New Chemotherapeutic Agents for the Treatment of Non-small Cell Lung Cancer*

The Japanese Experience

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Non-small cell lung cancer (NSCLC) is refractory to systemic chemotherapy, compared with small cell lung cancer. Until recently, only five drugs—cisplatin, vindesine, mitomycin, ifosfamide, and vinblastine—could produce overall response rates of 15% against NSCLC. However, recent efforts have contributed to the development of new drugs with activity against NSCLC, including irinotecan hydrochloride (CPT-11), paclitaxel, docetaxel, vinorelbine, and gemcitabine. Combination chemotherapy against NSCLC using these agents has demonstrated high response rates. In Japan, various combination chemotherapy and combined-modality regimens employing CPT-11 have been evaluated for their efficacy. Randomized controlled trials to establish new state-of-the-art treatments for NSCLC are ongoing.

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In Japan, non-small cell lung cancer (NSCLC) accounts for 80 to 90% of all lung cancer cases, and distant metastases have been demonstrated in >60% of patients at the time of diagnosis.1 Five-year survival rates are 22.2% and 7.5%, respectively, for patients with stage IIIA and IIIB disease. Although combination chemotherapy has achieved overall response rates of 25 to 50% against NSCLC, it remains questionable whether chemotherapy can really improve the survival of NSCLC patients. A recent meta-analysis of randomized controlled trials addressed the following question: does chemotherapy provide a true survival benefit in metastatic NSCLC? The meta-analysis demonstrated (1) that combination chemotherapy increases survival at 3, 6, and 9 months, but not at 12 months, and (2) that quality of life is significantly improved at a lower cost in patients receiving systemic chemotherapy vs supportive care alone.2 Another meta-analysis showed the best combination chemotherapy, including cisplatin, produces a survival benefit even in patients with advanced NSCLC.3 Combination chemotherapy also has proved beneficial in patients with locally advanced NSCLC when given with chest radiotherapy. In addition to classic anticancer agents, new agents like irinotecan hydrochloride (CPT-11), paclitaxel, docetaxel, vinorelbine, and gemcitabine appear promising in patients with stage IV NSCLC.4 Other new agents have also been evaluated or are under investigation for license in Japan. Phase I studies of NB-506, a new topoisomerase I inhibitor, KRN-5500, a spikycinomycin derivative, and UCN-01, a kinase inhibitor, are also ongoing. This article reviews the Japanese experience with recently developed drugs in the treatment of NSCLC.

Semisynthesized in Japan from camptothecin by Yakult Central Institute for Microbiological Research, CPT-11 showed potent antitumor activity against various transplantable murine tumors and human tumor xenografts.5-8 Extensive clinical trials of CPT-11 have been done in Japan, the United States, and Europe.9-16

CPT-11

Phase I study of CPT-11 was begun in 1986.17-19 Doses recommended for phase II studies included 100 mg/m2 weekly, 150 mg/m2 every 2 weeks, and 40 mg/m2 on days 1 to 3 every 3 weeks. In France, the dose of CPT-11 was escalated to 750 mg/m2 every 3 weeks against colon cancer.20-22 Demonstrated to be active clinically, CPT-11 was approved in Japan to treat NSCLC, small cell lung cancer (SCLC), uterine cervical cancer, and ovarian cancer by the Ministry of Health and Welfare (MHW) in 1994. It obtained additional approval to treat stomach cancer, colorectal cancer, breast cancer, skin cancer, and non-Hodgkin’s lymphoma in 1995.23-27

Phase II Study

A phase II study of CPT-11 in 73 patients with measurable NSCLC and no prior therapy was conducted between April 1989 and February 1990.28-30 Patient ages ranged from 34 to 75 years (median, 67 years). Most patients were men and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Forty-five percent of patients had locoregional disease (stage IV). CPT-11 was given at a dose of 100 mg/m2 by 90-min IV infusion weekly.31 The number of weekly doses given ranged from 1 to 17, with a median of 6 doses per patient. Of 72 evaluable patients, 23 (31.9%) showed a partial response (PR) to CPT-11 (95% confidence interval, 20.2 to 43.6%). Median duration of response was 15 weeks, and overall survival was 42 weeks. Leukopenia and diarrhea were the dose-limiting toxic reactions. No cystitis was observed. Pulmonary toxic reactions were observed in six patients. CPT-11 was shown to be very active and well tolerated in patients with NSCLC. In a phase II study against SCLC, CPT-11 showed significant antitumor activity even against refractory disease.32

