytochemistry to examine protein expression, detection of the thyroid transcription factor-1 (TTF-1), cytokeratin 7, and cytokeratin 20 were measured in both mucinous and nonmucinous BAC.[38] TTF-1 was detected in 17% of mucinous and 94% of nonmucinous BAC, cytokeratin 7 was detected in 100% of mucinous and 23% of nonmucinous BAC, and cytokeratin 20 was detected in 60% of mucinous and 0% of nonmucinous BAC.[38] In a study that examined MUC protein expression in AAH, BAC, and adenocarcinomas with BAC features, MUC1 decreased from

AAH to BAC and from BAC to adenocarcinoma, whereas MUC2, MUC5AC, MUC6, and depolarized MUC6 increased.[39] Alterations in p53 and the increased expression of MUC1, MUC5AC, and MUC6 were noted.

ADDITIONAL GENOMIC AND PROTEOMIC STUDIES

A comparison of normal lung tissue and BAC using oligonucleotide arrays was reported by Goodwin et al.[40] and identified 12 up-regulated and six down-regulated genes in the BAC tumors. Although this analysis provides some information, a comparison of BAC and adenocarcinomas was not included, which may be most relevant in defining critical genes involved in the development of these cancers. We used oligonucleotide arrays to examine gene expression in 14 BAC and 73 adenocarcinomas.[41] The most highly expressed genes that were significantly different between the BAC tumors and adenocarcinomas and higher in BAC included the surfactant pulmonary-associated proteins A1, A2, C and D, MUC1, TTF-1 and TTF-3, villin 2, and prostaglandin D2 synthetase. Interestingly, higher mRNA expression for both fos and jun B were detected in BAC, which may reflect an elevated AP-1 activity and upstream signaling events in these tumors. The higher level of expression of surfactant genes is consistent with the well-differentiated phenotypic characteristics of BAC. TTF-1 was the most differentially expressed gene between BAC and adenocarcinomas, consistent with the high TTF-1 protein expression reported in BAC.[38] Because of the small numbers of tumors for our analyses, it was not possible to divide the BAC tumors into separate categories such as mucinous, nonmucinous, and mixed histology. Although we found MUC1 mRNA present in both BAC and adenocarcinomas of the lung, the significantly increased expression in BAC is consistent with the higher MUC1 protein levels that have been reported in these tumors.[39]

Analysis of survival-related genes revealed prostaglandin D2 synthetase and neutrophil elastase 2 to be more highly expressed in BAC than the other adenocarcinomas. In contrast, much lower levels of vascular endothelial growth factor were detected in the BAC, possibly reflecting a lesser level of angiogenesis and hypoxia in these tumors relative to the adenocarcinomas. Adenocarcinomas also expressed increased levels of metallothionein 2A and thioredoxin reductase mRNA. We speculate that these genes may correspond to smoking-related alterations because these genes may change in response to reactive oxygen species originating from tobacco smoking or in response to inflammatory cells. Alternately, the expression of thioredoxin reductase and metallothionein 2 may reflect the higher rates of cell proliferation in the lung adenocarcinomas relative to BAC.

Few, if any, large-scale proteomic analyses of BAC have been reported. We examined the same BAC and lung adenocarcinomas for mRNA using oligonucleotide arrays and also at the protein level with two-dimensional gel electrophoresis and mass spectrometry.[42] A total of 682 protein spots were quantified, and 75 proteins were found to differ significantly ($p < 0.05$) between BAC and lung adenocarcinomas. Thirty-eight protein spots were successfully identified using mass spectometry. Of interest were the relatively higher expression of the ras-related protein RAB-14, glutathione-s-transferase-pi, cytokeratin 7, and three isoforms of the selenium-binding protein 1 in BAC compared with adenocarcinomas of the lung. Adenocarcinomas expressed higher levels of phosphoglycerate kinase 1, pyruvate kinase M1/M2, and stathmin (OP-18) compared with BACs. Increased phosphoglycerate kinase 1 is consistent with higher hypoxia-induced glycolysis in the adenocarcinomas of the lung relative to BAC.[42]

Future studies that include sufficient numbers of the various histological subtypes of BAC are needed to provide insight into the similarities and differences among these tumors and as compared with lung adenocarcinomas. The NCI Director's Challenge: Validation Study of Lung Adenocarcinomas will examine gene expression using Affymetrix 133A oligonucleotide arrays among approximately 500 tumors. Thus, a relatively large number of BACs will be included in this study, allowing potential gene pathways to be defined that may be relevant to our understanding of the growth- and cell-signaling systems in BAC. These analyses will also incorporate detailed pathologic assessment of each tumor so that the subtypes of each BAC can be compared. It is expected that these data, made available to the research community, will then stimulate further research into potential new markers for early diagnosis and possible therapeutic intervention strategies that may be effective for BAC.

FUTURE DIRECTIONS

The Committee responsible for Molecular Biology, Genomics, and Proteomics in Bronchioloalveolar Carcinoma outlined studies that will provide further insights into BAC. The most important part of the meeting was partial agreement and understanding about the interpretation of the pathological classification. The participants in the meeting agreed on a common set of descriptors for the pathological interpretation of BAC that will be used more consistently in the future.

TABLE 1. Different Biological Properties in Atypical Adenomatous Hyperplasia, Pure Bronchioloalveolar Cancer, Adenocarcinoma with Bronchioloalveolar Cancer Features, and Adenocarcinoma

	Atypical Adenomatous Hyperplasia	Bronchioloalveolar Carcinoma	Adenocarcinoma with Bronchioloalveolar Carcinoma Features	Adenocarcinoma of the Lung
EGFR mutation	↓ <5%	10%		↑ 40%
TP53 mutations	Not reported	↓ 0%	↓ 10%	↑ 50%
p53 by immunohistochemistry	Not reported	↓ 5%	↑ 30%	↑ 50%

Upcoming technological improvements will provide additional insights into the biology of BAC. These will include the increasing ability to detect genetic changes in BAC and adenocarcinomas including, but not be limited to, *EGFR*, HER-2/neu, B-raf, K-*ras*, and *TP53*. In addition, there is the ability to detect genetic loss in the whole genome using studies with single-polynucleotide polymorphisms or array chromosomal genomic hybridization. There is increasing ability to use small and smaller amounts of DNA and DNA from paraffin-embedded tissues. Future studies will provide information on the degree of genetic changes seen in early lesions (<1cm) that are being detected more often as computerized tomographic scanning of the chest is becoming more widely used. These findings can be compared with the more advanced lesions. The genetic changes can also provide insights into the clonality of the BACs to determine whether the multiple lesions in the lungs arise from single or multiple clones. Table 1

