Clinical Benefit of Chemotherapy for Small-Cell Lung Cancer Patients with Extremely Poor Performance Status (PS)

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Abstract

Purpose: We investigated whether small-cell lung cancer (SCLC) patients with The Eastern Cooperative Oncology Group Performance Status (PS) 4 could benefit from chemotherapy.

Methods: PS 4 patients were extracted from medical records, and their characteristics including administered drugs and relevant dosages were obtained. Response, toxicities, survival and changes in PS were retrospectively evaluated.

Results: Of the 314 patients, 25 patients exhibited PS 4. Excepted for 4 patients without chemotherapy, 21 patients were treated with reduced doses in the first cycle, and, with recovery of PS (42.9% improved PS), the doses were increased in subsequent cycles (median of 3 cycles). Response rate was 66.7%, and progression free survival of patients with chemotherapy was 94 days (95% confidence interval [CI], 81 to 107 days). Median survival time was 195 days (95% CI, 81 to 269 days). While, the range of survival times for 4 patients without chemotherapy was 10 to 32 days. Grade 4 neutropenia occurred in 10 patients, and one patient experienced treatment-related death. A significant difference in survival was observed between improved and non-improved PS groups (263 and 83.5 days, respectively; p = 0.029).

Conclusion: There could be a chance for chemotherapy in SCLC patients with PS 4.

Keywords: small cell lung cancer, performance status, overall survival, carboplatin, etoposide

(INTRODUCTION

Small-cell lung cancer (SCLC) represents 13-20% of all lung cancers. It arises from aberrant neuroendocrine cells, thereby differing in origin from non-small cell lung cancer (NSCLC). Although it is an aggressive malignancy with a high incidence of early onset metastases, SCLC displays higher sensitivity to chemotherapy and radiotherapy compared to NSCLC. Indeed, the response rate of patients with SCLC to combination chemotherapies can reach 85-95% in the context of limited disease (LD) and 65-85% in patients with extensive disease (ED). But these values of responses were for SCLC patients with good performance status (PS).

Performance status (PS) is a global assessment of a patient’s actual level of function and ability to self-care. The Eastern Cooperative Oncology Group (ECOG) PS, which was introduced in 1960, provides six points scale (zero to five). PS 4 is defined as being completely disabled, unable to carry out any self-care and/or totally confined to bed or chair. It has been recognized as a major prognostic factor in lung cancer, as well as most other cancer types. In the case of SCLC, poor initial PS has been reported to be an adverse prognostic factor.

In an ED SCLC patient with PS 3 or 4, if the decline in the PS is due to the SCLC itself, it is standard to select combination chemotherapy or supportive care according to the National Comprehensive Cancer Network (NCCN) guidelines. However, a reference point to select either chemotherapy or supportive care is not clear; furthermore, there have only been a few reports citing the use of chemotherapy for SCLC patients with extremely poor PS. Indeed, there have been only two retrospective reports mentioning PS 4 patients in this context. Sakuragi et al reported on five PS 4 patients. One patient improved from PS 4 to PS 1 following two cycles of carboplatin monotherapy, but the other 4 patients showed no improvement. The median survival time was 1.7 months. Baldotto et al reported on ten PS 4 patients treated with either cisplatin plus etoposide or carboplatin plus etoposide, with the MST being 7 days (95% CI: 0.00-14.7). While, there was a prospective phase III trial investigating oral etoposide included...
PS 4 patients\textsuperscript{10}. Although the registration rate of PS 4 patients was only 3%, it was concluded that oral etoposide 50 mg twice daily for 10 days every 3 weeks for four cycles is inferior to standard intravenous multidrug chemotherapy in the palliative treatment of patients with SCLC and poor performance status.

There were no chance for active treatments for PS 4 patients not only with SCLC but also with NSCLC before. We performed a multicenter phase II study named NEJ 001 to investigate the efficacy and feasibility of gefitinib treatment for advanced NSCLC patients harboring epidermal growth factor receptor (EGFR) mutations\textsuperscript{12}. The overall response rate in this patient group was 66%, and median progression free survival (PFS) and MST were 6.5 months and 17.8 months, respectively. PS improved by 79% of the patients. Thus the NCCN guideline has become to recommend use of EGFR tyrosine kinase inhibitor (TKI) for PS4 patients with EGFR mutations. In terms of SCLC, the sensitivity to chemotherapy is high at the first exposure like the relationship between EGFR-mutated tumors and EGFR-TKI, but strong side effects by chemotherapy in SCLC patients with poor PS is problematic compared to EGFR-TKI.

