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Preliminary results and toxicity of a modified schedule of chemo-radiotherapy in patients with limited stage small-cell lung cancer

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Introduction. Concurrent chemo-radiotherapy is considered the treatment of choice in patients with limited disease small-cell lung cancer (LD SCLC), and offers an increase in complete regression in the chest, as well as a reduction in the frequency of locoregional failures and metastases.
The aim of this paper is to present a preliminary estimate of toxicity and the results of the modified schedule of concurrent chemo-radiotherapy using conformal radiotherapy with accelerated dose hyperfractionation and early administration of prophylactic cranial irradiation.
Material and methods. Since 2002, patients with LD SCLC treated at the Department of Radiation Oncology in Krakow have been receiving concurrent chemo-radiotherapy. We administered 5 cycles of chemotherapy (Cisplatine and Etoposide) every 4 weeks. Chest irradiation was commenced immediately after the second cycle of chemotherapy. The total radiation dose was 54 Gy in 30 fractions (6 fractions in a week: 2 fractions in one day, and 1 fraction a day for 4 days). Prophylactic cranial irradiation was administered between the fourth and the fifth cycle of chemotherapy, with a dose of 30 Gy in 15 fractions given over 3 weeks.
The present analysis was performed on a group of 34 patients treated between June 2002 and July 2004. 24/34 (70.6%) received complete therapy as planned. The remaining 10 patients received fewer cycles of chemotherapy. In 3 cases chest irradiation was terminated earlier, while prophylactic cranial irradiation was not administered in 6 patients. The shortening of the treatment time in these 10 patients caused by complications (8 pts.) and death (1 pt.), while one patient refused further treatment.
Results. Complete response was observed in 22 patients (64.7%). The Kaplan – Meier method was applied to estimate the results. The 1-year overall survival rate was 87.1%, 1-year disease-free survival rate was 49.5%, and 1-year brain metastases-free survival rate was 100%. The tolerance of the modified schedule of chemo-radiotherapy was evaluated in respect to complications developed during therapy and immediately after therapy. Haematological complications were the most frequent. Thirty-one patients (91.2%) developed anaemia, and leucopoenia was observed in 28 patients (82.4%). Seventeen patients developed dysphagia, and loss of weight exceeding 5% of the initial value was observed in 11 patients (32.4%). Elevated plasma concentrations of urea and creatinine were recorded in 18 patients (52.9%). The of intensity haematological and/or renal complications caused treatment termination in 8 patients.
Conclusions. The modified schedule of concurrent chemo-radiotherapy appears to improve treatment results in patients with LD SCLC. Complete response after this treatment has been observed in 64.7% patients.

Key words: small-cell lung cancer, limited stage, concurrent chemo-radiotherapy, chest irradiation, accelerated hyperfractionation radiotherapy, prophylactic cranial irradiation

Introduction

Small cell lung cancer (SCLC) constitutes approximately 20% of all cases of lung cancer. At the time of diagnosis, only 30–40% of patients with SCLC can be classified as having limited stage (LD) of disease [1, 2].

The definition of limited stage small cell lung cancer (LD SCLC) varies. The most commonly used classical definition of LD SCLC is that the disease can be encompassed by a reasonable single radiation port. It means that the disease is limited to one hemithorax and the mediastinum. Controversies in the definition of LD refer to contralateral hilar lymphadenopathy, ipsilateral and contralateral supraclavicular lymphadenopathy, and ipsilateral malignant pleural effusion.

The Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) define LD as a disease confined to one hemithorax and exclude cases with contralateral hilar lymphadenopathy,

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contralateral supraclavicular lymphadenopathy, or malignant pleural effusion.

However, the European Organization for Research and Treatment of Cancer (EORTC) defines LD SCLC as involving less than 50% of the maximum transverse diameter of the thorax on a posteroanterior radiograph, before treatment [2].

Other investigators define LD SCLC as disease confined to one hemithorax incl. cases with ipsilateral hilar lymphadenopathy, bilateral mediastinal lymphadenopathy, bilateral supraclavicular lymphadenopathy or ipsilateral malignant pleural effusion. They include involvement of supraclavicular nodes and pleural effusion in the LD on the grounds of better prognosis in these patients, as compared to those with haematogenous distant metastases [3].