REFERENCES

1. Wistuba II, Gazdar A. Lung cancer preneoplasia. *Ann Rev Pathol Mech Dis* 2005;1:331–348.
2. Kerr KM. Pulmonary preinvasive neoplasia. *J Clin Pathol* 2001;54:257–271.
3. Westra WH. Early glandular neoplasia of the lung. *Respir Med* 2000;1: 163–169.
4. Ghaffar H, Sahin F, Sanchez-Cepedes M, et al. LKB1 protein expression in the evolution of glandular neoplasia of the lung. *Clin Cancer Res* 2003;9:2998–3003.
5. Kitaguchi S, Takeshima Y, Nishisaka T, et al. Proliferative activity, p53 expression and loss of heterozygosity on 3p, 9p and 17p in atypical adenomatous hyperplasia of the lung. *Hiroshima J Med Sci* 1998;47: 17–25.
6. Takamochi K, Ogura T, Suzuki K, et al. Loss of heterozygosity on chromosomes 9q and 16p in atypical adenomatous hyperplasia concomitant with adenocarcinoma of the lung. *Am J Pathol* 2001;159:1941–1948.
7. Tominaga M, Sueoka N, Irie K, et al. Detection and discrimination of preneoplastic and early stages of lung adenocarcinoma using hnRNP B1 combined with the cell cycle-related markers p16, cyclin D1, and Ki-67. *Lung Cancer* 2003;40:45–53.
8. Nakanishi K, Kawai T, Kumaki F, et al. Survivin expression in atypical adenomatous hyperplasia of the lung. *Am J Clin Pathol* 2003;120:712–719.
9. Yoshida Y, Shibata T, Kokubu A, et al. Mutations of the epidermal growth factor receptor gene in atypical adenomatous hyperplasia and bronchioloalveolar carcinoma of the lung. *Lung Cancer* 2005;50:1–8.
10. Yatabe Y, Kosaka T, Takahashi T, et al. EGFR mutation is specific for terminal respiratory unit type adenocarcinoma. *Am J Surg Pathol* 2005; 29:633–639.
11. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005;97:339–346.
12. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A* 2004;101:13306–13311.
13. Tang X, Shigematsu H, Bekele BN, et al. EGFR tyrosine kinase domain mutations are detected in histologically normal respiratory epithelium in lung cancer patients. *Cancer Res* 2005;65:7568–7572.
14. Miller VA, Kris MG, Shah N, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22:1103–1109.
15. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
16. Travis WD, Brambilla E, Muller-Hermelink HK, et al. Tumours of the lung. In Travis WD, Brambilla E, Muller-Hermelink HK, et al (Eds.), Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. World Health Organization Classification of Tumours. Pathology & Genetics. Lyon: IARC Press, 2004, pp 9–124.
17. Travis WD, Garg K, Franklin WA, et al. Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. *J Clin Oncol* 2005;23:3279–3287.
18. Noguchi M, Minami Y, Iijima T, et al. Reproducibility of the diagnosis of small adenocarcinoma of the lung and usefulness of an educational program for the diagnostic criteria. *Pathol Int* 2005;55:8–13.
19. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995;75: 2844–2852.
20. Koga T, Hashimoto S, Sugio K, et al. Clinicopathological and molecular evidence indicating the independence of bronchioloalveolar components from other subtypes of human peripheral lung adenocarcinoma. *Clin Cancer Res* 2001;7:1730–1738.
21. Kawasaki M, Noguchi M, Morikawa A, et al. Nuclear p53 accumulation by small-sized adenocarcinomas of the lung. *Pathol Int* 1996;46:486–490.
22. Slebos RJ, Baas IO, Clement MJ, et al. p53 alterations in atypical alveolar hyperplasia of the human lung. *Hum Pathol* 1998;29:801–808.
23. Terasaki H, Niki T, Matsuno Y, et al. Lung adenocarcinoma with mixed bronchioloalveolar and invasive components: clinicopathological features, subclassification by extent of invasive foci, and immunohistochemical characterization. *Am J Surg Pathol* 2003;27:937–951.
24. Aoyagi Y, Yokose T, Minami Y, et al. Accumulation of losses of heterozygosity and multistep carcinogenesis in pulmonary adenocarcinoma. *Cancer Res* 2001;61:7950–7954.
25. Maeshima AM, Niki T, Maeshima A, et al. Modified scar grade: a prognostic indicator in small peripheral lung adenocarcinoma. *Cancer* 2002;95:2546–2554.
26. Marchetti A, Buttitta F, Pellegrini S, et al. Bronchioloalveolar lung carcinoma: K-ras mutations are constant events in the mucinous subtype. *J Pathol* 1996;179:254–259.
27. Westra WH, Baas IO, Hruban RH, et al. K-ras oncogene activation in atypical alveolar hyperplasias of the human lung. *Cancer Res* 1996;56: 2224–2228.
28. Bellocq A, Antoine M, Flahault A, et al. Neutrophil alveolitis in bronchioloalveolar carcinoma: induction by tumor-derived interleukin-8 and relation to clinical outcome. *Am J Pathol* 1998;152:83–92.
29. Wislez M, Fleury-Feith J, Rabbe N, et al. Tumor-derived granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor prolong the survival of neutrophils infiltrating bronchoalveolar subtype pulmonary adenocarcinoma. *Am J Pathol* 2001;159:1423–1433.
30. Wislez M, Philippe C, Antoine M, et al. Upregulation of bronchioloalveolar carcinoma-derived C-X-C chemokines by tumor infiltrating inflammatory cells. *Inflamm Res* 2004;53:4–12.
31. Jackson JH, Vollenweider M, Hill J, et al. Stimulated human leukocytes cause activating mutations in the K-ras protooncogene. *Oncogene* 1997; 14:2803–2808.
32. Weitberg AB, Weitzman SA, Destrempes M, et al. Stimulated human phagocytes produce cytogenetic changes in cultured mammalian cells. *N Engl J Med* 1983;308:26–30.
33. Wislez M, Rabbe N, Marchal J, et al. Hepatocyte growth factor production by neutrophils infiltrating bronchioloalveolar subtype pulmonary adenocarcinoma: role in tumor progression and death. *Cancer Res* 2003;63:1405–1412.
34. Hoshi R, Tsuzuku M, Horai T, et al. Micropapillary clusters in early-stage lung adenocarcinomas: a distinct cytologic sign of significantly poor prognosis. *Cancer* 2004;102:81–86.
35. Ito A, Okada M, Uchino K, et al. Expression of the TSLC1 adhesion molecule in pulmonary epithelium and its down-regulation in pulmonary adenocarcinoma other than bronchioloalveolar carcinoma. *Lab Invest* 2003;83:1175–1183.
36. Marchetti A, Pellegrini S, Bertacca G, et al. FHIT and p53 gene abnormalities in bronchioloalveolar carcinomas. Correlations with clinicopathological data and K-ras mutations. *J Pathol* 1998;184:240–246.
37. Sasatomi E, Johnson LR, Aldeeb DN, et al. Genetic profile of cumulative mutational damage associated with early pulmonary adenocarcinoma: bronchioloalveolar carcinoma vs. stage I invasive adenocarcinoma. *Am J Surg Pathol* 2004;28:1280–1288.

38. Saad RS, Cho P, Silverman JF, et al. Usefulness of Cdx2 in separating mucinous bronchioloalveolar adenocarcinoma of the lung from metastatic mucinous colorectal adenocarcinoma. *Am J Clin Pathol* 2004;122: 421–427.
39. Awaya H, Takeshima Y, Yamasaki M, et al. Expression of MUC1, MUC2, MUC5AC, and MUC6 in atypical adenomatous hyperplasia, bronchioloalveolar carcinoma, adenocarcinoma with mixed subtypes, and mucinous bronchioloalveolar carcinoma of the lung. *Am J Clin Pathol* 2004;121:644–653.
40. Goodwin LO, Mason JM, Hajdu SI. Gene expression patterns of paired bronchioloalveolar carcinoma and benign lung tissue. *Ann Clin Lab Sci* 2001;31:369–375.
41. Beer DG, Kardia SL, Huang CC, et al. Gene-expression profiles predict survival of patients with lung adenocarcinoma. *Nat Med* 2002;8:816–824.
42. Chen G, Gharib TG, Wang H, et al. Protein profiles associated with survival in lung adenocarcinoma. *Proc Natl Acad Sci U S A* 2003;100: 13537–13542.

original article

Annals of Oncology 18: 317–323, 2007
doi:10.1093/annonc/mdl377
Published online 1 November 2006

Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan

Y. Ohe[1]*, Y. Ohashi[2], K. Kubota[3], T. Tamura[1], K. Nakagawa[4], S. Negoro[5], Y. Nishiwaki[3], N. Saijo[3], Y. Ariyoshi[6] & M. Fukuoka[4]
For the FACS Cooperative Group

[1]Department of Internal Medicine, National Cancer Center Hospital, Tokyo; [2]Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, The University of Tokyo, Tokyo; [3]Thoracic Oncology Division, National Cancer Center Hospital East, Kashiwa, Chiba; [4]Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Osaka; [5]Department of Thoracic Oncology, Hyogo Medical Center for Adults, Akashi, Hyogo; [6]Aichi Cancer Center Aichi Hospital, Okazaki, Aichi, Japan

Received 16 May 2006; revised 13 August 2006; accepted 30 August 2006

Background: To compare the efficacy and toxicity of three platinum-based combination regimens against cisplatin plus irinotecan (IP) in patients with untreated advanced non-small-cell lung cancer (NSCLC) by a non-inferiority design.
Patients and methods: A total of 602 patients were randomly assigned to one of four regimens: cisplatin 80 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, 15 every 4 weeks (IP) carboplatin AUC 6.0 min × mg/mL (area under the concentration–time curve) on day 1 plus paclitaxel 200 mg/m^2 on day 1 every 3 weeks (TC); cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1, 8 every 3 weeks (NP).
Results: The response rate, median survival time, and 1-year survival rate were 31.0%, 13.9 months, 59.2%, respectively, in IP; 32.4%, 12.3 months, 51.0% in TC; 30.1%, 14.0 months, 59.6% in GP; and 33.1%, 11.4 months, 48.3% in NP. No statistically significant differences were found in response rate or overall survival, but the non-inferiority of none of the experimental regimens could be confirmed. All the four regimens were well tolerated.
Conclusion: The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.
Key words: carboplatin, cisplatin, gemcitabine, irinotecan, non-small-cell lung cancer, paclitaxel, randomized phase III study, vinorelbine

introduction

Nearly 60 000 patients in Japan died of lung cancer in 2004, and the mortality rate is still increasing [1]. Even old-generation cisplatin-based chemotherapy provides a survival benefit and symptom relief in patients with inoperable non-small-cell lung cancer (NSCLC) [2]. Several anticancer agents including irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine, were developed in the 1990s and most of them have mechanisms of action that differ from those of the old-generation agents [3–7]. The combinations of platinum and these new agents developed in the 1990s are more useful against advanced NSCLC than old-generation combination chemotherapy, and doublets of platinum and new-generation anticancer agents are considered standard chemotherapy regimens for advanced NSCLC, although no consistent standard regimens have yet been established [8–17].

Two phase III studies comparing cisplatin plus irinotecan (IP) with cisplatin plus vindesine for advanced NSCLC have been conducted in Japan [18, 19]. Fukuoka et al. [20] reported the results of a combined analysis of the 358 eligible stage IV patients in these studies. They carried out a multivariate analysis using the Cox regression model with adjustment for well-known prognostic factors, and the Cox regression analysis demonstrated that treatment with IP was one of significant independent favorable factor. Based on their data, we selected IP for the reference arm in our study.

