Treatment of Small Cell Lung Cancer

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Among patients with lung cancer, approximately 15% have small cell lung cancer (SCLC). SCLC is usually staged as either limited and extensive. Extensive-stage SCLC is treated primarily with chemotherapy. A recent Japanese randomized trial compared cisplatin and irinotecan (IP) with cisplatin and etoposide (EP). Patients in the IP arm did significantly better than patients in the EP arm. In the IP arm, the response rate was 84%, and the median overall survival period was 12.8 months. Limited-stage SCLC is usually treated with concurrent chemotherapy and accelerated radiation therapy, and approximately 20% of patients are cured. Future research should focus on optimizing chemotherapy regimens and radiation therapy schedules. The role of molecular targeted drugs in the treatment of SCLC must also be evaluated. (Cancer Research and Treatment 2003;35:177-180)

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INTRODUCTION

An estimated 75,000 new cases of lung cancer were diagnosed in Japan in the year 2002. Approximately 15% of these cases were diagnosed as small cell lung cancer (SCLC). SCLC is strongly associated with tobacco use, as is non-SCLC (NSCLC). The clinical characteristics of SCLC tend to be more aggressive, but also more sensitive to chemotherapy and radiation therapy than those of NSCLC. Nearly one-third of patients with SCLC present with limited-stage SCLC. This stage is defined as a disease that is confined to one hemithorax, without pericardial or pleural effusion, that can be encompassed by a single radiotherapy port (1). Limited-stage SCLC is a potentially more curable form of SCLC than extensive-stage. Before the use of chemotherapy, patients diagnosed with limited-stage SCLC survived an average of only three months.

Treatment of Extensive-stage SCLC

Platinum-based chemotherapy remains the mainstream of treatment regimens for extensive-stage SCLC. In a meta-analysis of 19 randomized trials comparing a cisplatin-based regimen with a non-cisplatin-based regimen, patients randomized to a regimen containing cisplatin had a significantly higher probability of response and survival, with no significant increase in toxicity (2). Berghmans et al. presented a detailed analysis on the roles of etoposide and cisplatin in the treatment of SCLC (3). Thirty-six eligible trials were performed between 1980 and 1998; one trial compared cisplatin with no cisplatin, 17 trials compared etoposide with no etoposide, nine trials compared cisplatin/etoposide with no cisplatin/etoposide, and nine trials compared cisplatin/etoposide with etoposide alone. These trials concluded that the use of cisplatin and/or etoposide offered a significant survival advantage to patients with SCLC.

In another meta-analysis, Chute et al. evaluated all 21 cooperative group phase III trials performed in North America between 1972 and 1993 (4). Patients with extensive-stage SCLC who were treated during a similar time interval and were listed in the Surveillance, Epidemiology, and End Results database were also included in the analysis. The median of the median survival times of patients treated on the control arms of the phase III trials initiated between 1972 and 1981 was 7.0 months; for those patients enrolled onto control arms between 1982 and 1990, the median survival time was 8.9 months (p=0.001). Trends in the number of trials and the survival periods of patients over time were examined. As a result, a modest 2-month prolongation in the median survival period was demonstrated in patients with extensive-stage SCLC. This improvement in survival was independently associated with both a cisplatin-based therapy regimen and an improvement in best supportive care, measures.

Several agents with significant activities in SCLC were studied in the 1990s (Table 1) (5-15).

Irinotecan is a derivative of camptothecin, an inhibitor of nuclear enzyme topoisomerase I. Topoisomerase I creates single-stranded breaks in DNA during DNA replication. Two trials have evaluated the use of irinotecan in patients with SCLC (5,6). Negoro et al. evaluated 35 patients, 27 of whom had received prior treatment (5). Responses were seen in nine of the 27 previously treated patients and four of the eight previously untreated patients. The principal toxicities were neutropenia and diarrhea. Masuda et al. studied 16 previously treated patients with SCLC (6). Irinotecan (100 mg/m²) was administered weekly with dosages adjusted for toxicity. Responses were seen in seven of the 15 evaluable patients.
producing an overall response rate of 47%. The principal toxicities were diarrhea and neutropenia. Two patients suffered from grade 3 or 4 pulmonary toxicity, and one of these patients subsequently died.

Irinotecan has a complementary mechanism of action to that of cisplatin, which is highly active against SCLC. Studies in preclinical models have shown that these two agents exhibit synergistic activities. Their toxicity profiles also have a minimal amount of overlap. For these reasons, irinotecan was an ideal drug for clinical trials with cisplatin as a first-line combined therapy (16-18).

A phase II trial of cisplatin/irinotecan as a first-line combined therapy in patients with SCLC was conducted by the West Japan Thoracic Oncology Group (including 35 patients with extensive-stage SCLC). In this trial, both agents were administered at a dosage of 60 mg/m²; irinotecan was administered on days 1, 8, and 15 of each 28-day cycle, and cisplatin was administered on day 1 (19). For patients with extensive-stage SCLC, the overall response rate was 86%, with 29% of patients achieving complete responses. The median overall survival period was 13.0 months, with a 2-year survival rate of 17.5%.

