Chemotherapy Combined with Hyperthermia Improves the Prognosis for Non-small-cell Lung Cancer

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Abstract: Attempts were made to administer chemotherapy (CT) and/or radiotherapy (RT) combined with hyperthermia (HT) to treat advanced lung cancer, although HT has rarely been used in lung cancer treatments.

This report examines the survival rate in 30 non-small-cell lung cancer (NSCLC) patients who were treated with CT combined with HT beginning with initial therapeutic efforts. The average patient age was 65.1 years old. There were 28 male patients, and 2 female patients. Twenty one patients were classified as having adenocarcinomas, and 9 patients were classified as having squamous cell carcinomas. Stage classification indicated 1 patient was stage IIB, 3 patients were stage IIIA, 11 patients were stage IIIB, and 15 patients were stage IV. The performance status of all patients was good (0-2). Systemic chemotherapy we used were paclitaxel plus carboplatin, camptothecine plus cisplatin (CDDP), mitomycin-C plus vinorelbine plus CDDP, gemcitabin plus CDDP, and TS-1 alone. All patients were administered this therapy safely.

The survival rate for 1-year survival of this therapy was 89.0%, the rate for 2-year survival was 64.5%, and the rate for 3-year survival was 32.5%. The median survival time was 27 months.

It was concluded that this combined therapy can improve the prognosis for NSCLC, and that this therapy can be recommended for additional patients.

Key Words: non-small-cell lung cancer, chemotherapy, hyperthermia, survival rate, improving prognosis

Introduction

Lung cancer is a major cause of cancer-related death worldwide. Most non-small-cell lung cancer (NSCLC) patients have advanced and unresectable disease at diagnosis. These patients are therefore candidates for systemic therapy. A meta-analysis of randomized trial of chemotherapy (CT) compared with supportive care has demonstrated that cisplatin (CDDP)-based CT is beneficial in patients with...
NSCLC\(^{11}\). A number of randomized studies have demonstrated that the addition of platinum to any one of a number other single agents resulted in an improved outcome compared with the single agent alone and that the introduction of third-generation drug, such as gemcitabine (GEM), taxanes, and vinorelbine (VNR), in conjunction with platinum further improved CT in advanced NSCLC. On the basis of these studies, platinum-based third-generation CT doublets are recommended as standard of care for first-line treatment of advanced NSCLC\(^{22}\). Otherwise, hyperthermia (HT) is one of many anti-tumor therapies, and heat enhances cell killing effects and sensitized cells to radiation and many chemotherapeutic agents\(^{3-7}\). Although clinical experience with a combination of systemic CT with HT is limited, CT with HT has been used to treat with variety malignant tumor-head and neck cancer, breast cancer, lung cancer, gastric cancer, pancreatic cancer, cervical cancer, prostate cancer, colorectal cancer, bladder cancer and ovarian cancer\(^9\). In lung cancer, treatment CT combined with HT was rarely selected. Several trials reported that perioperative intrathoracic administration of chemotherapeutic agents with HT was effective against malignant pleural dissemination and effusion from lung cancer or malignant mesothelioma\(^{8-12}\). Matsuda et al. reported a multi-institutional analysis of CDDP based CT in patients with advanced lung cancer where it was not possible to achieve local control using CT alone: the results showed an objective response was achieved in 3 (21\%) of 14 patients\(^{13}\). This group also administered RT with HT to several lung cancer patients without extreme pain or other severe side effects. Based on these experiences and reports of HT sensitization of tumors to chemotherapeutic agents\(^{4-6}\), attempts were made to treat lung cancer with CT combined with HT. The number of patients who had been treated with HT was over 60 in April, 2008. Thirty patients of them were diagnosed in our hospital and treated with CT combined with HT beginning with the initial therapeutic efforts. This report documents the survival rate in these 30 NSCLC patients.

**Materials and methods**

**Patient characteristics**

The clinical characteristics of the patients are summarized in Table I. Thirty NSCLC patients were treated with CT combined with HT beginning with initial therapeutic efforts. A detailed explanation of the concepts used in combining cancer therapy with HT was provided to the patients and their families, and they indicated they understood the rationale for this treatment. The average patient age was 65.1 years old. There were 28 male patients, and 2 female patients. Twenty one patients were classified as having adenocarcinoma, and nine patients were classified as having squamous cell carcinomas. Stage classification indicated 1 patient was stage IIB, 3 patients were stage IIIA, 11 patients were stage IIIB, and 15 patients were stage IV. The performance status of all patients was good (0-2).

**CT**

Data from patients treated with systemic CT are summarized in Table I. Paclitaxel (PAC) plus carboplatin (CBDCA), MVP [mitomycin-C (MMC) plus VNR plus CDDP], GEM plus CDDP, camptothecine (CPT-11) plus CDDP, and TS-1 alone were used.