The Ministry of Health, Labour and Welfare of Japan approved the prescription of paclitaxel, gemcitabine, and

*Correspondence to: Dr Y. Ohe, Department of Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: x+81-3-3542-7006; E-mail: yohe@ncc.go.jp

vinorelbine for NSCLC in 1999 and requested a phase III study to confirm the efficacy and safety of these agents. The Japanese investigators and the pharmaceutical companies decided to conduct a four-arm randomized phase III study for NSCLC, the so-called FACS, Four-Arm Cooperative Study. The purpose of the study was to compare the efficacy and toxicity of three platinum-based combination regimens, carboplatin plus paclitaxel (TC), cisplatin plus gemcitabine (GP), cisplatin plus vinorelbine (NP), with IP as the reference arm.

patients and methods

patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for participation in the study. Each patient had to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardiac effusion, or metastatic lesion in the same lobe), at least one target lesion >2 cm, no prior chemotherapy, no prior surgery and/or radiotherapy for the primary site, age 20–74 years, Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, adequate hematological, hepatic and renal functions, partial pressure of arterial oxygen (paO_2) ≥60 torr, expected survival >3 months, able to undergo first course treatment in an inpatient setting, and written informed consent. The study was approved by the Institutional Review Board at each hospital. Written informed consent was obtained from every patient.

treatment schedule

All patients were randomly assigned to one of the four treatment groups by the central registration office by means of the minimization method. Stage, PS, gender, lactate dehydrogenase (LDH) and albumin values, and institution were used as adjustment variables. The first group received the reference treatment, 80 mg/m^2 of cisplatin on day 1 and 60 mg/m^2 of irinotecan on days 1, 8, and 15, and the cycle was repeated every 4 weeks. The second group received 200 mg/m^2 of paclitaxel (Bristol-Myers K.K., Tokyo, Japan) over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min × mg/mL on day 1 and the cycle was repeated every 3 weeks. The third group received 80 mg/m^2 of cisplatin on day 1 and 1000 mg/m^2 of gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. The fourth group received 80 mg/m^2 of cisplatin on day 1 and 25 mg/m^2 of vinorelbine (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. Each treatment was repeated for three or more cycles unless the patient met the criteria for progressive disease or experienced unacceptable toxicity.

response and toxicity evaluation

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors, and tumor markers were excluded from the criteria [21]. Objective tumor response in all responding patients was evaluated by an external review committee with no information on the treatment group. Toxicity grading criteria in National Cancer Institute Common Toxicity Criteria Ver 2.0 were used to evaluate toxicity.

quality of life assessment

Quality of life (QoL) was evaluated by means of the Functional Assessment of Cancer Therapy—Lung (FACT-L) Japanese version and the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoL-ACD), before treatment, immediately before the second cycles of chemotherapy, and 3 and 6 months after the start of treatment [22–24].

statistical analysis and monitoring

The primary end point of this study was overall survival (OS), and the secondary end points were response rate, response duration, time to progressive disease (TTP), time to treatment failure (TTTF), adverse event, and QoL. The 1-year survival rate of the control group in this study was estimated to be 43% based on the data in published papers, and the 1-year survival rate in the other treatment group was expected to be 50%. The lower equivalence limit for 1-year survival rate was set as '−10%'. The criterion for the non-inferiority of each treatment was a lower limit of the two-sided 95% confidence interval (CI) of the 1-year survival rate of treatment minus that of control larger than the lower equivalence limit. Because the non-inferiority of each treatment versus the control was to be evaluated independently, a separate null hypothesis was stated for each treatment, and for that reason no multiple comparison adjustment was included in the study. Based on the above conditions and binomial distribution, 135 patients were needed per arm for a one-sided Type I error of 2.5% and 80.0% power. In view of the possibility of variance inflation due to censoring, the sample size was set at 600 (150 per arm).

Central registration with randomization, monitoring, data collection, and the statistical analyses were independently carried out by a contract research organization (EPS Co., Ltd, Tokyo, Japan).

results

patient characteristics

From October 2000 to June 2002, a total of 602 patients were registered by 44 hospitals in Japan. All patients had been followed up for >2 years, and 447 patients had died as of June 2004. Of the 602 patients registered, 151 were allocated to the reference treatment, IP, and 150, 151, and 150 patients were allocated to TC, GP, and NP, respectively. Since 10 patients did not receive chemotherapy and 11 patients were subsequently found to be ineligible, 592 patients were assessable for toxicity and 581 patients were assessable for efficacy. Four patients did not receive chemotherapy due to electrolytic disorder, fever, symptomatic brain metastases, and rapid tumor progression in IP, two patients due to refusal and pneumonia in TC, four patients due to lower WBC counts (two patients), rapid tumor progression, and nephritic syndrome in NP. Two patents were ineligible due to wrong stage in IP, two patients were wrong stage and one patient had double cancer in TC, two patients were wrong diagnosis, one patient had massive pleural effusion, one patient received prior chemotherapy in GP, one patient had no target lesions in NP. Age, gender, PS, stage, and LDH and albumin values were well balanced in each arm (Table 1). Fewer patients with adenocarcinoma and more patients with squamous cell carcinona were, however, entered in three experimental arms than in IP.

objective tumor response and response duration

Objective tumor response is shown in Table 2. Forty-five partial responses occurred in the 145 assessable patients in the reference arm, IP, for an objective response rate of 31.0% with a median response duration of 4.8 months. The response rate and median response duration were 32.4% and 4.0 months in TC, 30.1% and 3.5 months in GP, and 33.1% and 3.4 months in NP. The response rates in TC, GP, and NP were not statistically different from the rate in IP according to the results of the χ^2 test.

Table 1. Patient characteristics and treatment delivery

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine
Assessable patients	145	145	146	145
Gender (male/female)	97/48	99/46	101/45	101/44
Age, median (range)	62 (30–74)	63 (33–74)	61 (34–74)	61 (28–74)
PS (0/1)	44/101	44/101	45/101	45/100
Histology				
Adenocarcinoma	121	104	108	109
Squamous cell carcinoma	16	31	29	29
Others	8	10	9	7
Stage (IIIB/IV)	31/114	28/117	30/116	26/119
No. of cycles				
Mean ± SD	3.0 ± 1.3	3.5 ± 1.5	3.2 ± 1.2	3.1 ± 1.3
Median	3	3	3	3
Range	1–7	1–10	1–7	1–8

PS, performance status; SD, standard deviation.

Table 2. Survival, TTP, TTTF, response rate, and response duration

	N	Median survival, months	1-year survival (%)	Difference in 1-year survival from IP	2-year survival (%)	TTP (median), months	TTTF (median), months	Response rate (%)	Response duration (median), months
Cisplatin + irinotecan	145	13.9	59.2	–	26.5	4.7	3.3	31.0	4.8 ($n = 45$)
Carboplatin + paclitaxel	145	12.3	51.0	−8.2% (95% CI −19.6% to 3.3%)	25.5	4.5 ($P = 0.355$)[a]	3.2 ($P = 0.282$)[a]	32.4 ($P = 0.801$)[b]	4.0 ($n = 47$)
Cisplatin + gemcitabine	146	14.0	59.6	0.4% (95% CI −10.9% to11.7%)	31.5	4.0 ($P = 0.170$)[a]	3.2 ($P = 0.567$)[a]	30.1 ($P = 0.868$)[b]	3.5 ($n = 44$)
Cisplatin + vinorelbine	145	11.4	48.3	−10.9% (95% CI −22.3% to 0.5%)	21.4	4.1 ($P = 0.133$)[a]	3.0 ($P = 0.091$)[a]	33.1 ($P = 0.706$)[b]	3.4 ($n = 48$)

[a]Compared with IP by the generalized Wilcoxon test.

[b]Compared with IP by the χ^2 test.

CI, confidence interval; IP, cisplatin plus irinotecan; TTP, time to progressive disease; TTTF, time to treatment failure.

OS, TTP disease, and TTTF

OS and TTP are shown in Figure 1. Median survival time (MST), the 1-year, and 2-year survival rate in IP were 13.9 months, 59.2%, and 26.5%, respectively. The MSTs, 1-year, and 2-year survival rates were, respectively, 12.3 months, 51.0%, and 25.5% in TC; 14.0 months, 59.6%, and 31.5% in GP; and 11.4 months, 48.3%, and 21.4% in NP. The lower limits of the 95% CI of the difference in 1-year survival rate between IP and TC (−19.6%), GP (−10.9%), and NP (−22.3%) were below −10%, which was considered the lower equivalence limit (Table 2). Thus, the results did not show non-inferiority in three experimental regimens compared with reference treatment. Median TTP and median TTTF were 4.7 and 3.3 months, respectively in IP. Median TTP and TTTF were, respectively, 4.5 and 3.2 months in TC, 4.0 and 3.2 months in GP, and 4.1 and 3.0 months in NP. There were no statistical differences in either TTP or TTTF in TC, GP, or NP, compared with IP according to the results of the generalized Wilcoxon test (Table 2).

hematologic and non-hematologic toxicity

In IP, 47.6% and 83.7% of patients developed grade 3 or worse leukopenia and neutropenia, respectively (Table 3). The incidences of grade 3 or worse leukopenia (33.1%, $P = 0.010$) and neutropenia (62.9%, $P < 0.001$) were significantly lower in GP than in IP. The incidence of grade 3 or worse leukopenia (67.1%, $P < 0.001$) was significantly higher in NP than in IP. Grade 3 or worse thrombocytopenia developed in 5.4% of the patients in IP, and the incidence was significantly higher in GP (35.1%, $P < 0.001$). The incidence of febril neutropenia in IP was 14.3%, and was significantly lower in GP (2.0%, $P < 0.001$).

