

Thoracic Oncology Division

Introduction

The incidence of lung cancer in Japan is increasing especially in female and elderly population, and lung cancer has remained the most common cancer death in male patients since 1994. The majority of lung cancer patients are diagnosed at the advanced stage, and the prognosis of these patients is still poor. It is extremely important to establish new effective treatments against advanced lung cancer.

The goals of the Thoracic Oncology Division are to provide the highest quality of treatment and also to establish new effective treatments against lung cancer and other thoracic malignancies through innovative clinical and laboratory research. The Thoracic Oncology Division includes seven staff physicians. A total of three chief residents and 13 residents joined the division during 2003. The division organizes a large clinical study group throughout Japan to develop rationally designed novel therapies and to establish the state-of-the-art therapy. The phase I study group was organized in 1996, and some members of the Thoracic Oncology Division play a key role in the phase I study group.

Routine Activities

The staff physicians attend outpatient service for thoracic diseases, and the division has approximately 80 beds in the hospital. Inpatient care is carried out by five subteams. Each subteam consists of one staff physician and one or two residents.

Protocol and case conferences are scheduled for every Monday morning and afternoon, respectively. The journal club is scheduled for Thursday mornings. A chest conference is held on Thursday evening to discuss with thoracic surgeons, pathologists, and radiation oncologists. A total of 361 new patients were admitted in 2003. Backgrounds and initial treatments of these patients are shown in the table. The initial treatments are chemotherapy in 186, chemoradiotherapy in 63, radiotherapy in 29, supportive care or others in 83.

The treatment strategy for the patients is based on the established evidence and/or the clinical protocols approved by the institutional review board. Patients with stage IV non-small cell lung cancer are treated with platinum-based two-drug combination chemotherapy with

cisplatin (CDDP) or carboplatin (CBDCA) plus paclitaxel (PTX), docetaxel (DTX), vinorelbine (VNR), gemcitabine (GEM) or irinotecan (CPT-11). For locally advanced stage III non-small cell lung cancer, combined modality treatment with concurrent CDDP-based chemotherapy and thoracic radiotherapy (TRT) is indicated. The standard treatment for patients with recurrent/refractory tumor as a second-line chemotherapy is monotherapy with DTX. Recently, gefitinib, a tyrosin kinase inhibitor of epidermal growth factor receptor(EGFR), showed a response rate of 30% as a second-line treatment, although the impact of gefitinib on survival is still unclear. The standard treatments for limited stage and extensive stage small cell lung cancer have been established based on the results of two JCOG phase III trials. Limited stage patients are treated with concurrent etoposide (ETOP)-CDDP chemotherapy and twice-daily TRT. Extensive stage patients are treated with combination chemotherapy with CDDP plus CPT-11. Patients with small cell lung cancer who achieve complete response to the initial treatment receive prophylactic cranial irradiation to prevent brain metastasis.

Research Activities

Research activities of the Thoracic Oncology Division can be divided into five diverse yet interrelated subjects: (1) multi-institutional phase III studies to establish new standard treatments against lung cancer and other thoracic malignancies; (2) combination phase I/II studies to develop new effective chemotherapy regimen, (3) phase I and phase II studies to evaluate new anticancer drugs, (4) pharmacokinetic and pharmacodynamic (PK/PD) studies to investigate interpatient variability, optimal administration schedule and drug-drug interactions; and (5) translational research from bench to bed-side or from bed-side to bench for the development of innovative treatment strategy.

A combined analysis of 240 patients with unresectable locally advanced non-small cell lung cancer who had received concurrent chemoradiotherapy in six JCOG trials during 1989 and 1997 resulted a median survival time of 16.1 months and a five-year survival rate of 14.4%. Mediastinal node status and age were significantly associated with survival of patients. Recent phase II study of concurrent CDDP/VNR chemotherapy and TRT followed by consolidation monotherapy with DTX achieved a response rate of 81% and a excellent median survival time

of 20 months in 93 patients with locally advanced non-small cell lung cancer. However, only 44% of the patients could complete the full treatment planned. In a retrospective study of 112 patients who received gefitinib at the NCCH during July and December 2002, interstitial lung disease(ILD) caused by gefitinib was observed in six patients(5.4%) and four of these patients died of ILD. The risk factors for developing ILD proved to be smoking history and pre-existing pulmonary fibrosis in a multivariate analysis. The response rate in 98 evaluable patients was 33%. Predictive factors for response to gefitinib were female, adenocarcinoma, and no previous history of smoking or TRT. JCOG phase III study of DTX versus

DTX plus GEM in patients with recurrent/refractory non-small cell lung cancer (JCOG0104) was stopped early because of high incidence of interstitial pneumonia in the DTX/GEM arm.

Clinical Trials

Clinical trials carried out in 2003 are shown in the table. Some studies are based on the research program of JCOG, and some are carried out under contract with pharmaceutical companies. Approximately 65% of our inpatients are treated in clinical trials.

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Clinical Trials Carried Out in 2003

Target disease	Stage	Phase	
NSCLC	advanced	II	gefitinib vs. CBDCA/PTX
NSCLC	advanced	II	weekly PTX
NSCLC	postope rec.	II	gefitinib
NSCLC (elderly)	advanced	III (JCOG 0207)	DTX vs. CDDP/DTX
NSCLC	III	II	VP/TRT-DTX
NSCLC	III	I/II	nedaplatin/PTX/TRT
NSCLC (elderly)	III	III (JCOG 0301)	CBDCA/TRT vs. TRT
NSCLC	recurrent	III (JCOG 0104)	DTX vs. DTX/GEM
NSCLC	recurrent	III	DTX vs. gefitinib
SCLC	limited	III (JCOG 0202-MF)	EP/TRT-EP vs. EP/TRT-IP
SCLC	extensive	II	IP vs. IEP
SCLC	recurrent	II	weekly EP/CPT-11
SCLC	recurrent	II	amurubicin
SCLC (elderly)	extensive	III (JCOG 9702)	ETP/CBDCA vs. EP
Thymoma	IV	II (JCOG 9606)	weekly CODE
Thymoma	III	II (JCOG 9605)	weekly CODE-Ope/TRT
NSCLC, pericardial effusion		III (JCOG 9811)	drainage +/- BLM
Lung cancer, anemia		PK/PD	KRN321
NSCLC		PK	gefitinib
Lung cancer (Phase I Team)		Pharmacogenomics	paclitaxel, gemcitabine, CPT-11
Solid tumor	advanced	I	ZD6474, Ro50-8231, E7070, CCI-779, CHC12103, JNS002, ZD6126, ABT-627, HTI-286

NSCLC; non-small cell lung cancer, SCLC; small cell lung cancer, CBDCA; carboplatin, PTX; paclitaxel, DTX; docetaxel, CDDP; cisplatin, VP; vinorelbine/cisplatin, GEM; gemcitabine, EP; etoposide/cisplatin, IP; irinotecan/cisplatin, IEP; irinotecan/etoposide/cisplatin, CPT-11; irinotecan, ETP; etoposide, CODE; cisplatin/vincristine/doxorubicin/etoposide, BLM; bleomycin, TRT; thoracic radiotherapy

Number of New Inpatients in 2003

Non-small cell lung cancer	302
Adenocarcinoma	192
Squamous cell carcinoma	53
Others	57
Small cell lung cancer	46
Thymoma/thymic cancer	6
Mesothelioma	0
Other solid tumor	7
Total	361

Initial Treatment for New Inpatients in 2003

Total number	361
Chemotherapy	186
Chemoradiotherapy	63
Radiotherapy	29
Supportive care	22
Others (no treatment, examination, etc.)	61