In our clinical practice, after obtaining informed consent to be treated by an active treatment, SCLC patients with PS 4 have been often treated by adjusting chemotherapies, starting at 60-80% of standard doses in the first cycle and increasing to normal doses in subsequent cycles after recovery of PS. As there are only limited reports regarding treatment of SCLC with PS 4, we perform this retrospective analysis.

PATIENTS AND METHODS

This retrospective study was approved by the institutional review board of the Saitama Medical University International Medical Center (SMUIMC; approved #15-272).

Patients evaluated

SCLC patients who were admitted to SMUIMC between April 2007 and October 2015 were reviewed. Among the SCLC patients, PS 4 patients were extracted from medical records, in which the term of “PS 4” was cited, and/or informed consent sheets, in which the content such as “best supportive care due to poor PS” is cited. Their characteristics of age, sex, stage, smoking history, and pretreatment laboratory tests, namely liver (AST/ALT) and renal (Cr) function, along with serum albumin, lactate dehydrogenase (LDH), pro-gastrin-releasing peptide (ProGRP), C-reactive protein (CRP), serum sodium, and carcinoembryonic antigen (CEA) levels, as well as leukocyte blood count (WBC) and platelet count were obtained. Information of tumor staging and ED/LD classification was obtained from a thoracic and abdominal computed tomography (CT), brain image by magnetic resonance imaging (MRI) or enhanced brain CT, and positron emission tomography (PET). Causes of PS 4 before treatment were evaluated via not only the above-mentioned imaging approaches and laboratory tests, but also patient medical records.

Treatments

In principle, the adjusting chemotherapies used in the first cycle to 60-80% of the standard dose used for patients with PS 0-2. In subsequent cycles, judging by the level of myelosuppression caused in the first cycle and recovery of PS, doses of chemotherapies were increased in a stepwise manner by approximately 20%. Actual treatment characteristics included chemotherapy regimen, dosage, and number of chemotherapy cycles received during first line chemotherapy were collected.

Observation

Response, toxicities, survival and changes in PS were observed. Responses were assessed using the RECIST, version 1.1. Survival was calculated from the first chemotherapy administration until death. Treatment-related early death was defined as that occurring within 4 weeks of the first chemotherapy cycle\textsuperscript{13}. AEs were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. PS changes were judged from the medical records.

Statistical analyses

We defined patients who improved from PS 4 to PS 1 or 2 as the PS improved group and those patients who were either unchanged or from PS 4 to change to PS 3 were the PS non-improved group. Overall survival (OS) and progression free survival (PFS) was investigated by the Kaplan-Meier method. Differences in OS between subgroups was analyzed by log rank test. A p value <0.05 was considered to be significant. All statistical analyses were performed using SAS version 9.4 by an independent statistical organization, Medical Toukei, Tokyo.

RESULTS

Patients evaluated

Between April 2007 and October 2015, a total of 314 patients with SCLC were admitted to our hospital; 181 patients (57.6%) with PS 0-1, 108 patients (34.4%) with PS 2-3, and 25 patients (8.0%) with PS 4. Four of the patients with PS 4 received no chemotherapy. For three of these patients, there was no consent for chemotherapy and the remaining patient exhibited acute exacerbation of interstitial pneumonia prior to planned chemotherapy.

The characteristics of the treated patients with PS 4 (n = 21) are summarized in Table 1. Fifteen males and six females had median age of 74 years. Most patients were ex-smokers or current smokers (median 50 pack-years). All of the patients displayed normal renal functioning (Cr < 1.0 mg/dl), but there were 4 patients with AST/ALT levels more than 100 IU/L due to liver metastasis.
Median values of LDH and serum albumin before chemotherapy were 354 U/L and 3.5 g/dL, respectively. Five patients experienced hyponatremia less than 125 mEq/L. Most patients had normal myeloid functions. CRP levels for 10 patients were greater than 2.0 mg/dL and 2 patients had CRP levels more than 10.0 mg/dL. All 21 patients exhibited ED. Brain metastasis were present in 6 patients (28.6%). Interstitial lung disease presented in one patient (4.8%) and emphysema presented in 14 patients (66.7%) as determined by initial chest CT.

The causes of PS 4 within the patient cohort included respiratory failure, disturbance of consciousness, paralysis, pain and general fatigue (Table 1). Respiratory failure was observed in six patients (28.6%) due to pleural effusion, atelectasis, and airway stenosis. Disturbance of consciousness was observed in six patients (28.6%) due to hyponatremia and brain metastasis. Paralysis was observed in five patients (23.8%) due to brain metastasis and spinal cord infiltration. Pain was observed in three (14.3%) patients due to bone metastasis. General fatigue was observed in one patient (4.8%) due to progression of SCLC itself.