SCLC is known to be highly sensitive to chemotherapy and radiotherapy. Chemotherapy ensures positive response rates in 70-80% SCLC patients and in 40 – 68% of such patients the response is complete [4]. Despite the high chemosensitivity of SCLC, a majority of patients develop locoregional failure and distant metastases which are very often localized in the brain [4-6].

The use of combined chemotherapy and chest irradiation results in better local control in the chest (of about 14 – 25%), longer remission time, and improved overall survival [7-11]. At the same time, the rates of failure in the chest are reduced by about 14% [9, 10, 12, 13].

Better results of combined treatment of SCLC are especially evident if chemotherapy and radiotherapy are used as a concurrent regimen. The rate of complete response in the chest increases by approx. 8% after concurrent therapy, as compared to sequential chemo-radiotherapy [14]. Concurrent chemo-radiotherapy may also reduce the rate of locoregional and distant failure by approx. 14 – 18% [15, 16]. The possible explanation for the better results obtained after concurrent, rather than sequential, chemo-radiotherapy, is the somatic mutation of chemotherapy resistance which may be responsible for the formation of clones resistant to treatment [4, 14].

The aim of the studies performed in patients with LS SCLC was to achieve an improvement of treatment results. These studies referred to some aspects of combined treatment:

- chest irradiation: the total dose, fractionation schedule, and time of starting of radiotherapy in relation to chemotherapy [14, 16-18],
- chemotherapy: dose intensification, use of new drugs [4, 19],
- prophylactic cranial irradiation: the total dose, time of administration in respect to chemo-radiotherapy [20-23].

Since 1994 patients with LD SCLC treated at the Department of Radiation Oncology in Krakow had been receiving concurrent chemo-radiotherapy. This treatment consisted of five courses of chemotherapy and chest irradiation performed at the same time. Chemotherapy was given according to the PE schedule (Cisplatine 30mg/m^2/day intravenously on 1st, 2nd and 3rd day of the course, and Etoposide 120 mg/m^2/day intravenously on 1st, 3rd and 5th day of the course).

The total dose for chest irradiation was 54 Gy given in 30 fractions (1 fraction a day, 5 fractions a week). Since 1995, patients with complete regression after chemo-radiotherapy, received prophylactic cranial irradiation of 30 Gy in 15 fractions over 3 weeks.

Between 1994 and May 2002, 80 patients with LD SCLC underwent such treatment and results have been already been published [24, 25].

A positive response to concurrent chemo-radiotherapy was observed in 66 pts (82.5%), out of whom 43 (53.8%) presented with complete regression (CR). PCI was performed in 42 pts with CR.

The Kaplan-Meier method was used to estimate 2-year results. The 2-year overall survival rate was 41%, disease-free survival rate was 27.9%, and brain metastases-free survival rate was 52.1%. The most frequent patterns of failure were: distant metastases (42 pts – 52.5%), recurrence in the chest (10 pts – 16.9%), and disease preserved in the chest. The brain was the most frequently observed site of distant metastases.

The performed analysis has shown that the development of brain metastases was observed in patients who had no CR after chemo-radiotherapy (42.9% in pts without CR versus 28.8% in pts with CR), and in patients who did not receive PCI – particularly those with CR (58.8% in pts without PCI versus 16.7% in pts who received PCI). In relation to administration of PCI, the 2-year brain metastases-free survival rate was 24.7% in pts who did not receive PCI, as compared to 80.1% in pts with PCI. These differences were statistically significant (log rank test: $p=0.00002$).

Since June 2002, basing on our previous results and literature data we have introduced a modified of concurrent chemo-radiotherapy schedule for the treatment of patients with LD SCLC. The modifications of the intensity of therapy consist of the following:

- chest irradiation starts at the same time or immediately after the second course of PE chemotherapy,
- we apply conformal techniques of radiotherapy with a multileaf collimator (MLC) to minimize the dose to critical organs and tissues,
- we apply accelerated hyperfractionation dosing: 54 Gy in 30 fractions given in 6 fractions a week (1 fraction a day over 4 days, and 2 fractions a day in 1 day),
- we commence early administration of PCI – between the 4th and the 5th course of chemotherapy (a 30 Gy dose to whole brain in 15 fractions given in 5 fractions per week).

The "modified" schedule of chemo-radiotherapy in LD SCLC is presented in Table I.

