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Oncothermia with chemotherapy in the patients with small cell lung cancer

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Abstract

Small cell lung cancer constitutes approximately 13% of all lung cancer types & SCLC is one of the most aggressive and lethal forms of lung cancer. And so chemotherapy including radiotherapy would be standard for SCLC, but it has very poor median survival of less than 4 months. This is why another form of additional treatment to chemotherapy would be necessary and so oncothermia will be one of the additive treatment for prolonged survival time.

We made a 6 year-long study of 31 patients with small cell lung cancer at the department of Thoracic & Cardiovascular surgery Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul from April 2006 to March 2012.

23 patients were treated with chemotherapy and oncothermia and 8 patients were treated with chemotherapy only.

1. Cases who have survived more than 3 years were 3. They have been treated with chemotherapy and oncothermia
2. Out of 31 cases, 14 patients died during the treatment, 7 cases with chemotherapy only died, including one long survival case of 28 months, 7 cases with chemotherapy and oncothermia died, including one long survival case of 26 months.
3. Out of 31 cases, 16 people are still alive: 4cases were treated with chemotherapy only, including one long survival case of 28.7 months, 11cases with chemotherapy and oncothermia including three long survival cases of more than 3 years
4. The combined use of chemotherapy and oncothermia has significantly enhanced the survival rate in comparison with the use of chemotherapy only (Log-rank test: p-value 0.0200). Combination of oncothermia treatment with chemotherapy enhance the effect of anticancer drugs to destroy cancer cells and is thought to be able to improve the survival of the patients with small cell lung cancer.

Introduction, background

Lung cancer is one of the most common causes of cancer-related deaths in both men and women worldwide. Its incidence as well as the mortality rates are high, and the prognosis is usually very poor, [1]. In 2006 its age-standardized incidence and mortality rates were estimated to be 75.3 and 64.8/100 000/year, respectively, in men, and 18.3 and 15.1/100 000/year in women in Europe, where the small-cell lung cancer (SCLC) accounts for 15%–18% of all cases [2].The small-cell lung cancer has a fast growth-rate, it quickly disseminates quickly around the mediastinal lymph nodes and forms distant metastases in late diagnosis, and then the median survival is only 2-4 months, the overall prognosis is very poor, [3], [4].

In almost all small-cell lung cancer cases, surgical treatment is not possible it could only be performed only in very limited disease (i.e. T1,N0) [2]; consequently, the main treatments are the chemo- and radiation therapy. In general case of SCLC, even if some reported long-term survival, the overall 2-year survival rate is less than 20%. 5-year survival rate is almost devoid. In limited SCLC, chemotherapy alone reached complete remission (CR) in 50% of relapse cases. Bulky primary tumors were completely destroyed but most of intrathoracic recurrence was difficult to discover. Added to radiation therapy [5] In this case, 30 - 60% recurrence rate has been reduced, radiation pneumonitis, esophagitis, and the overall survival rate was significantly improved. [6]. In addition, initially most of the extensive small-cell lung cancer with advanced small-cell lung cancer, chemotherapy response joteuna for anticancer drug resistance may occur and the overall survival rate was very poor, median survival was 7-10 months ,2-year survival rates of the less

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The most widely used chemotherapy is the Etoposide/Cisplatin (EP) treatment which has a median survival of 8-10 months for patients with extensive disease and 17-20 months for patients with limited-disease, [8].

The concurrent radiotherapy with chemotherapy is used as an optimal treatment for limited SCLC, [9].

Chemotherapy and radiation therapy were performed on the tumor after complete resection and the relationship did not cause death in 19 patients with autopsy and in 13 patients with small-cell lung cancer metastases have been cured [10]. The prognosis of SCLC is generally poor, because micro-metastases occur and surgical resection is not possible. There are frequently occurring insidious transitions [10], [11].

In a study of chemo- and radiation therapies [12] for 28 patients died of other causes than lung cancer has been reported, and 47% was clinically cured. The autopsy study [13] of patients who died from other causes than tumors found that residual cancer cells in the area of lung cancer and mediastinal lymph node regions are 64%.

The prognostic index was constructed for SCLC in Severance hospital, (Korea), retrospectively evaluation of 295 patients revealed 131 cases with limited and 164 cases with extended disease. The median survival was 20.4 months for limited and 7.7 months for extended disease, [14]. A prognostic index was constructed to create four classifications of SCLC considering the variables of the extension of the disease, the performance status, the CYFRA21-1 and the tumor-marker.