Grade 2 or worse nausea, vomiting, anorexia, and fatigue occurred in 60.5%, 51.0%, 65.3%, and 38.8%, respectively, of the patients in IP. The incidences of grade 2 or worse nausea (TC: 25.0%, $P < 0.001$, NP: 47.3%, $P = 0.022$), vomiting (TC: 22.3%, $P < 0.001$, NP: 36.3%, $P = 0.011$), and anorexia (TC: 32.4%, $P < 0.001$, NP: 49.3%, $P = 0.005$) were significantly lower in TC and NP than in IP. Grade 2 or worse diarrhea was

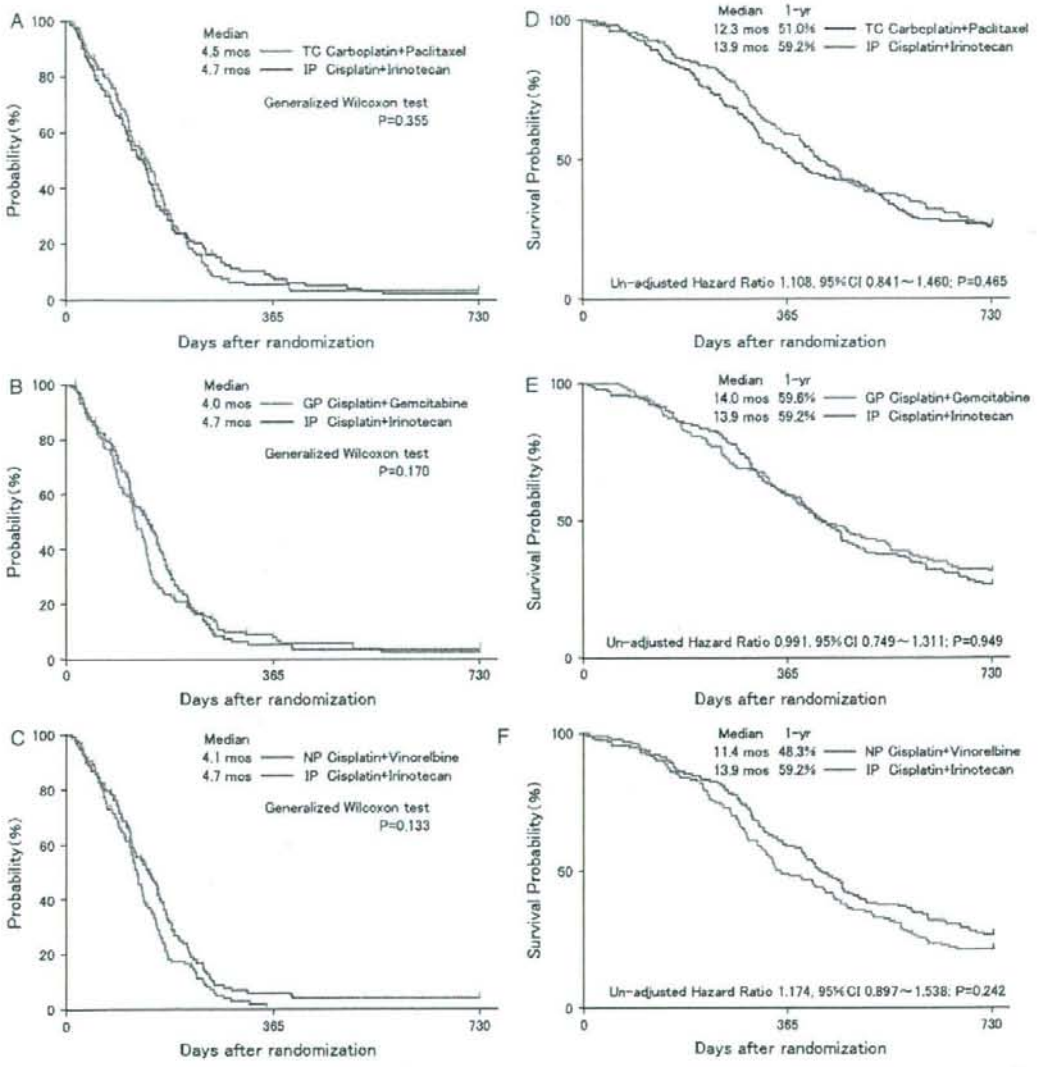

Figure 1. Overall survival (OS) and time to progressive (TTP) disease. TTP and OS in the carboplatin plus paclitaxel (TC) (A, D), cisplatin plus gemcitabine (GP) (B, E), and cisplatin plus vinorelbine (NP) (C, F) were not statistically significantly different from the values in the cisplatin plus irinotecan.

significantly less frequent in TC (6.8%), GP (8.6%), and NP (11.6%) than in IP (48.3%, $P < 0.001$). The incidences of grade 2 or worse sensory neuropathy (16.9%, $P < 0.001$), arthralgia (21.6%, $P < 0.001$), and myalgia (17.6%, $P < 0.001$) were significantly higher in TC than in IP. Grade 2 alopecia occurred in 30.6% of the patients in IP, and its incidence was significantly higher in TC (44.6%, $P = 0.013$) and significantly lower in GP (15.2%, $P = 0.001$) and NP (8.9%, $P < 0.001$). Grade 2 injection site reactions were more frequent in NP (26.7%) than in IP (4.8%, $P < 0.001$).

A total of five patients died of treatment-related toxicity: three in IP (cerebral hemorrhage, interstitial pneumonia, acute circulatory failure/disseminated intravascular coagulation: 2.0%), one in TC (acute renal failure: 0.7%), and one in NP (pulmonary embolism: 0.7%).

second-line treatment

Data on second-line treatment, but not third-line or later treatment, was available in this study, and they showed that

Table 3. Toxicity

	IP ($n = 147$)			TC ($n = 148$)			GP ($n = 151$)			NP ($n = 146$)		
	Grade (%)			Grade (%)			Grade (%)			Grade (%)		
	2	3	4	2	3	4	2	3	4	2	3	4
Leukocytes	42	43	5	39	42	3	40	31[a]	2[a]	25	51[b]	16[b]
Neutrophils	11	39	45	5	19	69	21	40	23[a]	5	16	72
Hemoglobin	42	24	7	42	13[a]	2[a]	44	22	5	43	25	5
Platelets	6	5	1	9	11	0	22	35[b]	0[b]	3	1[a]	0[a]
Febrile neutropenia	–	14	0	–	18	0	–	2[a]	0[a]	–	18	0
Nausea	32	29	–	14[c]	11[c]	–	35	23	–	33[c]	14[c]	–
Vomiting	38	13	0	17[c]	5[c]	0[c]	34	14	0	29[c]	7[c]	0[c]
Anorexia	30	33	2	15[c]	17[c]	1[c]	31	26	1	29[c]	20c	1[c]
Fatigue	27	12	1	26	2	1	17[c]	3[c]	0[c]	23[c]	3[c]	0[c]
Diarrhea	33	15	1	4[c]	3[c]	0[c]	7[c]	2[c]	0[c]	8[c]	4[c]	0[c]
Constipation	27	7	0	30	8	0	33	9	0	40[d]	14[d]	0[d]
Neuropathy, motor	1	0	0	1	1	1	0	0	0	0	0	0
Neuropathy, sensory	1	0	0	14[d]	3[d]	0[d]	0	0	0	0	0	0
Alopecia	31	–	–	45[d]	–	–	15[c]	–	–	9[c]	–	–
Arthralgia	2	0	0	20[d]	2[d]	0[d]	0	0	0	1	0	0
Myalgia	1	0	0	16[d]	2[d]	0[d]	0	0	0	1	1	0
Injection site reaction	5	0	–	5	0	–	5	0	–	27[d]	0[d]	–
Pneumonitis	0	1	1	0	1	0	0	0	0	0	1	0
Creatinine	8	1	0	2[c]	0[c]	0[c]	7	0	0	8	1	0
AST	7	1	1	5	1	0	6	3	0	1	3	0
Fever	2	0	0	5	1	0	1	0	0	1	0	0
Treatment-related death	3 (2.0%)			1 (0.7%)			0			1 (0.7%)		

[a]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) lower than that with IP.
[b]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) higher than that with IP.
[c]Incidence of grade 2 or worse toxicity is significantly ($P < 0.05$) lower than that with IP.
[d]Incidence of grade 2 or worse toxicity significantly ($P < 0.05$) higher than that with IP.
GP, cisplatin plus gemcitabine; IP, cisplatin plus irinotecan; NP, cisplatin plus vinorelbine; TC, carboplatin plus paclitaxel.
AST, aspartate aminotransferase; –, no category in the criteria.

60%–74% of the patients received chemotherapy and 6%–9% received thoracic irradiation as second-line treatment (Table 4). The percentages of patients in each treatment group who received second-line chemotherapy were not significantly different ($P = 0.081$).

quality of life

The details of the QoL analysis will be reported elsewhere. No statistically significant difference in global QoL was observed among the four treatment groups based on either the FACT-L Japanese version or the QoL-ACD. Only the physical domain evaluated by QoL-ACD was significantly better in TC, GP, and NP than in IP.

discussion

Many randomized phase III studies have compared platinum-plus-new-agent doublets in NSCLC, but, this is the first to evaluate the efficacy of an irinotecan-containing regimen in comparison with other platinum-plus-new-agent doublets in NSCLC [14–17]. Although non-platinum-containing chemotherapy regimens are used as alternatives, doublets of platinum and a new-generation anticancer agent, such as TC, GP, and NP, are considered standard chemotherapy regimens for advanced NSCLC worldwide [13–17, 25]. Although the non-inferiority of none of the three experimental regimens could be confirmed in this study, no statistically significant differences in response rate, OS, TTP, or TTTF were observed between the reference regimen and the experimental regimens. All four platinum-based doublets have similar efficacy against advanced NSCLC but different toxicity profiles. Nevertheless, IP was still regarded as the reference regimen in this study because the non-inferiority of none of the three experimental regimens could be confirmed.