Phase I Study of CPT-11/Cisplatin

The combination of CPT-11 and cisplatin is reported to have synergistic effect against NSCLC cell lines.33 Two phase I studies of this combination with or without granulocyte colony-stimulating factor (G-CSF) support were conducted in previously untreated patients with

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stage IV NSCLC. In both phase I studies, CPT-11 was given on days 1, 8, and 15 and cisplatin on day 1. This schedule was repeated every 4 weeks. Without G-CSF support, the recommended dose of CPT-11 for phase II study was 80 or 60 mg/m² in combination with 60 or 80 mg/m², respectively, of cisplatin. Fourteen PRs (54%) were observed among 26 evaluable patients during the phase I study without G-CSF. Dose-limiting toxic reactions were granulocytopenia and diarrhea. With G-CSF support, it was possible to increase the dose of CPT-11 to 80 mg/m² in the combination with 80 mg/m² cisplatin.

**Phase II Study of CPT-11/Cisplatin**

A multi-institutional phase II study of CPT-11 in combination with cisplatin was conducted in previously untreated patients with measurable stage IIIB or IV NSCLC, Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate organ function. Between February and August 1992, 70 patients were accrued to receive 60 mg/m² CPT-11 as a 90-min IV infusion on days 1, 8, and 15 in combination with 80 mg/m² of IV cisplatin on day 1. Of 69 evaluable patients, 33 (48%) responded to treatment, with one complete response. The most common side effects were leukopenia (46% grade ≥3) and diarrhea (19% grade ≥3). Other toxic reactions included anemia (35% of patients), thrombocytopenia (9%), nausea and vomiting (35%), and paralytic ileus (4%); two patients died of treatment-related paralytic ileus following severe diarrhea. This combination chemotherapy regimen was also shown to be active against SCLC.

**Phase I Study of CPT-11/Etoposide**

Combining topoisomerase I and topoisomerase II inhibitors is an extremely interesting strategy in cancer chemotherapy. Three phase I studies of CPT-11 in combination with etoposide have been conducted. In the first study, both drugs were administered on days 1, 2, and 3, and the regimen was repeated every 3 or 4 weeks. Four dose levels of CPT-11/etoposide (40/60, 60/60, 60/80, and 80/60 mg/m², respectively) were evaluated for toxicity and therapeutic efficacy. G-CSF was administered on days 4 through 17. Five of seven previously untreated patients with NSCLC achieved a PR. The dose-limiting toxic reaction was diarrhea. The recommended respective doses of CPT-11/etoposide for phase II study were 60/60 mg/m² given on days 1 through 3 every 3 to 4 weeks.

A phase I study of sequential administration of CPT-11/etoposide was conducted in untreated patients with metastatic NSCLC. Twenty-seven patients were randomly assigned to two treatment arms. In arm A, CPT-11 was given over 90 min on days 1 to 3, and etoposide was given over 60 min on days 4 to 6. In arm B, etoposide was given on days 1 to 3 and CPT-11 on days 4 to 6. G-CSF was given daily on days 7 to 17 in both arms. The starting doses were 60 mg/m² and 40 mg/m² for etoposide and CPT-11, respectively. The CPT-11 dose was to be escalated to 60 mg/m² in both arms. However, even at the starting doses, more than one third of patients in both arms experienced dose-limiting toxic reactions. It was concluded that the combination of CPT-11/etoposide, given in sequential schedules, showed intolerable toxic reactions without a reasonable response.

In the third study, a fixed dose of etoposide (80 mg/m² IV on days 1 to 3) was combined with weekly administration of CPT-11. The starting dose of CPT-11 was 60 mg/m². G-CSF was given on days 4 to 21, excluding days of CPT-11 administration. The maximum tolerated dose of CPT-11 was 90 mg/m². Diarrhea and leukopenia were the dose-limiting toxic reactions. The recommended doses of this combination for phase II studies in patients without prior chemotherapy are 80 mg/m² CPT-11 (days 1, 8, 15) and 80 mg/m² etoposide (days 1 to 3), plus 2 μg/kg of G-CSF (days 4 to 21, excluding days of CPT-11 administration).