Treatments administered

All 21 patients received at least one cycle of chemotherapy (Table 2). Due to oncological emergency, 5 patients (23.8%) were given first-line chemotherapy without pathological diagnosis. These 5 patients were clinically diagnosed by high ProGRP values and CT imaging, but thereafter they were pathologically diagnosed as SCLC. Nineteen patients were treated with carboplatin and etoposide at starting doses of median area under the curve (AUC) 4.0 (range 2.5 to 5.0) on day 1 and median 80mg/m² (range 60 to 100mg/m²) on days 1-3, respectively. One patient was treated with split dose cisplatin (17mg/m², days 1-3) plus etoposide (40mg/m², days 1-3) and another patient was treated with carboplatin (AUC 4.0, day 1) plus paclitaxel (160mg/m², day 1). The median number of cycles of chemotherapy was three, with a minimum of one and maximum of six cycles.

Response, side effects, survival and PS changes

Twenty patients were assessed for response (Table 2). Fourteen of these patients showed partial response (66.7%), while four patients exhibited stable disease (19.0%) and 2 patients displayed progression (9.5%). The overall response rate was 66.7% (95% confidence interval [CI], 46.5 to 86.8%). PFS of patients with chemotherapy was 94 days (95% CI, 81 to 107 days). The median OS from the first line treatment was 195 days (95% CI, 81 to 269 days) (Figure 1). While, the range of survival time for 4 patients without chemotherapy was 10 to 32 days. Ten patients (47.6%) could be discharged due to improvement in PS following chemotherapy.

All 21 patients exhibited some evidence of toxicity (Table 3). Myelosuppression was the major toxicity observed. Grade 3 and 4 neutropenia occurred in 71.4%

| Table 1 Summary of baseline characteristics |
|--------------------------------------------|
| Characteristics                            | N (%) |
| Sex                                        |       |
| Male                                       | 15 (71.4) |
| Female                                     | 6 (28.6) |
| Age median (range), years                  | 74 (50-90) |
| Smoking status                             |       |
| Pack-years, median (range)                 | 50 (0-124) |
| Stage                                      |       |
| Limited disease                            | 0 (0) |
| Extensive disease                          | 21 (100) |
| Brain metastasis                           | 7 (33.3) |
| Laboratory data                            |       |
| ProGRP median value (range), pg/ml         | 989.9 (20.2-41146.4) |
| CEA median value (range), ng/ml            | 5.7 (0.6-89.8) |
| AST median value (range), U/l              | 32 (16-121) |
| ALT median value (range), U/l              | 19 (10-155) |
| LDH median value (range), U/L              | 354 (134-9822) |
| Scr median value (range), mg/dL            | 0.55 (0.36-0.88) |
| Na median value (range), mEq/L             | 136 (110-144) |
| CRP median value (range), U/l              | 1.75 (0.14-24.71) |
| Alb median value (range), U/l              | 3.5 (1.9-5.0) |
| WBC (range), /μl                           | 8940 (4460-17960) |
| Plt (range), /μl                           | 25.0 (6.6-62.5) |
| CT findings                                |       |
| Interstitial lung disease                  | 1 (4.8) |
| Emphysema                                  | 14 (66.7) |
| Symptomatic reasons of PS 4                |       |
| Respiratory failure                        | 6 (28.6) |
| Disturbance of consciousness               | 6 (28.6) |
| Paralysis                                  | 5 (23.8) |
| Pain                                       | 3 (14.3) |
| General fatigue                            | 1 (4.8) |

| Table 2 Treatment outcome of first-line chemotherapy in 21 SCLC patients with PS 4 |
|-----------------------------------------------------------------------------------|
| Number of patients (%) n=21                                                       |
| Regimen of first-line chemotherapy                                                |       |
| Carboplatin/Etoposide                                                             | 19 (90.5) |
| Cisplatin/Etoposide                                                               | 1 (4.8) |
| Carboplatin/Paclitaxel                                                            | 1 (4.8) |
| Treatment cycles median (range), cycles                                           | 3 (1-6) |
| Response for first-line chemotherapy                                              |       |
| Partial response                                                                  | 14 (66.7) |
| Stable disease                                                                     | 4 (19.0) |
| Progressive disease                                                               | 2 (9.5) |
| Not evaluable                                                                     | 1 (4.8) |
| Overall response rate                                                             | 66.7 % |
| Disease control rate                                                              | 85.7 % |
| Second-line chemotherapy                                                          |       |
| Yes                                                                                | 7 (33.3) |
| No                                                                                 | 14 (66.7) |

