Original Study

Prognostic Factor Analysis in Patients With Small-Cell Lung Cancer Treated With Third-Line Chemotherapy

Koichi Saruwatari,[1] Shigeki Umemura,[1] Shogo Nomura,[2] Keisuke Kirita,[1] Shingo Matsumoto,[1] Kiyotaka Yoh,[1] Seiji Niho,[1] Hironobu Ohmatsu,[1] Yuichiro Ohe,[3] Koichi Goto[1]

Abstract

We retrospectively analyzed 202 small-cell lung cancer patients receiving third-line chemotherapy. Eastern Cooperative Oncology Group performance status (PS) 0-1 and time to treatment failure after second-line chemotherapy (TTF2) ≥ 5 months were associated with a favorable prognosis. These 2 factors might be helpful for the selection of candidates for third-line chemotherapy and for patient stratification when conducting clinical trials.

Background: There is little information on the clinical outcome of patients with small-cell lung cancer (SCLC) treated with third-line chemotherapy. The purpose of this study was to clarify the prognostic factors of SCLC patients receiving third-line chemotherapy. **Patients and Methods:** Between November 2001 and October 2011, 202 of 648 consecutive SCLC patients at the National Cancer Center Hospital East received third-line chemotherapy. Multivariate Cox regression analysis was performed to identify the prognostic factors for overall survival after third-line chemotherapy. **Results:** The demographics of the 202 patients were as follows: median age 66 years, 83% male, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, 2, and 3 values of 22, 122, 49, and 9, respectively. Median time to treatment failure after second-line chemotherapy (TTF2) was 4.5 months (TTF2 $\geq$ 5/$<$ 5 months, 82/120). The median overall survival after third-line chemotherapy was 5.1 months. Multivariate Cox regression analysis showed that PS 0-1 (hazard ratio, 0.38; 95% confidence interval, 0.27-0.54; $P < .001$) and TTF2 $\geq$ 5 months (hazard ratio, 0.57; 95% confidence interval, 0.41-0.79; $P < .001$) were independent prognostic factors. TTF2 threshold of 5 months was determined on the basis of concordance probability adjusted by PS. **Conclusion:** PS 0-1 and TTF2 $\geq$ 5 months were associated with a favorable prognosis among SCLC patients receiving third-line chemotherapy. These 2 factors might be helpful for the selection of candidates for third-line chemotherapy and for patient stratification when conducting future clinical trials in the third-line setting.

Clinical Lung Cancer, Vol. ■, No. ■, ■-■

Keywords: Performance status, Prognostic factor, Small-cell lung cancer, Third-line, Time to treatment failure

Introduction

Small-cell lung cancer (SCLC) accounts for approximately 12% of all cases of lung cancer and follows a very aggressive course.[1] SCLC is divided into limited disease (LD) and extensive disease (ED) in view of treatment selection and prognosis. LD is generally determined to be limited to one hemithorax, with hilar and mediastinal nodes that can be included within one tolerable radiation portal. ED is any disease beyond the boundaries of LD.[1,2]

The standard therapy for LD-SCLC and ED-SCLC is chemoradiotherapy and chemotherapy, respectively.[3,4] Despite a high sensitivity to the initial treatment, most patients experience disease progression and require salvage therapy. Second-line chemotherapy

Presented in part at the annual meeting of the American Society of Clinical Oncology, May 30 to June 3, 2014, Chicago, IL.

[1]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[2]Biostatistics Division, Center for Research Administration and Support, National Cancer Center, Kashiwa, Japan
[3]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

Submitted: Mar 14, 2016; Revised: May 29, 2016; Accepted: May 31, 2016

Address for correspondence: Shigeki Umemura, MD, PhD, Department of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
Fax: +81-4-7131-4724; e-mail contact: sumemura@east.ncc.go.jp

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.cllc.2016.05.022

can induce tumor regression and improve quality of life. A randomized phase 3 trial comparing oral topotecan with best supportive care revealed the benefits of topotecan in survival and symptom relief in the second-line setting.[5] Several phase 2 trials of other agents, such as amrubicin, irinotecan, or etoposide, had modest efficacy in recurrent SCLC.[6-9]

However, SCLC patients responding to second-line treatment will eventually experience disease progression. At such time, patients with good performance status (PS) are routinely considered for further chemotherapy. In general, 18% to 22% of SCLC patients receiving first-line chemotherapy will receive third-line chemotherapy.[10,11] Several retrospective studies of third-line chemotherapy in SCLC reported a response rate of 18% to 26%, with median survival after third-line chemotherapy of only 4.7 to 5.0 months.[10,11] The role of third-line chemotherapy for patients with disease progression after second-line treatment remains unclear.

We retrospectively analyzed the clinical outcomes of a relatively large cohort of SCLC patients receiving third-line chemotherapy and identified prognostic factors in subsets showing benefit. Identification of these prognostic factors may assist in the selection of candidates for third-line chemotherapy and in patient stratification when conducting future clinical trials in the third-line setting.

Patients and Methods

Patient Selection and Clinical Data

Between November 2001 and October 2011, 648 consecutive patients were histologically or cytologically diagnosed with SCLC in our institute. The patient flow diagram is shown in Figure 1. Among these 648 patients, 39 underwent surgical resection for initial treatment and 12 did not receive any chemotherapy. The remaining 597 patients (92%) received first-line chemotherapy. A total of 370 patients (57%) were treated with second-line chemotherapy, and 202 patients (31%) received third-line chemotherapy. These 202 patients were retrospectively analyzed in this study. The following characteristics at the initiation of first-, second-, and third-line chemotherapy were extracted: age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) PS, stage (LD or ED), chemotherapeutic agents administered, best objective response, time to treatment failure (TTF), and use of prophylactic cranial irradiation or whole-brain radiotherapy. The best objective response was evaluated using chest radiography, computed tomography, and/or magnetic resonance imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with complete response (CR) and partial response (PR) were defined as experiencing a response, and those with stable disease (SD), progressive disease, and disease that was not evaluable were defined as those with nonresponse. TTF was measured from the start of treatment to disease progression or the date of subsequent therapy. This study was approved by our institutional review board (IRB number 2013-326).

Outcome Parameters

The objective response rate (ORR) was determined as the proportion of CR or PR on the basis of the best objective response in each lines. The disease control rate (DCR) was determined as the proportion of patients who experienced CR, PR, or SD. Progression-free survival after third-line chemotherapy (PFS3) was measured from the start of third-line treatment to disease progression or any cause of death. The overall survival after third-line chemotherapy (OS3) was defined as the time from the start of third-line chemotherapy to death or last follow-up.

Figure 1 Distribution of Small-Cell Lung Cancer Patients According to Receipt of First-, Second-, and Third-Line Chemotherapy