Heat therapy could be a feasible option to treat SCLC. The classical loco-regional heat treatment (conventional oncological hyperthermia) has a localized area selection [15]. This boosts the chemo-efficacy, [16], [17], [18] and also increases the effectiveness of radiation therapy [19], [20].

Some successful clinical trials had shown the feasibility of the hyperthermia method for lung cancer. Most of these are applied for non-small-cell lung cancer (NSCLC), combined with radiotherapy, having 14÷70 Gy dose in the given session. The measured response rate (RR) was surprisingly high RR=75%, (n=12, [21]), and RR=100% (n=13, [22]). Others had a comparison to a control-arm (not randomized), increasing the RR from RR=70% (n=30), and RR=53.8% (n=13), to RR=94.7% (n=19, [23]), and RR=76.9% (n=13, [24]), respectively. The second year survival also increased remarkably: from 15% and 15.4% to 35% and 44.4%, respectively. (The first year survival was measured as well, increasing from 30% to 55%, [23]).

The chemo-thermotherapy combination was also investigated for NSCLC with success. In preclinical trials the cisplatine was shown to be effective, [25], so the clinical studies were concentrating on this drug combination. A special case report showed the feasibility [26], and the median survival gain (from 15 (n=20) to 25 (n=32) months), [27]. The median survival was measured in another study [28], as 19.2 months, the RR=73% and the 1 year-survival is 75%. The 5year median survival was measured in another study [29], showing rather high numbers (24.5%, n=30).

However, a problem arises by the classical hyperthermia. The cancer tissue is more active than the surrounding normal tissue, its cell proliferation and metabolism require a lot of energy. When temperature tries to equalize itself in the surrounding, it grows around the tumor. In consequence the surrounding blood vessels expand, the blood flow increases delivers extra nutrition for tumor accelerating its stable proliferation. In this case, the temperature rise of the cancerous tissue will have more metabolic and proliferation activity. Furthermore, hyperthermia effects the intracellular Heat-Shock Proteins (HSP), developing thermo-tolerance of the cells, [30].

The extracellular matrix surrounding the tumor is overburden by ionic metabolites and final metabolic products, which changes their electric properties [31]. [32]. This is used by oncothermia when selecting

the tumorous region, and at the same time absorbing the energy selectively on the malignant cells. The temperature rises only very locally on the malignant cells, and does not rise all over the large volume and does not affect the surrounding normal tissue. In consequence no vasodilatation occurs, no extra proliferation is supported by the blood vessels, the absorbed energy concentrates on the job: destroy only the tumor [33].The method works by impedance tuned, capacitive coupled radiofrequency, with modulated 13.56 MHz.

One of the most advanced hyperthermia-modalities devoted to oncology is oncothermia [33]. The actions widely affect the targeted malignant cells: passing through the malignant cell membrane 1500 nW/μm2 heat-flow, while the normal tissue membranes have only 20 nW/μm2 Oncothermia treatment induces Na+ influx current 150 pA/μm2 while normal Na+ efflux is 12 pA/μm2, [34]. Na+ moves into the malignant cell, the water is also pumped in by electro-osmotic way, increasing the pressure within the cell. By these actions the cell membrane is destroyed and will destroy the cancerous tissue. [35]. For these reasons we expect the effect on the disseminated SCLC lesions with the combination of chemotherapy and radiation therapy. We supposed improved survival rates, when appropriate amount of energy, proper temperature, well-chosen doses, are used in the study [33].

In the preliminary reports [36], [37], [38] the feasibility of oncothermia application was demonstrated on NSCLC and some preliminary case reports and statistical summaries on SCLC were presented in local conferences too, [39], [40]. Systematic study of oncothermia applications for SCLC is still missing. Our present study tries to provide more details in this important field of oncology.

Materials and methods

A prospective, double arm, monocentric study for SCLC was performed. The small-cell lung cancer cases were treated with a combination of chemotherapy and radiation therapy, with complementary oncothermia in our study. It is considered that the applied complex protocol completed by oncothermia maximizes the effectiveness of chemotherapy and may improve the survival rate. We treated 31 patients in duration of 6 years, from April 2006 to March 2012.