**Phase II Study of CPT-11/Etoposide**

A phase II study of CPT-11/etoposide was conducted by the Japanese Clinical Oncology Group (JCOG) in previously untreated patients with measurable NSCLC. Patients had to have adequate organ function, an expected survival of at least 6 weeks, measurable or evaluable lesions, Eastern Cooperative Oncology Group performance status ≤1, and no prior chemotherapy and thoracic radiotherapy. Between October 1993 and March 1994, 61 patients were enrolled in the study. Among 59 evaluable patients, 13 achieved a PR for an overall response rate of 21.3%. Dose-limiting toxic reactions were granulocytopenia, diarrhea, and interstitial pneumonitis. One patient died of treatment-related hypovolemic shock induced by hematemesis. Median survival was 10 months, and the 1-year survival rate was 36.1%. The authors concluded that concurrent administration of CPT-11/etoposide with recombinant human G-CSF support was modestly active against metastatic NSCLC.

**Phase I/II Study of CPT-11/Cisplatin Plus Concurrent Thoracic Radiation Therapy**

The radiosensitizing effects of CPT-11 and cisplatin have been demonstrated preclinically. Based on these results, a phase I/II study of concurrent chemoradiotherapy with CPT-11 and cisplatin was conducted to determine the regimen’s maximum tolerated doses and efficacy in patients with locally advanced NSCLC. From September 1994 to January 1995, 12 previously untreated patients with unresectable stage IIIA/B NSCLC were enrolled. Chemotherapy (CPT-11 on days 1, 8, and 15 with cisplatin on day 1) was scheduled to be repeated every 4 weeks for three courses. Thoracic radiation therapy was started on day 2 of the first course of chemotherapy and given to a total dose of 60 Gy in 30 fractions over 6 weeks. Six patients were enrolled in each of two dose levels of chemotherapy. At level 1 (CPT-11, 40 mg/m², and cisplatin, 60 mg/m²), four patients completed three courses; the other two patients could receive only one and two courses because of prolonged leukopenia and neutropenic fever with hypotension, respectively. At level 2, three patients completed other courses of chemotherapy; among the other three patients, each of whom received only one...
course, two patients refused further treatment due to diarrhea and one patient died of pneumonia. Three patients were withdrawn from thoracic radiation therapy because of neutropenia after receiving doses of 16, 36, and 38 Gy. Since the dose intensity of CPT-11 and thoracic radiation therapy in this trial was low, the trial was discontinued at level 2. The authors concluded that concurrent chemoradiotherapy with CPT-11 and cisplatin was unacceptable.

Phase III Studies

Two and one randomized controlled studies, evaluating the efficacy of CPT-11, 60 mg/m², and cisplatin, 80 and 60 mg/m², are ongoing against NSCLC and SCLC, respectively. For patients with NSCLC, two manufacturers (Yakult Honsha Co, Ltd; Tokyo, Japan, and Daiichi Pharmaceutical Co, Ltd; Tokyo, Japan) have organized two study groups based on MHW governmental guidelines for the approval of new anticancer drugs. The eastern and western Japan groups are conducting two- and three-armed randomized controlled studies. The sample size of each study group is 100 and 130 cases per arm, respectively. Patient accrual is scheduled to be completed within 2 years.

For patients with extensive SCLC, JCOG is conducting a randomized controlled trial comparing CPT-11/cisplatin with etoposide/cisplatin. The schedule of CPT-11/cisplatin is the same as that used in the arm of NSCLC. For etoposide/cisplatin, 100 mg/m² of etoposide is administered for 3 consecutive days, and 80 mg/m² of cisplatin is given on day 1. This regimen is repeated every 3 or 4 weeks. One hundred fifty patients are expected to be accrued in each arm over 2.5 years.

