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The influence of time of radio-chemotherapy and other therapeutic factors on treatment results in patients with limited disease small cell lung cancer

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ABSTRACT

Purpose: The evaluation of effect of therapeutic parameters such as time of starting thoracic radiotherapy in relation to chemotherapy, schedule of combination chemo- and radiotherapy and SER, on treatment results in patients with limited disease small cell lung cancer (LD SCLC).
Methods: Between 2000 and 2007, 212 patients with LD SCLC received combined therapy: chemotherapy and thoracic radiotherapy. All patients received chemotherapy according to PE schedule (4–6 cycles), in combination with thoracic radiotherapy. The total dose applied to GTV was 54 Gy given in 27–30 fractions using fraction dose of 1.8–2.0 Gy. The concurrent treatment was performed in 112 patients (52.8%): the conventional fractionation (once a day, every five days a week) in 35 patients while 77 patients received "moderate" accelerated fractionation (one fraction a day, every four days a week and two fractions within one day, a week apart, with 6 h gap). The remaining 100 patients (47.2%) received sequential treatment. The time from the first day of chemotherapy to the end of thoracic radiotherapy (SER) was evaluated in all patients. The SER ranged from 57 to 337 days with the median value of 121 days.
Results: The complete response in the thorax was observed in 143 out of 212 patients (67.5%). Out of these, 82 patients received concurrent chemo-radiotherapy (given in 22 patients as conventional dose fractionation and in 60 patients according to "moderate" accelerated dose fractionation), and the remaining 61 patients were treated with sequential therapy. The 5-year survival rates were: 17.7% for overall survival (OS), and 19.3% for disease-free survival (DFS). The relationship of therapeutic factors to survival rates showed statistically significant improvement of survival ratios in relation to early starting of thoracic radiotherapy and application of concurrent chemo-radiotherapy. The results of logistic regression revealed significant relationship between the value of SER and OS and DFS. The analysis shows that each day of extension of the SER resulted in increased probability of death (decrease of OS) by 0.28% and in increased the risk of development failure (decrease of DFS) by 0.31%. The influence of SER on lowered probability of complete response frequency was not statistically significant.
Conclusions: The concurrent chemo-radiotherapy with early administration of thoracic radiotherapy, results in improved complete response in the thorax and increase of overall and disease-free survival rates. The 5-year survival rates were: 17.7% for overall survival and 19.3% for disease-free survival. Our analysis and data from the literature suggest that shorter SER may play prognostic role in patients with LD SCLC treated with combination chemo- and radiotherapy. However, these observations require the confirmation in following studies.

1. Introduction

Small cell lung cancer (SCLC) accounts for about 20% of all lung cancer cases. SCLC is characterized by rapid doubling time, early dissemination and high sensitivity to chemotherapy and radiotherapy [1–3].

According to Veterans Administration Lung Study Group (VASG) the stages of SCLC are categorized as limited disease (LD) or extensive disease (ED) [4]. At the time of diagnosis, only 30–40% of patients with SCLC can be classified as having LD [5].

The most effective therapy in patients with LD SCLC seems to be chemotherapy (using platinum-based regimens) and thoracic radiotherapy. According to the published results of studies and meta-analyses, the use of this combined therapy offers in better

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Table 1
The clinical characteristics and therapeutic parameters in 212 patients with LD SCLC.

Feature	No of pts.	%
Gender		
Females	67	31.6
Males	145	68.4
Primary tumour localization at side:		
Left	100	47.2
Right	112	52.8
Involvement of supraclavicular nodes	14	6.6

	Range	Mean	Median
Age	35–78	59.9	59.0
Chemo-radiotherapy:			
Concurrent		112	52.8
MACDF[a]		*77*	*36.3*
CDF[b]		*35*	*16.5*
Sequential		100	47.2
No of PE cycles			
	4	74	34.9
	5	95	44.8
	6	43	20.3
Radiotherapy after cycle			
	1–2	92	43.4
	≥3	120	56.6
SER [days]			
Whole group	57–337	141.2	121
Concurrent	57–196	86.2	74
MADF[a]	*57–103*	*74.0*	*72.0*
CDF[b]	*57–196*	*113.9*	*111.5*
Sequential	97–337	202.2	204

[a] "moderate" accelerated dose fractionation.
[b] conventional dose fractionation.

local control (of about 14–25%) and improved overall survival [2,6–13].