7 out of 8 cases in control arm who underwent only chemotherapy were men, and in one case was a woman. The youngest was 54 years old and the oldest was 84 years old. The active arm, 23 patients had the combination of chemotherapy and oncothermia treatment, 19 males and four females. The youngest was 54 years old, the oldest was 79 years old (see table 1.). There was no significant difference between these two groups (Fisher's exact test:> 0.9999; t-test: p-value => 0.8665). The real end-point of the study was the survival time.

All patients had proven SCLC and received chemotherapy. 23 patient received oncothermia in combination with chemotherapy. Oncothermia was provided with EHY-2000 device (Oncotherm GmbH, Germany).

Anticancer drugs in the first-line were Irinotecan (60 mg/ m²) and Cisplatin (60 mg / m²) three times after the chest CT was taken. When the progression of tumor or metastases was detected we replaced the chemotherapy regime by Etoposide (110 mg / m²) and Cisplatin (70 mg / m²) in the second line.

Oncothermia was performed from the first anti-cancer drug treatment period up to 150Watt, 1,490.5 kJ energy by 60 minutes, every second day, with rise in temperature from 38.5°C-42.5°C. In this study we used a 30 cm diameter electrode applied for thorax. Other technical details are shown elsewhere [33], [41].

	CTX.* only			CTX. + Oncothermia			
Age	M	F	Total	M	F	Total	Total
51 – 60	2	-	2	5	1	6	8
61 - 70	4	-	4	8	2	10	14
71 - 80	1	-	1	6	1	7	8
81 - 90	-	1	1	-	-	-	1
	7	1	8	19	4	23	31

Table 1. Patient's profile

Characteristic cases

A male patient aged 67 who had visited our Department with chief complaints of slight fever and sputum in August 2008 was hospitalized for a thorough examination and then diagnosed as a case of limited small cell lung cancer. For treatment, Irinotecan (60mg/m²) and Cisplatin (60mg/m²) were administered 12 times and at the same time, oncothermia was given 24 times (2 cycles) in total, 2 times per week. Then, chest PA and chest CT revealed that he was in complete remission from small cell lung cancer. So, treatments of chemotherapy and oncothermia were stopped from October 2009 and then he was an outpatient follow-up on a regular basis. On Oct. 25th 2010 PET CT showed a normal finding. In April 2011 he was treated by chemotherapy in the Department of Urology, our hospital, for prostatomegaly. Because of the fact that PSA was increased to 4.96 in June 2011, he got a prostate tissue biopsy and was diagnosed with a case of adenocarcinoma. Finally he was treated with the prostate cancer resection using the Da Vinci robot in July 2011. Chest CT was done in July 2011, it found mediastinal lymphadenopathy, and after mediastinoscopy, he was diagnosed as a case of metastatic small cell lung cancer. For chemotherapy, Etoposide (110mg/m²) and Cisplatin (70mg/m²) were 12 times administered in replacement, and another one-cycle treatment of oncothermia was given. In Dec. 2011 and Feb. and April 2012, follow up chest CT found that the patient was in complete remission. During outpatient follow-ups in Sept. 2012, chest CT found multiple nodes in the left upper and lower lobes on possible suspicion of metastasis. Under the patient's personal circumstances including general weakness, chemotherapy and oncothermia were stopped, and he had been now observed in outpatient follow-up for more than 3 years. [6]

Three month later, the check up showed good partial remission (PR) on the lesion, (figure 1.), patient is free from symptoms.

Our case to present is a 67-year-old male, registered with symptoms of cough, low-grade fever in August 2009. The diagnosis was SCLC, (see Figure 1.).

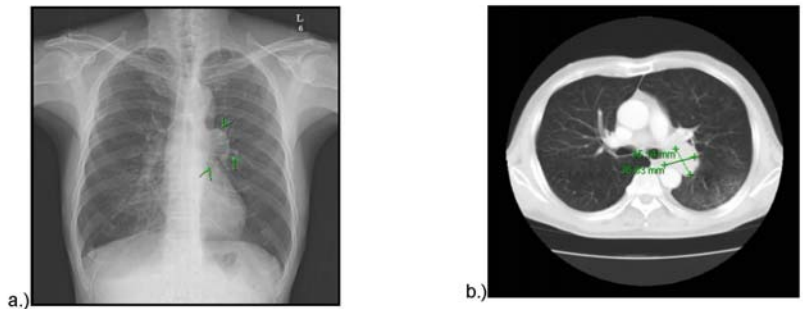

Figure 1. (a) Chest X-ray: in the left hilar lung tumors are found . (b) Chest CT: Left hilar lung tumor approved [21. Jul. 2009]