of the patients during the first cycle even at the reduced doses of chemotherapies used. One patient (4.8%) experienced pneumonitis related to drug administration. Gastrointestinal toxicity was mild, and grade 3 appetite loss was 4.8%. One treatment-related death due to pneumonia occurred (4.8%), but the patient was not associated with febrile neutropenia.
The PS of nine patients (42.9%), whose responses were all PR, were improved by the first cycle of chemotherapy, suggesting that a good response to chemotherapy could assist in recovery of PS. The median survival time for the PS improved group was 263 days (95% CI, 160 to 528 days) and that for the PS non-improved group was 83.5 days (95% CI, 38 to 310 days) (Figure 2). A significant difference was indicated between the two subgroups by log-rank test (p = 0.029).

Eleven patients (52.3%) had neurological complications before chemotherapy. Six patients had paralysis or disturbance of consciousness due to brain metastasis, 3 patients had disturbance of consciousness due to hyponatremia, and 2 patients were paralysis due to bone metastasis and spinal cord infiltration. Six out of 11 patients (55%) improved PS by chemotherapy, but 5 patients (45%) did not improve PS.

**DISCUSSION**

This retrospective study clearly showed that there is a subpopulation of SCLC patients with PS 4 whom are candidates for chemotherapy. Our study indicates some critical points. First, patients who had normal myeloid and renal function but displayed PS 4 due to progression of SCLC itself should be selected. Second, reduced doses of chemotherapy in the first cycle to 60-80% of the standard dose used for patients with PS 0-2 should be employed, and, in subsequent cycles, the doses of chemotherapies were increased in accordance with PS recover. Third, there are no prognostic factors for predicting survival before starting chemotherapy, but PS improvement after the first cycle of chemotherapies teach us a possibility of long survival.

It was found that 95% of causes of PS 4 were classified as oncological emergencies in our study. Oncological emergency diseases, such as the superior vena cava syndrome, stenosis of air tracts, massive pleural effusion, paralysis due to vertebral and/or brain metastasis and hyponatremia were detected as causes of the PS 4 categorization, indicating that SCLC itself worsened PS. It was necessary to evaluate the cause of PS 4 quickly and...
start treatment as soon as possible.

There is currently no fixed opinion on the adjustment of doses of first-line chemotherapy for such poor PS patients. In our observation, although 19 patients underwent carboplatin plus etoposide therapy at reduced doses during the first cycle, 71.4% of patients showed grade 3 or 4 neutropenia, indicating that PS 4 might effect on pharmacodynamics. This adjustment of chemotherapy facilitated PS improvement, and the doses of chemotherapies were increased in the second cycle. This tactic of adjusting chemotherapy is considered to be necessary for SCLC patients with PS 4.

It is very critical to have a reference point to select chemotherapy or supportive care. The observation that all of the treated patients showed normal renal and myeloid function was also considered important. We were unable to identify any prognostic factors for predicting survival before starting chemotherapy. However, PS improvement after the first cycle of chemotherapies was found to correlate with survival. The response rate was 66.7%, but PS was improved in 42.7% of the patients. Some patients with good response could not improve PS because of no recovery of oncologic emergencies especially in neurological complications. And the response to chemotherapy could not predict survival in our series (data not shown).

Two small-scale randomized control trials (RCTs) from the 1970s suggested that first-line chemotherapeutic treatment provides a survival benefit in comparison with supportive care or placebo infusion in patients with extensive SCLC. Results of these clinical trials for extensive SCLC indicated a MST of 56-93 days in those patients receiving best supportive care. However, in our series, the mean MST was 195 days (6.4 months), which is clearly prolonged compared to patients receiving best supportive care in these RCTs. Therefore, even in the case of patients with PS 4, it was considered there was clinical benefit from first-line chemotherapy. In addition, the effects seen in our study were slightly inferior to the results of a prospective clinical trial in patients under 70 years having PS 3, which showed a MST of 6.9 to 7.1 months.

There is a limitation to our study. Major point is a retrospective study in a single institution. However, it was difficult to start a prospective study without any information in this field from the point of ethical issue. As cited in the text, there have been only a few reports describing SCLC patients with PS 4. Based on this retrospective study, we will investigate this theme in a prospective study.

In conclusion, our data supports there is a subpopulation in SCLC patients with PS 4 who are candidates for chemotherapy. Starting with a reduced dose of chemotherapy allows this treatment to be tolerable for PS 4 patients and, after improvement in PS, the chemotherapy level can be increased. However, in case of no improvement of PS, discontinuation of chemotherapy and substitution with best supportive care might be employed.

**Conflict of interest statement:** None declared.

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