OS in this study was relatively longer than previously reported. The estimated 1-year survival rate in the reference arm was 43%, but the actual 1-year survival rate was 59.2%, much higher than expected. The MSTs reported for patients treated with TC, GP, and NP in recent phase III studies have ranged from 8 to 10 months, and in the present study they were 12.3, 14.0, and 11.4 months, respectively [14–17]. One reason for the good OS in this study was the difference in patient selection criteria, for example exclusion of PS2 patients. Ethnic differences in pharmacogenomics have also been indicated as a possible reason for the good OS in this study [26]. The OS in IP in this study, however, was better than in previous Japanese studies [18, 19]. TTP in this study ranged from 4.0 to 4.7 months, and was similar to the TTP of 3.1–5.5 months reported in the literature [15, 16]. OS not TTP was longer in this study

Table 4. Second-line treatment

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine	
Number of patients	145	145	146	145	
Chemotherapy	107 (74%)	87 (60%)	101 (69%)	95 (66%)	$P = 0.081$
Docetaxel	39	25	50	51	
Gefitinib	11	9	18	12	
Paclitaxel	15	14	7	11	
Gemcitabine	24	28	17	28	
Vinorelbine	9	12	2	9	
Irinotecan	15	4	3	3	
Thoracic irradiation	8	10	13	10	

than previously reported, and higher 2-year survival rates, 21.4%–31.5%, were observed in the minimum 2-year follow-up in this study. Second-line or later treatments may affect survival, because docetaxel has been established as standard second-line chemotherapy for advanced NSCLC [27, 28]. Gefitinib is also effective as second-line or later chemotherapy for advanced NSCLC, especially in Asian patients, never smokers and patients with adenocarcinoma [29–32].

The toxicity profile of each treatment differed and the toxicity of all four regimens was well tolerated. Overall QoL was similar in the four platinum-based doublets. Only physical domain QoL evaluated by the QoL-ACD was statistically better in TC, GP, and NP than in IP. This finding is presumably attributable to the fact that diarrhea is a statistically less frequent adverse effect of TC, GP, and NP than of IP.

In conclusion, all four platinum-based doublets had similar efficacy for advanced NSCLC but different toxicity profiles. All the four regimens can be used to treat advanced NSCLC patients in clinical practice.

appendix

Institutions of the FACS Cooperative Group: National Hospital Organization (NHO) Hokkaido Cancer Center, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Niigata Cancer Center Hospital, Tochigi Cancer Center, NHO Nishigunma National Hospital, Saitama Cancer Center, National Cancer Center Hospital East, Chiba University Hospital, National Cancer Center Hospital, Tokyo Medical University Hospital, Japanese Foundation for Cancer Research, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kanagawa Cardiovascular and Respiratory Center, Aichi Cancer Center Hospital, Prefectural Aichi Hospital, Nagoya City University Hospital, NHO Nagoya Medical Center, Nagoya University Hospital, Gifu Municipal Hospital, NHO Kyoto Medical Center, Osaka City General Hospital, Osaka City University Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, NHO Toneyama Hospital, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Kinki University School of Medicine, Rinku General Medical Center Izumisano Municipal Hospital, Kobe Central General Hospital, The Hospital of Hyogo College of Medicine, Hyogo Medical Center for Adults, Tokushima University Hospital, Kagawa Prefectural Central Hospital, NHO Shikoku Cancer Center Hospital, Hiroshima University Medical Hospital, NHO Kyushu Cancer Center Hospital, Kyushu University Hospital, National Nagasaki Medical Center, Nagasaki Municipal Hospital, Nagasaki University Hospital of Medicine and Dentistry, Kumamoto Chuo Hospital, Kumamoto Regional Medical Center, NTT West Osaka Hospital.

acknowledgements

This study was supported by Bristol-Myers K.K., Tokyo; Eli Lilly Japan K.K., Kobe; and Kyowa Hakko Kogyo Co. Ltd, Tokyo, Japan.

references

1. Cancer Statistics in Japan 2005: The Editorial Board of the Cancer Statistics in Japan. Tokyo, Japan: Foundation for Promotion of Cancer Research 2005.
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995; 311: 899–909.
3. Fukuoka M, Niitani H, Suzuki A et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 1992; 10: 16–20.
4. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med 1995; 332: 1004–1014.
5. Gelmon K. The taxoids: paclitaxel and docetaxel. Lancet 1994; 344: 1267–1272.
6. Hertel LW, Border GB, Kroin JS et al. Evaluation of the antitumor activity of gemcitabine (2',2'-difluoro-2'-deoxycytidine). Cancer Res 1990; 50: 4417–4422.
7. Binet S, Fellous A, Lataste H et al. Biochemical effects of navelbine on tubulin and associated proteins. Semin Oncol 1989; 16 (2 Suppl 4): 9–14.
8. Kubota K, Watanabe K, Kunitoh H et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 2004; 22: 254–261.
9. Le Chevalier T, Brisgand D, Douillard JY et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: results of a European multicenter trial including 612 patients. J Clin Oncol 1994; 12: 360–367.
10. Belani CP, Lee JS, Socinski MA et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005; 16: 1069–1075.
11. Yana T, Takada M, Origasa H et al. New chemotherapy agent plus platinum for advanced non-small cell lung cancer: a meta-analysis. Proc Am Soc Clin Oncol 2002; 21: 328a.
12. Baggstrom MQ, Socinski MA, Hensing TA et al. Third generation chemotherapy regimens (3GR) improve survival over second generation regimens (2GR) in stage IIIB/IV non-small cell lung cancer (NSCLC): a meta-analysis of the published literature. Proc Am Soc Clin Oncol 2002; 21: 306a.

13. Hotta K, Matsuo K, Ueoka H et al. Addition of platinum compounds to a new agent in patients with advanced non-small-cell lung cancer: a literature based meta-analysis of randomised trials. Ann Oncol 2004; 15: 1782–1789.
14. Kelly K, Crowley J, Bunn PA et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: a Southwest Oncology Group Trial. J Clin Oncol 2001; 19: 3210–3218.
15. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92–98.
16. Scagliotti GV, De Marinis F, Rinaldi M et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002; 20: 4285–4291.
17. Fossella F, Pereira JR, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 Study Group. J Clin Oncol 2003; 21: 3016–3024.
18. Negoro S, Masuda N, Takada Y et al. Randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer. Br J Cancer 2003; 88: 335–341.
19. Niho S, Nagao K, Nishiwaki Y et al. Randomized multicenter phase III trial of irinotecan (CPT-11) and cisplatin (CDDP) versus CDDP and vindesine (VDS) in patients with advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 1999; 18: 492a.
20. Fukuoka M, Nagao K, Ohashi Y et al. Impact of irinotecan (CPT-11) and cisplatin (CDDP) on survival in previously untreated metastatic non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2000; 19: 495a.
21. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92: 205–216.
22. Cella DF, Bonomi AE, Lloyd SR et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995; 12: 199–220.
23. Kurihara M, Shimizu H, Tsuboi K et al. Development of quality of life questionnaire in Japan: quality of life assessment of cancer patients receiving chemotherapy. Psychooncology 1999; 8: 355–363.
24. Matsumoto T, Ohashi Y, Morita S et al. The quality of life questionnaire for cancer patients treated with anticancer drugs (QOL-ACD): validity and reliability in Japanese patients with advanced non-small-cell lung cancer. Qual Life Res 2002; 11: 483–493.
25. Pfister DG, Johnson DH, Azzoli CG et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004; 22: 330–353.
26. Gandara DR, Ohe Y, Kubota K et al. Japan-SWOG common arm analysis of paclitaxel/carboplation in advanced stage non-small cell lung cancer (NSCLC): a model for prospective comparison of cooperative group trials. Proc Am Soc Clin Oncol 2004; 22: 618a.
27. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18: 2095–2103.
28. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18: 2354–2362.
29. Kris MG, Natale RB, Herbst RS et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003; 290: 2149–2158.
30. Fukuoka M, Yano S, Giaccone G et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). Clin Oncol 2003; 21: 2237–2246.
31. Takano T, Ohe Y, Kusumoto M et al. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. Lung Cancer 2004; 45: 93–104.
32. Takano T, Ohe Y, Sakamoto H et al. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. J Clin Oncol 2005; 23: 6829–6837.

Clinical Trials for Lung Cancer in Progress in Japan

Ikuo Sekine, Yuichiro Ohe, Nagahiro Saijo and Tomohide Tamura

39

Contents

39.1 Introduction

Lung cancer has been the leading cause of death from cancer in many countries, despite extensive basic research and clinical trials. About 80% of patients with lung cancer have already developed distant metastases, either by the time of the initial diagnosis or by the time recurrence is detected after surgery for local disease. Systemic chemotherapy is the mainstay of lung cancer treatment, although its efficacy is still limited. Therefore, new chemotherapeutic agents continue to be developed against lung cancer [1].