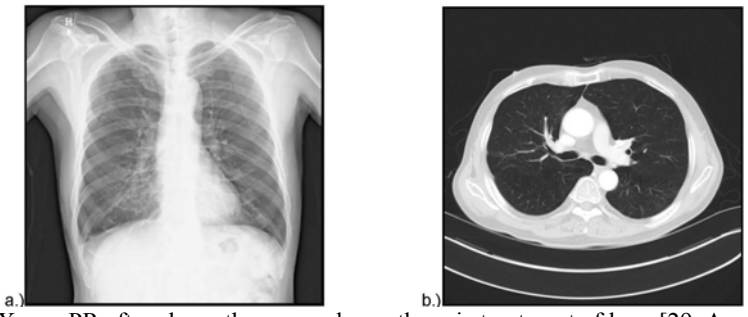

Figure 2. (a) Chest X-ray: PR after chemotherapy and oncothermia treatment of lung [29. Apr. 2010], (b) Chest CT: approved the PR [30th. Apr. 2010]

Nine month later PR was observed, (see Figure 2.), patient is free from symptoms.

Another case to present is a male patient 65 years old, registered in January 2010, diagnosed by SCLC, (see Figure 3.).

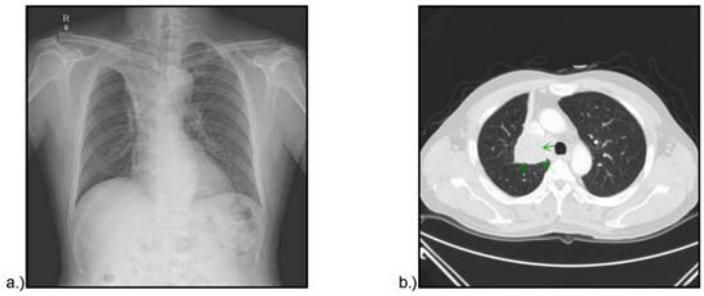

Figure 3. (a) Chest X-ray:: the right upper lobe bronchus obstruction due to cancer as atelectasis is observed, [6th. Jan. 2010]. (b) Chest CT: right upper lobe bronchus and bronchial cancer is proven in the right upper lobe atelectasis, [7th. Jan. 2010]

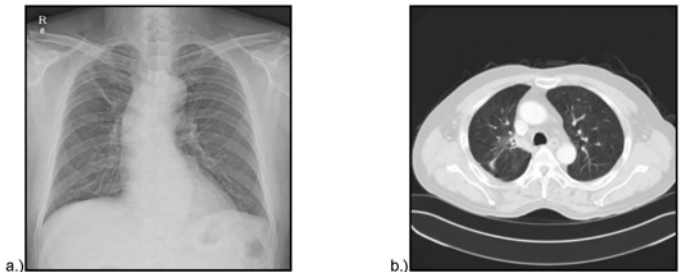

Figure 4. (a) Chest X-ray: after chemotherapy and oncothermia treatment of the right upper lobe atelectasis was not observable. (b) Chest CT: right upper lobe bronchus, bronchial cancer was disappeared [23. Nov. 2010]

Eleven months later we reached complete remission (CR), (see Figure 4.).
He is follow-up on OPD to now more than 1year after chemotherapy and oncothermia was stopped with good general condition for more than 3 years.

Study results

Chemotherapy alone (without oncothermia) was applied for eight cases. The survival time ranged from 2 months up to 29 months. With the combination of chemotherapy and oncothermia, the survival time was from 2 months to up to 36 months.
The treatment was terminated for only 1 patient. It was within 1 month after the diagnosis and treatment with chemotherapy only. All other 31 patients underwent chemotherapy and 23 had combined treatment with oncothermia.
1. Among 23 cases, one paient died within one month after the date of diagnosis, who was treated with chemotherapy only. Cases who have survived more than 3 years were 3, all of whom were treated with the combined use of chemotherapy and oncothermia.
2. Out of 31 cases, 14 died during the treatment; (i) 7 were treated with chemotherapy only, including one long survival case of 28 months, and (ii) 7 ones treated by the combined use of chemotherapy and oncothermia, including one long survival case of 26 months.
3. Out of 31 cases, 16 people are alive up to the present: 4 got chemotherapy only, including one long survival case of 28.7 months, and (ii) 11 were treated by the combined use of chemotherapy and oncothermia, including three long survival cases of more than 3 years.
4. The combined use of chemotherapy and oncothermia has significantly enhanced the survival rate in comparison with the use of chemotherapy only (Log-rank test: p-value = 0.0200)