PACLITAXEL

Paclitaxel has been evaluated extensively in the United States, and early results of combination trials are extremely encouraging with respect to response, survival, and toxicity. The first clinical trial in Japan began October 1991 as a phase I study of paclitaxel by 24-h IV infusion. The administration method and premedication used were identical to those employed in the US trials.49 The maximum tolerated dose of paclitaxel was determined to be 180 mg/m², and dose-limiting toxic reaction was febrile neutropenia. The recommended dose for patients in the phase II study was 135 mg/m². Based on the results of a European-Canadian trial comparing high- vs low-dose and 24- vs 36-h infusion of paclitaxel in patients with ovarian cancer,50 the next Japanese phase I trial was designed to determine the maximum tolerated dose of paclitaxel in patients with solid tumors.51 Twenty-seven patients each received one of six dose levels of paclitaxel (105, 135, 150, 210, 240, or 270 mg/m²) with premedication. Two patients given 240 mg/m² and one patient given 270 mg/m² unexpectedly had grade 3/4 hypotension immediately following the paclitaxel infusion. Peripheral neuropathy was also dose limiting at 270 mg/m². More than half of the patients experienced grade 4 toxicity at doses of 240 or 270 mg/m². The recommended dose for phase II study was 210 mg/m². Pharmacokinetic/pharmacodynamic analysis demonstrated that the duration of the plasma paclitaxel concentration >0.05 μg/mL, and the percent decrease of granulocytes fits a sigmoid Emax model.52

Phase II Study

Paclitaxel has shown response rates of 21% and 24% against NSCLC when given by 24-h infusion.53,54 Two independent phase II studies administered paclitaxel at a dose of 210 mg/m² for 3 h every 3 weeks (K. Furuse, MD; personal communication; Oct 10, 1997).55 All 60 patients enrolled in each study were evaluable. Response rates in both studies were 38.3% and 31.6%, for a total overall response rate of 35.0% (42/120). The median duration of response was 11.2 months, and the 1-year survival rate was 48%. Fifty percent of patients developed grade 4 neutropenia. Nonhematologic toxic reactions such as myalgia and neuralgia were mild; however, one case of pulmonary toxicity required mechanical ventilatory support for 4 days. Based on these data, dose-escalating studies and phase II studies of paclitaxel given in combination with cisplatin or carboplatin are ongoing in the United States.56,57

DOXETAXEL

A phase I trial of docetaxel was conducted from December 1991 to May 1992.58 The dose of docetaxel was escalated from 10 to 90 mg/m² using six dose levels. Granulocytopenia, the dose-limiting toxic reaction, reached a nadir 9.5 to 19.5 days after administration. Fluid retention was not observed. The recommended dose for phase II study was 60 mg/m² at 3- to 4-week intervals.

Phase II Study

Phase II studies of docetaxel in the United States and Europe showed a >30% response rate in patients no matter what their prior chemotherapy status.59 In all the studies, patients with stage IIIB to IV NSCLC received 100 mg/m² IV as a 1-h infusion every 3 weeks.

Preliminary results of studies by the Memorial Sloan-Kettering Cancer Center, the European Organization for Research and Treatment of Cancer, and the M.D. Anderson Cancer Center showed response rates of 38%, 33%, and 33%, and median durations of response of 5.3+, too early to evaluate, and 5+ months, respectively.60-62 Major toxic reactions were National Cancer Institute Common Toxicity Criteria grade 3 or 4 neutropenia of short duration, mild to moderate hypersensitivity reactions, skin reactions, alopecia, mild reversible peripheral neuropathy, diarrhea, and chronic cumulative nonlife-threatening fluid retention.

In Japan, two independent phase II studies administered docetaxel at a dose of 60 mg/m² by 1-h IV infusion every 3 weeks.63,64 Seventy-seven and 78 patients were accrued, and 75 and 72 cases were evaluable, respectively; PIs were seen in 14 (18.7%) and 18 (25%) patients, respectively, for an overall response rate of 21.7%. Neutropenia (grade >3) was observed in 87% of patients. No fluid retention was observed in patients receiving this dose. The 60-mg/m² dose of docetaxel was demonstrated to be active against NSCLC with tolerable side effects.
Vinorelbine

Vinorelbine has already been approved commercially to treat patients with NSCLC in the United States and European countries. A phase I study of vinorelbine in Japan was conducted from April 1988 to January 1989. Vinorelbine was given IV once or twice weekly for 4 weeks. The starting dose was 10 mg/m², and the maximum tolerated doses were 30 mg/m² (single administration) and 25 mg/m² (repeated administration). The dose-limiting toxic reaction was leukopenia. The recommended doses for phase II study were 20 to 25 mg/m²/wk.

