Lung Cancer (2005) **49**, 85—94

ELSEVIER

LUNG CANCER

IASLC

www.elsevier.com/locate/lungcan

Postoperative adjuvant cisplatin, vindesine, plus uracil-tegafur chemotherapy increased survival of patients with completely resected p-stage I non-small cell lung cancer

Munehisa Imaizumi*

Study Group of Adjuvant Chemotherapy for Lung Cancer (Chubu, Japan)

Department of Thoracic Surgery, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Received 27 September 2004; received in revised form 19 November 2004; accepted 23 November 2004

KEYWORDS
Adjuvant chemotherapy;
Stage I;
Non-small cell lung cancer;
Randomized controlled trial;
Five-year survival;
UFT

Summary
Purpose: To evaluate the efficacy of postoperative adjuvant chemotherapy for completely resected p-stage I non-small cell lung cancer (NSCLC).
Materials and methods: Patients who underwent complete resection with lymph node dissection for p-stage I NSCLC (T_1N_0, T_2N_0, adenocarcinoma or squamous cell carcinoma, were eligible. After surgery, 150 patients were stratified according to tumor size and histologic type, and then randomly assigned to 1 of 3 groups (50 patients each group): surgery alone (control group), surgery with chemotherapy; PVU group (2 courses of cisplatin 80 mg/m^2, i.v. $\times$ 1 (day1), vindesine 3 mg/m^2, i.v. $\times$ 1 (days 1 and 8) and UFT 400 mg/day, p.o. for a period of 2 years), and UFT group (UFT 400 mg/day, p.o. for 2 years).
Results: The 5-year survival rates of the PVU group, the UFT group, and the control group were 87.9, 67.7, and 66.3%, respectively. The difference in 5-year survival between the PVU group and the control group was statistically significant ($p = 0.045$, log rank). The 5-year disease-free survival rate of the PVU group (81.1%) was also significantly better than that of the control group (66.5%) ($p = 0.042$, log rank). According to multivariate analysis using Cox's proportional hazard model, the only significantly positive factor on outcome was PVU chemotherapy after surgery.
Conclusion: Postoperative PVU chemotherapy is effective for Japanese patients with completely resected p-stage I NSCLC.

* Tel.: +81 52744 2375; fax: +81 52744 2383.
E-mail address: imaizumi@aiseikan.or.jp.

0169-5002/$ — see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2004.11.025

1. Introduction

Lung cancer is now the most common cause of death from cancer in Japan. Non-small cell lung cancer (NSCLC) accounts for 75—80% of lung cancer cases. It is generally accepted that curative surgery provides important survival benefits for NSCLC, especially in patients with clinical stages I and II. However, even in patients with early stage NSCLC, undetectable distant metastasis at surgery has been reported [1,2]. The 5-year survival rate was only 60—70% for patients with completely resected stage I cancer. Since 1989, taking the possibility of undetectable metastasis into consideration, we have conducted a series of prospective randomized controlled studies to evaluate the efficacy of postoperative chemotherapy for completely resected NSCLC.

Concerning stages I to III cancers, Mountain reported that cyclophosphamide/adriamycin/cisplatin (CAP) chemotherapy is less effective than other types of cisplatin-combination chemotherapy, including cisplatin/vindesine (PV) chemotherapy [3]. However, Wada et al. [4] reported that in a randomized trial by the West Japan Surgery Group, the 5-year survival rates for the uracil-tegafur (UFT) group (64.1%) and the PV + UFT (PVU) group (60.6%) were higher than that for the surgery-alone group (49.0%) (UFT versus surgery alone: $p = 0.02$, log rank). From the results of our second cooperative study of postoperative adjuvant chemotherapy in NSCLC [5], the cisplatin/adriamycin/UFT (PAU) chemotherapy group (5-year survival rate, 61.8%) had a significantly higher survival rate than the surgery-alone group (58.1%) ($p = 0.044$) after adjustment made for patients' clinical characteristics according to Cox's proportional hazards model. In particular, when these cases were divided into tumor size and nodal involvement subgroups, the 5-year survival rates of pT_1N_0 and pT_2N_0 in the PAU chemotherapy group (79.6 and 65.5%, respectively) were higher than such subgroups in the surgery-alone group (70.0 and 55.9%, respectively). These findings suggest the necessity of further studies on adjuvant chemotherapy, even in pathologic (p-) stage I disease.

Postoperative adjuvant chemotherapy is not generally chosen for treatment of p-stage I patients. In fact, early-stage postoperative adjuvant chemotherapy trials examining the CAP regimen failed to achieve statistically significant prolongation of survival [6,7]. However, Wada et al. recently showed that PVM (cisplatin + vindesine + mitomycin C and UFT) therapy improved the postoperative survival of patients with resected $pT_1N_0M_0$ NSCLC (5-year survival rates: 75.3% for the control group [surgery without chemotherapy], 90.7% for the chemotherapy-treated group [$p < 0.05$]) [8]. This suggests that prolongation of survival can be achieved in patients with p-stage I (T_1N_0 and T_2N_0) NSCLC by postoperative chemotherapy including long-term oral administration of UFT. Therefore, we performed a prospective randomized trial of p-stage I NSCLC with strictly defined stratification criteria and evaluated the efficacy of postoperative adjuvant chemotherapy to improve surgery results.

2. Patients and methods

2.1. Eligibility criteria and patient selection

We registered only patients with completely resected NSCLC who had to fulfilled the following eligibility criteria: (1) p-stage I disease (pT_1N_0, pT_2N_0) defined by pathological TNM classification, mediastinal lymph nodes had to have been dissected and the resected margin had to be microscopically cancer free; (2) histologic type had to be adenocarcinoma or squamous cell carcinoma; (3) patients must have had chemotherapy or radiotherapy before surgical resection; (4) patient age <75 years at operation; (5) performance status (Eastern Cooperative Oncology Group Scale) of 0 to 2; (6) no other cancer, unless disease-free for 5 years after surgical resection without any other treatment; (7) good renal function (serum creatinine activity <1.5 mg/dl and creatinine clearance >70 ml/min), liver function (aspartate aminotransferase and alanine aminotransferase less than the normal upper limit), hematologic function (white blood cell count >4000/mm^3, platelets >100,000/mm^3 and hemoglobin >11 g/dl), and cardiac function (neither acute myocardial infarction nor congestive heart failure). All patients gave written informed consent before enrollment. The trial was approved by the local medical ethics committees.

2.2. Study design and treatment schedule

After informed consent, histologic type, and pathological TNM classification were recorded by a central telephone registration office, the enrolled patients were divided randomly into 3 groups according to permuted block randomization with stratification for tumor size ($T_1 \leq 3$ cm and $T_2 > 3$ cm) and histologic type (adenocarcinoma and squamous cell carcinoma): surgery alone (control group, $n = 50$); and surgery with chemotherapy; PVU group (2 courses of cisplatin 80 mg/m^2, i.v. $\times 1$ [day 1], vindesine 3 mg/m^2, i.v. $\times 1$ [days 1 and 8], and then 400 mg/day UFT, p.o. for a period of