The survival analysis shown by the Kaplan-Meier curve survival distribution (see Figure 5.) shows significant difference between the arms of chemotherapy with and without oncothermia. The log-rank test to compare survival distributions between the two groups, had hazard ratio and 95% confidence interval using Cox proportional hazard regression shown p=0.02. The summary is shown in Table 2.

Summary of the Number of Censored and Uncensored Values					
Stratum	Group1	Total	Failed	Censored	Percent Censored
1	chemotherapy	8	7	1	12.50
2	oncothermia in parallel	23	12	11	47.83
Total		31	19	12	38.71

Table 2. Comparison of the arms with chemotherapy without and with oncothermia in parallel

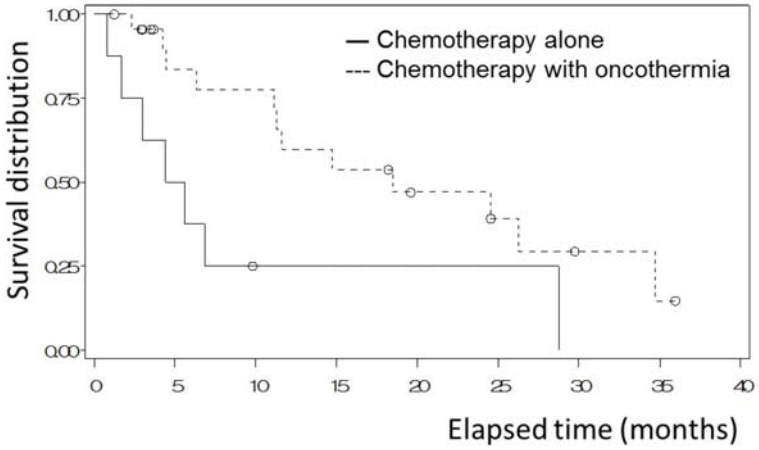

Figure 5. Kaplan-Meier survival curve. ⇒log-rank test, p-value=0.0200

Conclusion

1. In the cases of small cell lung cancer, we obtained a better treatment efficacy than with the treatment of chemotherapy only, by the combined use of chemotherapy and oncothermia (one hour per each time, 2 times per week, and more than 12 times (= one cycle)). Based on this, our thought is that the treatment of oncothermia, 3 times per week and more than 3 cycles, can create a good treatment efficacy
2. Small cell lung cancer can primarily be covered by chemotherapy (and radiotherapy sometimes), but tolerance against the anti-cancer agent is frequently created and then the return of the disease or metastasis takes place very often, which indicates a poor prognosis. We think that the combined use of oncothermia can enhance the treatment efficacy of chemotherapy, thus getting a higher rate of survival against small cell lung cancer.
3. However, we have some limitations of not so many cases with chemotherapy and oncothermia and short periods of follow-up. We consider that more cases and longer periods of follow-up are required for a good verification.
4. Several matters including the most suitable size of energy, time of administration and the number of administrations should be the subjects of subsequent studies.
5. Combination of oncothermia treatment applied to enhance the effect of anticancer drugs to destroy cancer cells is thought to be able to improve the survival of small-cell lung cancer. However, the author of chemotherapy and hyperthermia our case, less than the observation period is shorter than many cases and long-term follow-up will be necessary.

The hyperthermia dose, that is the amount of energy, and the appropriate time of administration, the number of doses, should be further studied.

Chemotherapy in SCLC, the authors and twice a week, one hour of treatment, more than 12 times (1 cycle), treatment with a combination of hyperthermia treatment effects compared to chemotherapy underwent example was good. It three times a week, 3 cycles or hyperthermia treatment effect is good thought.

In case of small cell lung cancer recurrence or metastasis, chemotherapy, and in some cases, radiation therapy may be added frequently, the anti-cancer drug for the treatment of resistant wounds, the prognosis is poor.

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