Phase II Study

A phase II study of vinorelbine was conducted in 75 NSCLC patients who had not received prior chemotherapy. Vinorelbine was given at least five times at a dose of 25 mg/m²/wk IV. PR was obtained in 23 patients (30.7%). Neutropenia (grade >3) was observed in 83.3% of patients. Other side effects, such as anorexia, nausea, vomiting, general fatigue, and peripheral neuropathy, were mild and occurred infrequently.

Phase II Trial Comparing Vinorelbine With Vindesine

A randomized controlled trial comparing vinorelbine with vindesine with respect to tumor response and toxicity was conducted in patients with NSCLC. Patients received either vinorelbine, 25 mg/m², or vindesine, 3 mg/m², every week for 4 weeks. Patients refractory to treatment with one drug were crossed over to a regimen containing the other drug (ie, vindesine, 3 mg/m²/wk×3 or vinorelbine, 20 mg/m²/wk×3) in combination with cisplatin, 80 mg/m² every 3 weeks. The combination chemotherapy was repeated for at least two courses. The response rate for vinorelbine (20.3%, 22/105 patients) was significantly higher than that for vindesine (9.3%, 7/75). Leukopenia, the main adverse effect, occurred with equal frequency in both treatment groups. Among the refractory patients, PRs were observed in 10 of 34 patients receiving vinorelbine/cisplatin and 0 of 28 patients receiving vindesine/cisplatin.

Dose Escalation Study of Vinorelbine in Combination With Cisplatin and Mitomycin

A dose escalation study of vinorelbine in combination with cisplatin and mitomycin was conducted in NSCLC patients who had received no prior chemotherapy. The dose of cisplatin was fixed at 50 mg/m². The starting doses of vinorelbine and mitomycin, 20 mg/m² and 4 mg/m², respectively, were escalated to 25 mg/m² and 8 mg/m². Three, 4, 9, and 10 patients were accrued to each dose level; 1 patient in level 4 refused to receive treatment and thus was unevaluable. The dose-limiting toxic reaction was granulocytopenia. Grade 4 thrombocytopenia and ileus were observed in one patient each. Three patients experienced febrile neutropenia and infection at level 4. The recommended doses for phase II study were vinorelbine, 25 mg/m² every week, cisplatin, 80 mg/m² every 4 weeks, and mitomycin, 8 mg/m² every 4 weeks. In the phase II study with this combination at these doses, 11 of 19 patients (57.9%) had a PR. A phase II study comparing the response rate of this regimen with that of vindesine, cisplatin, and mitomycin is scheduled.

New Drugs in Phase I Study and in Preclinical Evaluation

NB-506

NB-506, the novel anticancer compound of glucosyl indolocarbazole derivative, exhibits a potent inhibitory effect on DNA topoisomerase I and shows strong in vitro cytotoxicity against various human cancer cell lines, including NSCLC. Compared with other agents, NB-506 is less toxic and has superior in vitro antitumor activity against various solid tumors. The therapeutic ratio of NB-506 is outstanding because its associated toxic reactions are very low. Between February and November 1994, a single-dose phase I study was conducted using increasing doses of NB-506 given by 1-h IV infusion every 4 weeks. Dose levels of NB-506 were 37.5, 75, 120, and 180 mg/m². Toxic reactions, including nausea, vomiting, and liver dysfunction, were dose related. Half of the patients receiving 180 mg/m² experienced dose-limiting reversible toxic reactions, including noninfectious fever, liver dysfunction, and hypotension. Myelosuppression was mild and well tolerated. The 1-h IV infusion dose recommended for phase II study was 120 mg/m². Based on preclinical data, which show that NB-506 is more effective when given in divided consecutive administrations than in a single bolus infusion, a phase I study of NB-506 given consecutively over 5 days is ongoing (Y. Sasaki, MD; personal communication; April 1, 1996). The starting dose in this trial was 24 mg/m²/d, and the dose has been escalated to 64 mg/m²/d.