PAC+CBDCA was administered to 15 patients (Case 1-15). The dosage of PAC used ranged from 60 to 100 mg/treatment and it was administrated three times every week. The dose of CBDCA ranged from 350 to 600 mg/treatment and it was administrated once at first week. PAC had a high frequency
Lung cancer treated with CT and HT • A. Toki et al.

Table I. Patient characteristics.

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1) Ad, adenocarcinoma; SCC, squamous cell carcinoma.
2) TNM classification of lung cancer by International Union Against Cancer (UICC).
3) CT, chemorapy; PAC, paclitaxel; CBDCA, carboplatin; MVP, mitomycin C plus vinorelbine plus cisplatin; CDDP, cisplatin; GEM, gemcitabine; CPT-11, camptothecine.
4) RT, radiotherapy.
5) IP, interstitial pneumonia.
side effect of depilation, thus other CT agents were used with patients who wished to avoid depilation.

MVP was administered to 8 patients (Case 16-23). MMC was administered once at first week, and VNR and CDDP were administered three times every week. The dosage of MMC used ranged from 8 to 15 mg/treatment, that of CDDP ranged from 30 to 40 mg/treatment, and that of VNR ranged from 20 to 30 mg/treatment.

Treatment with GEM+CDDP was administered to with 4 patients (Case 24-27) three times every week. The dosage of GEM used ranged from 1,000 to 1,600 mg/treatment, and that of CDDP ranged from 30 to 40 mg/treatment.

Treatment with CPT-11+CDDP was administered with 1 patient (Case 30) 3 times every week. The dosage of CPT-11 used ranged from 60 to 100 mg/treatment, and that of CDDP ranged from 30 to 40 mg/treatment, and these agents were administered 3 times.

TS-1 that was given orally to 2 patients (Case 28 and 29). Both patients were over 80 years old and could not cope with an intravenous drip type delivery. In addition, 1 patient (Case 29) had gastric cancer, and TS-1 was selected as an anti-gastric cancer agent. The dosage of TS-1 was 100 mg/treatment.

**HT**

The hyperthermia device used a RF-capacitive heating apparatus (Thermotron-RF8, Yamamoto Vinita Co. Ltd., Osaka, Japan). The heating duration for HT ranged from 30 to 50 min, and the power output ranged from 600 to 1,500 W. Heating times and power output were limited by the physical and mental conditions of each patient. The temperature of tumor during HT was not measured. Communications with the patients were maintained as closely as possible, and responses to each patient were made for each individual complaint. Discomfort and pain for each patient varied, and individual responses were required for each individual patient.

**Combination protocols for CT and HT**

The schedules used to administer combination therapies of CT and HT are shown in Fig. 1. HT was used at the time that chemotherapeutic agents, excluding GEM, were delivered dripwise intravenously. When GEM administration was complete, HT was given before 24 h, or 48 h had elapsed. When orally-administrated TS-1 was taken, HT was used once or twice a week, and was continued for 2 or 3 weeks, and was repeated monthly. If patients were able to cope with HT, HT was used up to 3 times a week.

**Data analysis**

The survival rate in April, 2008 was calculated using the Kaplan-Meier method. Survival times are displayed for every month.

**Results**

All patients were able to tolerate CT combined with HT without significant side-effects. Treatment with PAC+CBDDCA with HT was administered to 15 patients and 5 patients of them were given chest RT with HT after their initial CT. The range of their survival times was 5 to 96 months. At the time of the data analysis, 2 patients were alive, and 9 patients were deceased as a consequence of lung cancer. One patient had been moved to another hospital on the 9th month, and 1 patient who had been introduced to gefitinib on the 9th month passed away as a consequence of interstitial pneumonia (IP).
The other patient passed away during the 13th month after developing pulmonary fibrosis which was not drug induced. MVP with HT was administered to 8 patients. Five patients of them were given chest RT with HT to after their initial CT and 2 patients were treated with CT and RT with HT at the same time. The range of the survival times was 13 to 66 months. One patient was moved to another hospital on the 25th month. Treatment with GEM+CDDP with HT was administered to 4 patients. One patient of them was given chest RT with HT to after their initial CT. The range of their survival times was 3 to 14 months. At the time the data was analyzed, 1 patient was alive, 2 patients were deceased as a consequence of IP after being treated with gefitinib on the 3rd and 6th month, and 1 patient died from heart failure on the 14th month. Treatment with CPT-11+CDDP with HT was administered to 1 patient. That patient passed away as a consequence of lung cancer on the 14th month. TS-1 was administered to 2 patients. One was alive and one had passed away on the 8th month.