Several studies suggest that concurrent chemotherapy and thoracic radiotherapy yield better results. This treatment increases the rate of complete response in the thorax and it may also reduce the rate of locoregional and distant failures by approximately 14–18% [14–20]. The studies on LD SCLC carried out to improve the treatment effects referred to some aspects of combined treatment such as starting time of thoracic radiotherapy in relation to chemotherapy and intensification of treatment [18,21–28]. Some authors propose to use the time parameter which describes the time from the start of any treatment to the end of thoracic radiotherapy (SER) as quantative measure reflecting proliferation of cells in the primary tumour [11,29–31].

The purpose of this paper is evaluation of effect of therapeutic parameters such as time of starting thoracic radiotherapy in relation to chemotherapy, schedule of combination chemo- and radiotherapy and SER (time of Start therapy End of Radiotherapy), on treatment results in patients with LD SCLC.

2. Methods and materials

Between 2000 and 2007, 212 patients with LD SCLC received combined therapy: chemotherapy and thoracic radiotherapy, at Oncology Centre in Cracow (Poland).

The initial work-up to define limited stage SCLC included history, physical examination, pathology review, computer tomography (CT) of the chest, upper abdomen and brain, the chest radiography and laboratory tests and evaluation of pulmonary and cardiac functions tests. In our study the limited stage was defined as disease enclosed to hemithorax. And the supraclavicular nodes involved at the same side was included to LD.

Table 1 shows clinical characteristics and therapeutic parameters in 212 patients with LD SCLC.

Majority of patients were males. The patient age ranged from 35 to 78 years, with the median of 59 years. The performance status according to Karnofsky's scale was evaluated in all patients and it was over 70. In 14 patients (6.6%) metastases in supraclavicular nodes at the side of primary tumour were present at diagnosis.

All patients received chemotherapy according to PE schedule, in combination with thoracic radiotherapy. The concurrent treatment was performed in patients who did not received any treatment before the first visit at our Oncology Centre. Whereas in patients who received chemotherapy out of our centre radiotherapy was performed sequentially. The concurrent treatment was performed in 112 patients (52.8%), and the remaining 100 patients (47.2%) received sequential treatment.

2.1. Chemotherapy

All patients received chemotherapy consisting of 4–6 cycles of cisplatin–etoposide (cisplatin 30 mg/m^2 intravenously – every 3 days of cycle, etoposide 120 mg/m^2 intravenously – every 3 days of cycle). The cycles were repeated every 28 days.

2.2. Radiotehrapy

In patients treated with concurrent therapy, the thoracic radiotherapy was administered during first cycles of chemotherapy. In 92 from 112 patients (82.1%) thoracic radiotherapy was started immediately after first or second PE cycle.

In patients receiving sequential therapy, thoracic radiotherapy was performed after end of chemotherapy.

Thoracic radiotherapy was performed using 6 MV or 18 MV photons produced in the linear accelerator. We applied 3D planning using CT and conformal radiotherapy employing a multileaf collimator in order to obtain optimal tumour dose distribution and minimize the dose to adjacent normal tissues and organs at risk (especially spinal cord, lung, heat and oesophagus). Two phase treatment was used. The GTV was defined on the base of CT scans made before the start of treatment. The GTV included the primary tumour and involved nodes. The CTV covered GTV and mediastinal and hilar nodes as elective irradiated nodes with adequate margins in the first phase of radiotherapy. In the second phase, the CTV covered GTV with adequate margins (8 mm added isotropically). The PTV in both phases covered CTV with adequate margins: of 7 mm axially and 12 mm longitudinally were added to account for tumour motion.

In the first phase, the two parallel anterior and posterior fields technique was applied. In the second phase, the three-fields technique was usually used, chosen to minimize lung and spinal cord dose.

In 112 patients receiving concurrent therapy the two schedules of dose fractionation were used: the conventional fractionation (once a day, every five days a week) in 35 patients (CDF) and "moderate" accelerated fractionation (one fraction a day, every four days a week and two fractions within one day, a week apart, with 6 h gap) in remaining 77 patients (MADF).

In patients who received sequential therapy, conventional dose fractionation during thoracic radiotherapy was used.

The total dose applied to GTV was 54 Gy given in 27–30 fractions, using fraction dose of 1.8–2.0 Gy.

The time from the first day of chemotherapy to the end of thoracic radiotherapy (SER) was evaluated in all patients. The SER ranged from 57 to 337 days, with the median value of 121 days. When chemo-radiotherapy was given concurrently, the SER was shorter (median: 74 days) in comparison to patients who received sequential therapy (median: 204 days). This shortening of SER was