39.2 Drug Approval System in Japan

Since 1955, 23 anticancer drugs have been approved for use against lung cancer in Japan. Of these, 9 were discovered and developed in Japan, including mitomycin, bleomycin, and the topoisomerase I inhibitor irinotecan, and are routinely used all over the world. The Japanese Pharmaceutical Affairs Law (PAL) was enacted in 1948, and was first amended in 1960 to provide for regulations to ensure the maintenance of the quality, efficacy, and safety of drugs and medical devices, and to promote research and development of these medical and pharmaceutical products. Good Clinical Practice was enforced by the Bureau Notification of the Ministry of Health and Welfare of Japan in 1989. In 1996, PAL and its related laws were amended to strengthen Good Clinical Practice, Good Laboratory Practice, Good Postmarketing Surveillance Practice, and standard compliance reviews, conforming to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [2]. In contrast to the laws prevailing in the US and EU, in Japan, marketing approval for anticancer agents can be granted based on reports of the antitumor effects of the new agents in phase II studies. Two independently conducted comparative phase III trials with survival as the endpoint are required after the approval, with at least one of these conducted as a post-marketing sponsored (PMS) trial in Japan [2].

39.3 Recent Clinical Trials for Non-Small-Cell Lung Cancer

Several randomized phase III trials for previously untreated advanced non-small cell lung cancer (NSCLC) have been conducted by Japanese pharmaceutical companies. A three-arm trial of cisplatin + vindesine versus cisplatin + irinotecan versus irinotecan alone conducted on 398 patients with stage IIIB or IV NSCLC between 1995 and 1998 showed that the overall response rate (31%, 43%, and 21%, respectively, $p < 0.001$), but not the overall survival rate (median survival time [MST], 47, 52, and 47 weeks, respectively, $p = 0.099$), was significantly better in the cisplatin + irinotecan arm than in the other two arms [3]. A second trial conducted on 210 patients with advanced NSCLC, comparing cisplatin + vindesine versus cisplatin + irinotecan, showed no statistically significant difference in the overall response rate (22% versus 29%) or survival rate (MST, 50 versus 45 weeks) between the two arms [4]. A randomized phase III trial of docetaxel + cisplatin versus vindesine + cisplatin was conducted between 1998 and 2000 on 305 patients with stage IV NSCLC. Both the overall response rate and the survival rate were significantly superior in the docetaxel + cisplatin arm as compared to the vindesine + cisplatin arm (response rate, 37% versus 21%, re-

spectively, $p < 0.01$; MST, 11.3 versus 9.6 months, respectively, $p = 0.014$) [5, 6]. After the commercial use of paclitaxel, gemcitabine, and vinorelbine was approved for NSCLC in 1999, a phase III study was conducted to confirm the efficacy and safety of these agents, to fulfill the requirements of PAL. A four-arm randomized phase III study of these agents for NSCLC was conducted in cooperation with three pharmaceutical companies. The four arms consisted of cisplatin (80 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1, 8, and 15) administered every 4 weeks as the reference arm; carboplatin (area under the curve [AUC] 6 on day 1) + paclitaxel (200 mg/m^2 on day 1) administered every 3 weeks; cisplatin (80 mg/m^2 on day 1) + gemcitabine (1,000 mg/m^2 on days 1 and 8) every 3 weeks; and cisplatin (80 mg/m^2 on day 1) + vinorelbine (25 mg/m^2 on days 1 and 8) administered every 3 weeks. Of a total of 602 patients registered from 44 institutes in Japan between 2000 and 2002, 581 were assessable for response, toxicity, and survival. The overall response rates in the four arms were 31%, 32%, 30%, and 33%, respectively, and the MST was 14.2, 12.3, 14.8, and 11.4 months, respectively. Non-inferiority of the three experimental arms as compared to the reference arm was not demonstrated in this study [5, 6].

Docetaxel monotherapy is the standard second-line treatment for NSCLC patients, based upon the demonstration of improved survival and quality of life in phase III studies [7, 8]. The Japan Clinical Oncology Group (JCOG) conducted a phase III trial (JCOG0104) to evaluate the efficacy and toxicity of gemcitabine combined with docetaxel in NSCLC patients with a history of prior platinum-based chemotherapy. The chemotherapeutic regimens compared in this study consisted of docetaxel alone (60 mg/m^2 on day 1) or docetaxel (60 mg/m^2 on day 8) + gemcitabine (800 mg/m^2 on days 1 and 8), repeated every 21 days until disease progression, with a planned sample size of 142 patients per arm. Between January 2002 and April 2003, 65 patients were accrued for each arm. However, this trial was terminated early because of the unexpectedly high incidence of interstitial lung disease (ILD) and three treatment-related (all due to ILD) deaths (5%) in the docetaxel + gemcitabine arm. While the incidence of grade 3–4 neutropenia and febrile neutropenia was similar in both the arms, the incidence of dyspnea (23% versus 14%) and ILD (21% versus 2%) was higher in the docetaxel + gemcitabine arm [9]. A randomized, double-blind, parallel-group, international, multicenter trial of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was conducted in patients with advanced NSCLC with recurrent or refractory disease following therapy with one or two chemotherapeutic regimens, at institutes in Europe, Australia, South Africa, and Japan. Patients were randomized to receive either 250 or 500 mg/day gefitinib using blinded tablets, until disease progression, intolerable toxicity, or withdrawal of consent. Between October 2000 and January 2001, 102 patients were enrolled from 19 institutes in Japan. The objective tumor response rate in the Japanese patients was 28% in both the 250- and the 500-mg/day arms. Thus, there was no difference in the objective response rate depending on the dose of gefitinib, although the incidence of toxicities, including rash, diarrhea, liver damage, and nausea, was relatively lower in the 250-mg/day arm [10]. A randomized, open-labeled phase III trial of second-line chemotherapy with docetaxel versus gefitinib in patients with advanced NSCLC previously treated with platinum-based chemotherapy is in progress in Japan as a PMS trial,

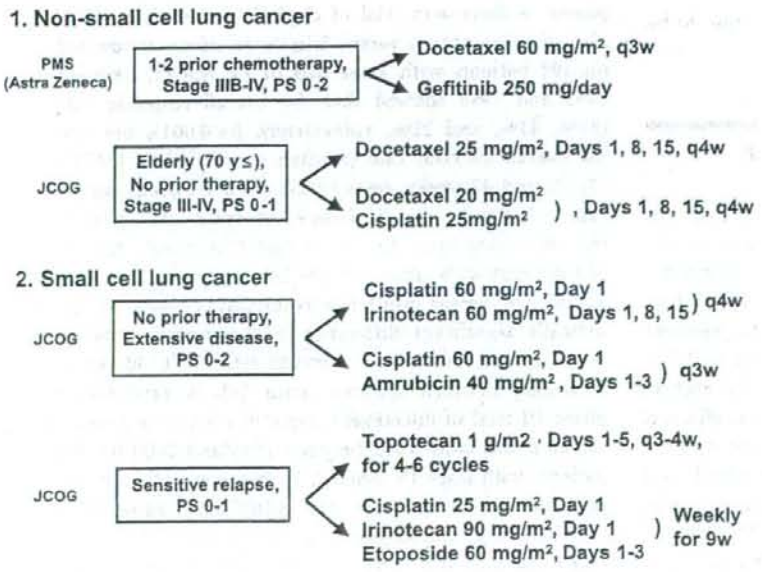

Fig. 39.1. Phase III trials in progress or being planned in Japan. *PMS* Post-marketing sponsored, *JCOG* Japan Clinical Oncology Group

since December 2003. The projected accrual for this study is a total of 484 patients (242 patients per treatment arm) (Fig. 39.1).

Monotherapy with a third-generation cytotoxic agent is widely accepted for the treatment of advanced NSCLC in the elderly, after demonstration of the survival benefit of vinorelbine over standard supportive care alone, without deterioration of the quality of life, in a phase III trial [11]. The West Japan Thoracic Oncology Group (WJTOG) is conducting a phase III trial (WJTOG 9904) of docetaxel (60 mg/m^2 on day 1) versus vinorelbine (25 mg/m^2 on days 1 and 8) administered every 3 weeks for advanced NSCLC in patients aged 70 years or older with no prior history of chemotherapy, a performance status of 0–2, and adequate organ function, as indicated by routine blood counts and blood chemistry, and electrocardiography. The projected sample size for this trial is 90 patients for each arm, and patient accrual for this study has recently been completed.

There are limited data to support the use of platinum-based combination chemotherapeutic regimens in patients over 70 years of age, although platinum doublet is standard treatment for younger patients. A retrospective analysis of 401 patients 65 years of age or older in a large phase III trial of docetaxel + cisplatin versus docetaxel + carboplatin versus vinorelbine + cisplatin revealed no significant differences in the therapeutic outcomes based on the age, although a moderately higher incidence of grade 3–4 asthenia, infection, pulmonary toxicities, diarrhea, and sensory neurotoxicity was noted in the elderly patients [12]. A phase I and a phase II study showed that a combination of cisplatin and docetaxel administered as three consecutive weekly infusions was safe and effective in elderly patients with advanced NSCLC [13, 14]. Based on these data, a JCOG phase III trial of weekly docetaxel versus weekly docetaxel + cisplatin (JCOG0207) is under way (Fig. 39.1). The primary endpoint of this study is the overall survival of the patients treated with these regimens. The secondary endpoints are the response rate, progression-free survival, toxicity, and symptom score. Eligibility includes stage IV or IIIB disease, no history of previous chemotherapy, performance status of 0 or 1, age 70 years or older, and adequate organ functions. The chemotherapeutic regimens consisted of docetaxel (25 mg/m^2) administered on days 1, 8, and 15 every 4 weeks, or docetaxel (20 mg/m^2) + cisplatin (25 mg/m^2) administered on days 1, 8, and 15 every 4 weeks. The projected accrual for this study is a total of 230 patients (115 patients per treatment arm).