Eighteen patients were received RT: 13 patients were chest RT and almost patients received 58-60 Gy, 5 patients received brain RT, 30 Gy and 2 patients were bone RT, 30 Gy. When patients experienced pain, excessive heat, etc, during HT, appropriate responses and adjustments were made in every case. In many cases, patients experienced reduced pain, not only from the cancer, but overall and also in the waist and shoulder areas. These patients were able to experience better sleep after HT. HT was used safely with older patients. Twenty four patients were treated with HT since these therapies were initiated. The survival rate of patients treated with combination therapy was calculated using the Kaplan-Meier

\[ a) \]

\[
\begin{array}{ccccccc}
\text{day} & 0 & 1 & 2 & 3 & 4 & 5 & 6 \\
\hline
& \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} \\
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Chemo drug

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& \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} \\
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Hyperthermia

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\begin{array}{ccccccc}
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& \text{↓} & \text{↓} & \text{↓} & \text{↓} \\
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\[ b) \]

\[
\begin{array}{ccccccc}
\text{Sun} & \text{Mon} & \text{Tue} & \text{Wed} & \text{Thu} & \text{Fri} & \text{Sat} \\
\hline
& \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} & \text{↓} \\
\end{array}
\]

Fig. 1. Schedule for combination therapy with CT and HT. a) HT was performed at the same time or the day before the anti-cancer drugs (MVP, PAC+CBDC, CPT-11+CDDP and GEM+CDDP) were administered. b) TS-1 was administered every other day. HT was used during a 7 day weekly cycle. HT was performed twice a week, and this was continued for 2 weeks. This combination pattern was repeated every 2 or 3 months subsequently.
method. The 1-year survival rate was 89.0%, the 2-year rate was 64.5% and the 3-year rate was 32.5%. The median survival time (MST) among all of the patients was 27 months (Fig. 2).

![Fig. 2. Survival rate for patients treated with CT and HT.](image)

Discussion

Combination of doublets platinum and a new-generation anticancer agent, such as PAC + CBDCA, GEM + CDDP are considered standard CT regimens for NSCLC, and many studies have reported 1-year survival rate for NSCLC patients of 40-60%\(^{16-18}\), although older CT regimens (e.g., MMC, ifosfamide and CDDP) for NSCLC patients resulted in survival rates of 10 to 15% at 1-year. Ohe et al. treated CT (CBDCA + PAC, CPT-11 + CDDP, GEM + CDDP and GEM + CDDP) to stage IIIB or IV NSCLC patients who had good performance status (PS) (0-1) as randomized phase III study, and reported that MST, 1-year and 2-year survival rate in CBDCA + PAC were 12.3 months, 51.0% and 25.5%; 13.9 months, 59.2%, and 26.5% in CPT-11 + CDDP; 14.0 months, 59.6% and 31.5% in GEM + CDDP; 11.4 months, 48.3% and 21.4% in VNR + CDDP. In this report, the 60-74% patients were administered CT, and 4-6% patients received chest RT as a second-line treatment\(^{19}\). In our study, we treated CT with HT to stage advanced NSCLC patients who had good PS (0-1) except 1 patient (Case 28). Eighteen patients were given RT and 28 patients had been received CT as a second-line treatment and 22 patients received treatments combined HT after initial CT. The incredible results to us were obtained that MST was 27 months and 1-year, 2-year and 3-year survival rate were 89%, 64.5% and 32.5%.

PS is a critical prognostic factor in advanced NSCLC\(^{17}\) and RT is one of the effective therapies of NSCLC. It is certain that good PS of patients, RT received comparatively a lot of patients, and using HT are the causes of this result. However, only these factors do not seem to have led to such a result. It is necessary to examine the causes of leading this result.
Although the treatment described here using HT appears to produce improved results in survival when compared to these earlier studies, it is not yet possible to confirm the efficacy of using HT for NSCLC based on the results reported here. The current trial was very small, and there were other factors which may have affected the results such as the greatly skewed sex ratio (29 males and 2 females). Heating conditions of each patient were not examined enough. Additional clinical trials using HT for the treatment of NSCLC are necessary. Through such additional clinical trials, it should be possible to confirm that effective HT can be safely delivered while treating patients with a minimum of pain and discomfort. Most patients agreed to be subjects for HT therapy and were comfortable with the treatment and results, although HT is not a comfortable treatment. One study has indicated that HT improves the quality of life (QOL) for cancer patients, especially for lung cancer patients\(^{(2)}\). Currently, drug kinetics and the biological reactions involved with HT therapy are still not completely known. Thus, the combinations of CT with HT which were used here are undoubtedly not optimal. However, the results reported here appear promising. It is necessary to establish and define new methods to combine CT with HT, and this will require additional knowledge and an understanding of drug kinetics and of the biological reactions involved in responses to HT. In view of these results, it is reasonable to expect that CT combined with HT can be developed to produce new therapeutic protocols to improve the prognosis for patients with NSCLC.

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References

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