Based on the results of the phase II trial, the Japan Clinical Oncology Group (JCOG) conducted a multi-institutional randomized phase III trial (JCOG-9511) comparing cisplatin/irinotecan (IP) with cisplatin/etoposide (EP) in patients with previously untreated extensive-stage SCLC. (20) The patient characteristics in this trial included an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and an age of 70 years or less. Patients with symptomatic central nervous system metastases requiring radiation or corticosteroid treatment were excluded from the study. The experimental arm consisted of irinotecan (60 mg/m²) administered on days 1, 8, and 15 of each four-week cycle, along with cisplatin (60 mg/m²) administered on day 1 for a total of four four-week cycles (IP). This treatment regimen was compared with a regimen of etoposide (100 mg/m²) administered on the first 3 days of each 3-week cycle along with cisplatin (80 mg/m²) administered on day 1 for a total of 4 3-week cycles (EP). The principal endpoint was overall survival. The projected accrual for this trial was 230

patients (115 patients per arm). An interim analysis conducted after 77 patients had been accrued in each arm showed a significant survival advantage for the IP arm. Therefore, further enrollment in the trial was discontinued. The response rate was significantly higher in the IP arm than in the EP arm (84% vs 68%; p=0.02). Additionally, the IP arm showed a statistically significant improvement in the progression-free survival period (6.9 months vs 4.8 months; p=0.003) and the median overall survival period (12.8 months vs 9.4 months; p=0.002) (Fig. 1). The results of this trial were the most exciting to be seen in patients with previously untreated SCLC. The IP regimen is thus another platinum-based combination that should be considered for the treatment of extensive-stage SCLC. Appropriately, the combination of cisplatin and irinotecan has become the new standard treatment for patients with extensive-stage SCLC in Japan. However, several points must be examined before the establishing IP regimen is established as the new standard treatment for extensive-stage SCLC. Three randomized controlled trials comparing the EP regimen with the IP regimen are on going.

### Treatment of Limited-stage SCLC

SCLC has long been recognized to be clinically responsive to radiation therapy, and in vitro radiation of SCLC cell lines has shown that they often have a greater intrinsic radiosensitivity than adenocarcinomas or squamous cell lung cancer cell lines. Consequently, many early trials combining radiation therapy with chemotherapy in patients with SCLC used low total radiation dosages.

A number of trials conducted in the 1970s and 1980s compared chemotherapy alone with chemotherapy and thoracic radiation therapy (TRT) in patients with limited-stage SCLC. These trials varied with regard to the radiation dosage, timing, and choice of chemotherapeutic agents that were used. Wardle and Payne analyzed these trials and found that the addition of TRT improved the local control and survival rates (21). Pigmon et al. obtained individual patient data from these trials and were
able to update the analyses after their original publication (22). They found that the addition of TRT increased the 3-year survival rate from 8.9 to 14.3%, an absolute improvement of 5% and a relative improvement of nearly 50%.

In the 1990s, a number of trials were conducted examining whether radiation therapy and chemotherapy should be administered concurrently or sequentially and whether radiation therapy should be administered early or late in the overall course of treatment. Murray and Coldman performed a meta-analysis of trials that combined chemotherapy and TRT, using 3-year progression-free survival as a surrogate end point for long-term survival (23). The best results were seen when TRT was performed 3 to 5 weeks after the start of chemotherapy. When radiation therapy was further delayed, the survival benefit decreased and approached that seen with chemotherapy alone. The rapid growth of many SCLC cell lines encouraged the exploration of accelerated radiation treatment schedules, with two fractions administered per day with a modest reduction in the fraction size from the usual 1.8 to 2.0 Gy to 1.5 Gy. Two prospective trials compared this approach with conventional daily fractionation. Turrisi et al. compared doses of 45 Gy administered in 25 fractions for >5 weeks with the doses of 45 Gy administered in 30 fractions for >3 weeks. The chemotherapy regimen in this study consisted of four cycles of cisplatin-etoposide. The accelerated regimen resulted in an improved local control rate (intransoracic failure: accelerated therapy arm, 36%; standard therapy arm, 52%) and 5-year survival rate, which was 26% for the twice-daily regimen and 16% for the standard regimen. Although an increased incidence of grade 3 esophagitis (26% vs 11%, respectively) was observed, no other significant differences in toxicity were seen (24).

CONCLUSIONS

The incidence of SCLC has been decreasing; in 1998, SCLC was reported to be account for only 13.8% of all lung cancers. A two-tiered staging system is generally utilized for diagnosis. Platinum-based chemotherapy is the standard for treating extensive-stage SCLC. The combination of cisplatin and irinotecan has become the new standard treatment for patients with extensive-stage SCLC in Japan. Limited-stage SCLC is treated with concurrent chemotherapy and accelerated radiation therapy, enabling approximately 20% of all patients to be cured. Future research should be focused on optimizing chemotherapy regimens and radiation therapy schedules. The effects of molecular targeted drugs, such as STI-571 and farnesyltransferase inhibitor, on treatment are examined. But they could not show any activity against SCLC. The role of the molecular targeted drug in the treatment of SCLC must also be examined.

REFERENCES