39.4 Recent Clinical Trials for Small-Cell Lung Cancer

The JCOG conducted a phase III study of cisplatin (60 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1, 8, and 15) administered every 4 weeks versus cisplatin (80 mg/m^2 on day 1) + etoposide (100 mg/m^2 on days 1, 2, and 3) administered every 3 weeks for untreated extensive small-cell lung cancer (E-SCLC) (JCOG9511). The projected sample size for this study was 230 patients (115 patients per treatment arm), however, enrollment was stopped early because of a statistically significant difference in the survival observed between the two treatment arms on interim analysis. In this interim analysis, 154 patients were randomized to the two treatments, 77 into each arm. The overall response rate and survival were significantly better in the cisplatin + irinotecan group (response rate, 84% versus 68%, respectively, $p = 0.02$; MST, 12.8 versus 9.4 months, respectively, $p = 0.002$) [15]. Based on these observations, the combination of cisplatin + irinotecan is used as the standard chemotherapeutic regimen for E-SCLC in Japan. A three-drug combination of cisplatin, irinotecan, and etoposide was investigated. The maximum tolerated dose of each of the three drugs was determined in phase I studies using two different schedules: a weekly (JCOG9507) and a 4-weekly (JCOG9512) schedule. The antitumor effects of these regimens were evaluated in a randomized phase II study (JCOG9902DI) [16]. The weekly arm consisted of cisplatin (25 mg/m^2 on day 1 at weeks 1–9), irinotecan (90 mg/m^2 on day 1 at weeks 1, 3, 5, 7, and 9), and etoposide (60 mg/m^2 on days 1–3 at weeks 2, 4, 6, and 8), administered with granulocyte colony-stimulating factor (G-CSF) support. The 4-weekly arm consisted of cisplatin (60 mg/m^2 on day 1), irinotecan (60 mg/m^2 on days 1, 8, and 15), and etoposide (50 mg/m^2 on days 1–3) administered with G-CSF support. From August 1999 to October 2000, 30 patients were entered in each of the two treatment arms of this study. Although 70% of all the patients received full cycles of chemotherapy in both arms, treatment delay in the weekly arm and skipping of irinotecan on day 15 in the 4-weekly arm were common because of toxicity. The complete and partial response rates and the MST were 7%, 77%, and 8.9 months, respectively, in the weekly arm, and 17%, 60%, and 12.9 months, respectively, in the 4-weekly arm. Since no overall survival benefit was obtained with the weekly schedule, and the dose of irinotecan on day 15 frequently needed to be skipped in the 4-weekly schedule, a 3-week schedule with irinotecan administered only on days 1 and 8 every 3 weeks might be appropriate for subsequent trials. A randomized phase II trial of cisplatin (60 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1 and 8) versus the same three-drug combination of cisplatin and irinotecan combined with etoposide (50 mg/m^2 on days 1–3) administered

every 3 weeks with G-CSF support in patients with previously untreated E-SCLC is in progress.

Amrubicin (SM-5887) is an entirely synthetic anthracycline that has been shown to possess topoisomerase II inhibitory activity. It has been shown to exert more potent antitumor activity than doxorubicin against various experimental tumors and human tumor xenografts in mice, without any cardiotoxicity. A phase II study of single-agent amrubicin using a schedule of 45 mg/m^2 administered on days 1–3 every 3 weeks yielded an overall response rate of 76%, a complete response rate of 9%, and an MST of 11.7 months in 33 previously untreated E-SCLC patients [17]. The recommended dose of amrubicin when combined with cisplatin was determined to be 40 mg/m^2 on days 1–3 every 3 weeks, and the response rate and MST for E-SCLC patients receiving this combination were 88% and 13.6 months, respectively [18]. The next JCOG phase III trial for this patient population should be of a combination of cisplatin + amrubicin versus cisplatin + irinotecan (Fig. 39.1).

Despite a high response rate to chemotherapy, the majority of SCLC patients eventually develop recurrent disease. At the time of recurrence, the tumor is broadly resistant to second-line chemotherapy and death occurs within a few to several months [19]. Thus, there is need for further development of effective salvage chemotherapy. We conducted a phase II study of cisplatin (25 mg/m^2) administered weekly for 9 weeks, etoposide (60 mg/m^2) administered for 3 days on weeks 1, 3, 5, 7, and 9, and irinotecan (90 mg/m^2) administered on weeks 2, 4, 6, and 8, with G-CSF support, in patients with sensitive relapsed SCLC [20]. Since the drug dose and treatment schedule can be easily modified according to the patient condition in the weekly regimen, it is considered that this regimen may be the most suitable for relapsed SCLC patients, who usually present with severe hematological toxicities during salvage chemotherapy because of poor bone marrow reserve. In a total of 40 patients registered, the overall response rate was 78% with 5 complete responses and 26 partial responses, and the MST was 11.8 months. Grade 3–4 neutropenia and thrombocytopenia were observed in 73% and 33% of the patients, respectively, and the non-hematological toxicities were mild and transient in all the patients. The JCOG is planning a phase III study to compare the efficacy of this regimen with that of topotecan monotherapy in sensitive relapsed SCLC patients (Fig. 39.1).

At diagnosis, 25–40% of patients with SCLC are 70 years old or older, and this percentage is expected to increase with the growing population of geriatric patients. Carboplatin is especially useful for the elderly because only minimum hydration of the patients is required, its non-hematological toxicity is mild, and the dose can be adjusted according to the patient's creatinine clearance [21]. The JCOG evaluated the toxicity and efficacy of this drug in a phase II study (JCOG9409), and observed grade 4 neutropenia and thrombocytopenia in 44% and 12% of the patients, respectively, and complete response and partial response in 6% and 69% of the patients, respectively [22]. We started a large phase III trial in 1998, to compare the clinical efficacy of etoposide (80 mg/m^2 on days 1–3) + carboplatin (AUC = 5) versus etoposide (same dose) + cisplatin (25 mg/m^2 on days 1–3) in elderly patients with SCLC (JCOG9702). The sample size was 220 patients (110 patients for each arm), and registration was completed in February 2004.

39.5 New Agents for the Treatment of Lung Cancer

The development of oral preparations of 5-fluorouracil (5-FU) began in Japan in 1971, based on the finding that 5-FU acts in a time-dependent manner and on the possibility of treating patients on an outpatient basis, without deterioration of the quality of life, when drugs can be administered orally. S-1 (Taiho Pharmaceutical) is a novel oral fluoropyrimidine derivative consisting of tegafur, a prodrug of 5-FU, and two modulators, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [23]. CDHP enhances the serum 5-FU concentrations by competitive inhibition of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU catabolism. Oxo reduces 5-FU-induced diarrhea by inhibiting orotate phosphoribosyltransferase, a phosphoenzyme for 5-FU in gastrointestinal tissue. In a phase I trial, the maximum tolerated dose of S-1 was 75–100 mg/body, and the dose-limiting toxicity was myelosuppression. In a phase II trial of S-1 administered orally at approximately 40 mg/m^2 twice a day for 28 days followed by a 2-week rest period in 59 advanced NSCLC patients without prior history of chemotherapy, the response rate was 22% and the MST was 10.2 months, and the incidence of toxicity was relatively low, including grade 3–4 neutropenia in 7%, thrombocytopenia in 2%, diarrhea in 9%, and stomatitis in 2% of the patients [24]. A combination of S-1 and cisplatin was evaluated in a phase II trial for locally advanced and metastatic NSCLC, in which S-1 was administered orally (40 mg/m^2, twice daily) for 21 consecutive days and cisplatin was administered intravenously (60 mg/m^2 on day 8), and this schedule was repeated every 5 weeks. An overall response rate of 47% and MST of 11 months were obtained, with a mild toxicity profile, including grade 3–4 neutropenia in 29%, grade 3 anorexia in 13%, vomiting in 7%, and diarrhea in 7% of the patients [25]. This drug was approved for use in cases of advanced NSCLC by the Ministry of Health, Labor and Welfare of Japan in December 2004, on condition that a phase III trial of S-1 combined with platinum be conducted for advanced NSCLC patients with a reference arm of the standard regimen for this disease.

Several antifolates have been evaluated for the treatment of NSCLC, but none has as yet gained recognition as a useful drug in standard clinical practice. Pemetrexed (LY231514; Eli Lilly Japan) is a novel antifolate with multiple intracellular targets, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase, all key folate enzymes involved in the de novo synthesis of purines and pyrimidines [26]. The recommended dose of pemetrexed from early phase I trials is 600 mg/m^2 administered every 3 weeks, and the dose-limiting toxicity was myelosuppression [27]. Phase II studies conducted with this drug at the dose of 500 mg/m^2 yielded response rates of 15–23% in untreated patients and 9% in previously treated patients with advanced NSCLC [28, 29]. A phase III trial of pemetrexed versus docetaxel as a second-line chemotherapy for NSCLC showed that this drug had the same antitumor activity as docetaxel, but with less toxicity [30]. Because folic acid and vitamin B_{12} supplementation was found to decrease the toxicity of this agent [31], a Japanese phase I trial of the drug was conducted with such vitamin supplementation [32]. In a total of 31 patients (19 with NSCLC, 7 with malignant pleural mesothelioma, 2 with thymoma, 1 with rectal cancer, and 2 others), grade 3 neutropenia was observed in 4 patients, elevated liver transaminase levels in 2 patients, and skin rash in 1 patient, and the recommended dose of pemetrexed was determined to be 1,000 mg/m^2 every 3 weeks. The pharmacokinetic profile of pemetrexed with vitamin supplementation in Japanese patients was essentially similar to that in western patients, with or without vitamin supplementation. In a total of 20 patients who were evaluable for antitumor activity, a partial response was observed in 4 of the 13 patients with NSCLC, and 1 of 2 patients with thymoma. A phase II trial of this drug in previously treated cases of NSCLC is under way in Japan.