KRN-5500

The spikamycins are antitumor antibiotics isolated from Streptomyces alanosinicus and initially identified during screening for novel differentiation inducers of myeloid leukemia cells. The spikamycin derivative KRN-5500, having a tetrodecadine acyl group, was found to have the highest therapeutic index against human gastric and colon tumor xenografts. KRN-5500 mainly inhibits protein synthesis (IC₅₀ [50% inhibitory concentration] = 15 µmol/L.). KRN-5500 could be converted to SAN-glycine, an active metabolite, after its incorporation into tumor cells. KRN-5500 is extremely active in a number of colon, ovarian, lung, and renal cell lines. An ongoing phase I study started in July 1995 is evaluating single administration of KRN-5500 at a starting dose of 3.0 mg/m² and escalated according to the modified Fibonacci’s method.

UCN-01

UCN-01, a compound of indolocarbazole derivatives, was discovered during screening for a protein kinase C inhibitor.
inhibitor. UCN-01 inhibits not only protein kinase C, but also other protein kinase such as cdc2 kinase, resulting in the hypophosphorylation of RB (retinoblastoma protein), cycline A, and CDK2 (cyclin-dependent kinase 2). UCN-01 inhibits cell cycle progression and causes G1 arrest. It inhibits the growth of various tumor cells in vivo and in vitro, but it does not show any intercalation with DNA and does not inhibit DNA-relating enzymes. Based on its unique mode of action, a phase I study of UCN-01 is scheduled to begin this year.

KW-2149

KW-2149 is a mitomycin derivative with disulfide structure (developed by the Kyowa Hakko Co; Tokyo, Japan). Unlike other mitomycin derivatives, however, it does not need a bioreductive enzyme such as DTNADPH dehydrogenase (Quinone)-diaphorase for metabolic activation. It is known to be activated by nonprotein SH (sulfhydryl), including glutathione. It shows antitumor activity against mitomycin- and cisplatin-resistant cell lines. For example, cells transfected with γ-glutamyl cysteine synthetase gene became resistant to mitomycin but not to KW-2149. In a clinical phase I trial conducted by the European Organization for Research and Treatment of Cancer, the dose-limiting toxicity of KW-2149 was pulmonary toxicity but not myelotoxicity. It showed antitumor activity against NSCLC. Preclinical experiments have shown that the use of steroid hormone combined with KW-2149 could inhibit pulmonary toxicity (K. Inoue, PhD; personal communication; Oct 10, 1997). A phase I study of this combination has been scheduled in Japan.

DX-8951f

DX-8951f is a water-soluble and nonprodrug analogue of camptothecin (developed by Daiichi Pharmaceutical Company). It has shown high in vitro potency against a series of malignant cell lines and significant topoisomerase I inhibition, and seems to overcome p-glycoprotein-mediated multidrug resistance. In vivo tumor activity of DX-8951f against gastric adenocarcinoma SC-6 xenografts was greater than that of CPT-11 or topotecan. A clinical phase I study is scheduled.

DISCUSSION

Combination chemotherapy including cisplatin has produced a survival benefit in patients with metastatic and locally advanced NSCLC and seems to be active against stage IIIA NSCLC if used preoperatively. However, it has been argued that any survival benefit for combination chemotherapy is nullified by severe side effects that impair quality of life. The results of early clinical trials of several new anticancer drugs seem to be very interesting. The superiority of new combination chemotherapy is being evaluated in phase III randomized controlled trials. The clinical trial process in Japan has been much improved. The MHW has developed several guidelines that are matched for International Conference of Harmonization-good clinical practice. The JCOG uses the same regulations for clinical trials as the MHW. Following the suggestion of President Clinton, the US Food and Drug Administration has decided to quicken the approval process for anticancer drugs. Under the new rules, a company only has to show that a drug can measurably shrink the size of a tumor, even if only for a short time. In lieu of requiring lengthy testing in the United States, the Food and Drug Administration also will accept evidence of an anticancer drug’s effectiveness from 26 other countries, essentially all those with some system for reviewing and approving drugs. Japan should also discuss efforts to quicken the approval of effective anticancer drugs.

REFERENCES

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