Erlotinib (Chugai Pharmaceutical) is another selective inhibitor of EGFR tyrosine kinase sharing a common chemical backbone with gefitinib. Erlotinib was consistently twice as potent as gefitinib in preclinical studies, from cell-free systems to in vivo toxicity and efficacy studies [33]. At the dose of 150 mg, the recommended dose for phase II trials, the plasma AUC of erlotinib was higher by one order of magnitude than that of gefitinib administered at the dose of 250 mg/day [33]. The response rate of erlotinib in phase II trials in the USA was 12% in patients with NSCLC and 26% in patients with bronchoalveolar carcinoma. Phase III trials of standard platinum-based doublet with erlotinib versus placebo in patients with stage IIIB or IV NSCLC (TALENT and TRIBUTE) failed to show any survival benefit of erlotinib over placebo in a whole patient population [34]. A Japanese phase I trial of erlotinib was conducted in 11 patients with NSCLC, 3 patients with colon cancer, and 1 patient with head and neck cancer, using a dose in the range 50–150 mg/day [35]. The toxicity profile was mild, with grade 1–2 skin rash in 87%, grade 1 diarrhea in 53%, and grade 1–2 elevation of liver transaminases in 40% of patients, except for 1 patient who developed fatal ILD following treatment with 100 mg/day erlotinib. The C_{max} increased in a dose-related manner, but there was no clear trend in the AUC. A partial response was observed in 4 (36%) of the 11 NSCLC patients. A phase II trial in previously treated patients with NSCLC is in progress.

Vascular endothelial growth factor (VEGF) is a potent and specific mitogen for endothelial cells that activates the angiogenic switch in vivo through binding to two distinct receptors on endothelial cells: Flt-1 (VEGFR-1) and Flk-1/KDR receptor (VEGFR-2). Enhanced expression of VEGF is generally correlated with increased neovascularization within the tumor [36]. ZD6474 (AstraZeneca) is an orally bioavailable, small-molecule VEGFR-2 tyrosine kinase inhibitor that also possesses activity against the EGFR tyrosine kinase [37]. Oral administration of ZD6474 to athymic mice bearing various established human tumor xenografts produced a dose-dependent regression of the tumors in all the cases [37]. In addition, ZD6474 inhibited the growth of tumors resistant to EGFR inhibitors [38]. A phase I trial of ZD6474 in 18 Japanese patients with solid tumors refractory to standard therapy showed that ZD6474 was well tolerated when administered at the dose of 100–300 mg/day, with common toxicity, including skin rash in 14, asymptomatic QTc prolongation in 11, diarrhea in 10, and hypertension in 7 patients [39]. The C_{max} and AUC of ZD6474 increased linearly with the dose, and the terminal half-life was long, ranging from 72 to 167 h (median 96 h). The dose level of 100–300 mg/day yielded trough concentrations of the non-protein-bound drug of 0.08–0.31 μmol/l in 10 patients, which was over the IC_{50} (0.04 μmol/L) of ZD6474 for VEGFR-2. Preliminary suggestion of tumor regression was observed in 4 out of 9 patients with NSCLC. A phase II trial in advanced NSCLC patients with a history of prior chemotherapy is in progress in Japan.

Since 1995, the quality of clinical trials has improved remarkably in Japan, and large-scale phase III trials have been conducted with the support of the JCOG, WJTOG, and Japanese pharmaceutical companies:

1. Molecular-target drugs, including gefitinib, erlotinib, and ZD6474, have been evaluated in phase II–III trials of NSCLC in Japan.
2. Amrubicin, a new anthracycline, is promising for the treatment of SCLC, and phase III trials are being planned.

Acknowledgements

We thank Ms. Yuko Yabe for her assistance in the preparation of this manuscript.

Key Points

- Since 1995, 23 anticancer drugs have been approved for use against lung cancer in Japan. Of these, 9 were discovered and developed in Japan, including mitomycin, oleomycin, and the topoisomerase I inhibitor irinotecan, and are routinely used all over the world.
- Since 1995, the quality of clinical trials has improved remarkably in Japan, and large-scale phase III trials have been conducted with the support of the JCOG, WJTOG, and Japanese pharmaceutical companies.

References

1. Sekine I, Saijo N. Novel combination chemotherapy in the treatment of non-small cell lung cancer. Expert Opin Pharmacother 2000; 1:1131.
2. Fujiwara Y, Kobayashi K. Oncology drug clinical development and approval in Japan: the role of the pharmaceuticals and medical devices evaluation center (PMDEC). Crit Rev Oncol Hematol 2002; 42:145.
3. Negoro S, Masuda N, Takada Y, et al. Randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer. Br J Cancer 2003; 88:335.
4. Niho S, Nagao K, Nishiwaki Y, et al. Randomized multicenter phase III trial of irinotecan (CPT-11) and cisplatin (CDDP) versus CDDP and vindesine (VDS) in patients with advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 1999;18:492a.
5. Kubota K, Nishiwaki Y, Ohashi Y, et al. The Four-Arm Cooperative Study (FACS) for advanced non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2004; 23:616.
6. Kubota K, Watanabe K, Kunitoh H, et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 2004; 22:254.
7. Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective randomized phase III trial. Lung Cancer 2004; 43:183.
8. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18:2095.
9. Takeda K, Negoro S, Tamura T, et al. Docetaxel (D) versus docetaxel plus gemcitabine (DG) for second-line treatment of non-small cell lung cancer (NSCLC): results of a JCOG randomized trial (JCOG0104). Proc Am Soc Clin Oncol 2004; 23:622.
10. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (the IDEAL 1 trial) [corrected]. J Clin Oncol 2003; 21:2237.
11. ELVIS. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999; 91:66.
12. Fossella F, Belani C. Phase III study (TAX 326) of docetaxel-cisplatin (DC) and docetaxel-carboplatin (DCb) versus vinorelbine-cisplatin (VC) for the first-line treatment of advanced/metastatic non-small-cell lung cancer (NSCLC): analyses in elderly patients. Proc Am Soc Clin Oncol 2003; 22:629.
13. Ohe Y, Niho S, Kakinuma R, et al. Phase I studies of cisplatin and docetaxel administered by three consecutive weekly infusions for advanced non-small cell lung cancer in elderly and non-elderly patients. Jpn J Clin Oncol 2001; 31:100.
14. Ohe Y, Niho S, Kakinuma R, et al. A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients. Ann Oncol 2004; 15:45.
15. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002; 346:85.
16. Sekine I, Nishiwaki Y, Noda K, et al. Randomized phase II study of cisplatin irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI). Ann Oncol 2003; 14:709.
17. Yana T, Negoro S, Takada Y. Phase II study of amrubicin (SM-5887) a 9-amino-anthracycline in previously untreated patients with extensive stage small-cell lung cancer (ES-SCLC): a West Japan Lung Cancer Group trial. Proc Am Soc Clin Oncol 1998; 18:450a
18. Ohe Y, Negoro S, Matsui K, et al. Phase I–II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer. Ann Oncol 2005; 16:430.
19. Glisson BS. Recurrent small cell lung cancer: update. Semin Oncol 2003; 30:72.
20. Goto K, Sekine I, Nishiwaki Y, et al. Multi-institutional phase II trial of irinotecan cisplatin and etoposide for sensitive relapsed small-cell lung cancer. Br J Cancer 2004; 91:659.
21. Sekine I, Yamamoto N, Kunitoh H, et al. Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials. Cancer Treat Rev 2004; 30:359.
22. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol 1999; 17:3540.
23. Shirasaka T, Nakano K, Takechi T, et al. Antitumor activity of 1 M tegafur-0.4 M 5-chloro-24-dihydroxypyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. Cancer Res 1996; 56:2602.
24. Kawahara M, Furuse K, Segawa Y, et al. Phase II study of S-1 a novel oral fluorouracil in advanced non-small-cell lung cancer. Br J Cancer 2001; 85:939.
25. Ichinose Y, Yoshimori K, Sakai H, et al. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. Clin Cancer Res 2004; 10:7860.
26. Shih C, Chen VJ, Gossett LS, et al. LY231514 a pyrrolo[23-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 1997; 57:1116.
27. Rinaldi DA. Overview of phase I trials of multitargeted antifolate (MTA LY231514). Semin Oncol 1999; 26:82.
28. Rusthoven JJ, Eisenhauer E, Butts C, et al. Multitargeted antifolate LY231514 as first-line chemotherapy for patients with advanced non-small-cell lung cancer: a phase II study. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1999; 17:1194.
29. Smit EF, Mattson K, von Pawel J, et al. Alimta (pemetrexed disodium) as second-line treatment of non-small-