The aim of this paper is to present the preliminary results and toxicity of the "modified" schedule of concurrent chemo-radiotherapy with the use of conformal accelerated hyperfractionation radiotherapy and early administration of prophylactic cranial irradiation (PCI).

Table I. The "modified" schedule of chemo-radiotherapy applied in patients with LD SCLC treated at the Radiotherapy Department in Krakow since June 2002

Week of treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Chemotherapy (PE)	X				X				X				X				X
Chest radiotherapy						X	X	X	X	X	X						
PCI														X	X	X	

The results of our "modified" concurrent chemo-radiotherapy regimen (administered since 2002) have been compared with the results and toxicity observed after the "classic" regimen of concurrent chemo-radiotherapy (administered between 1994 and 2002).

Material and method

Between June 2002 and September 2004, 44 patients with LD SCLC were qualified to receive the "modified" schedule of concurrent chemo-radiotherapy at the Department of Radiation Oncology in Krakow. Of this group, in 34 cases (77.3%) treatment was finished before July 2004, and they are the subject of the present analysis.

Before the onset of treatment LD SCLC was confirmed by bronchoscopy with biopsy, histological examination of the biopsy material, cytological examination of pleural effusion, biopsy and histological examination of supraclavicular lymphadenopathy, bacteriogram of bronchial lavage, radiological imaging (conventional chest radiograph, computerized tomography of the chest and the abdomen, ultrasonography of the abdomen, and MRI of the brain), coulter blood count (CBC), and clinical chemistry liver and renal function tests (serum concentration of urea, creatinine, bilirubine, proteins with their fractions, enzyme activity: transaminases: alanine (AlAT) and asparagine (AspAT), alkaline phosphatase, gamma- glutamyl transpeptidase (GGTP), lactic dehydrogenase (LDH-L)), concentration of neuronspecific enolase (NSE), bone marrow biopsy, bone scan, spirometric parameters, neurological status, nourishment status (weight, albumins concentration in serum).

LD SCLC was defined as a disease confined to one hemithorax as well as ipsilateral hilar lymphadenopathy, bilateral mediastinal lymphadenopathy, ipsilateral supraclavicular lymphadenopathy or ipsilateral malignant pleural effusion.

Patients

Table II shows the clinical characteristics of LD SCLC patients treated with the "modified" regimen (34 pts treated between 2002 and 2004), as compared to patients treated with the "classical" regimen (80 pts treated between 1994 and 2002) of concurrent chemo-radiotherapy.

Chemotherapy

All patients received chemotherapy according to the PE schedule with an intent of admiistering 5 courses of PE repeated every 28 days.

Chest irradiation and prophylactic cranial irradiation (PCI) were performed during chemotherapy.

Radiotherapy (RT)

Chest irradiation was performed using 6 MV or 18 MV photons produced in the linear accelerator. We applied 3D planning using CT and a conformal radiotherapy technique employing a multileaf collimator in order to maximize tumour dose and minimize the dose to adjacent normal tissues and organs at risk [26].

The GTV was defined on the base of CT scans made before the start of treatment.

We applied two-phase treatment. Phase one employed the technique of two parallel anterior and posterior fields, the PTV covered the GTV and hilar and mediastinal nodes with adequate margins. The planned dose was 45 Gy in 25 daily fractions given 5 days a week. Additionally, once a week, after a 6-hour gap, the second fraction was given planned as a second phase of RT. In this phase the PTV covered the GTV with adequate margins. This phase was usually delivered with the three-field technique, chosen to minimize lung and spinal cord dose. In this technique, the tumour dose was raised to 9 Gy. The total dose given to GTV was 54 Gy in 30 fractions.

Table II. The clinical parameters of patients with LD SCLC treated with the "modified" schedule of concurrent radio-chemotherapy (i.e. between 2002 and 2004), as compared to patients treated with the "classical" schedule (i.e. between 1994 and 2002)

Feature		„classical" schedule	„modified" schedule	P (Chi square test)
No of patients		80	34	
age:	range	28 – 73	45 -70	
	mean	54.3	58.2	0.0433
	median	53.5	59	
sex:	females	32 (40%)	11 (32.4%)	0.4409
	males	48 (60%)	23 (67.7%)	
localization in lung:	left	44 (55%)	15 (44.1%)	0.2873
	right	36 (45%)	19 (55.9%)	
supraclavicular lymphadenopathy		13 (16.3%)	3 (8.8%)	0.2963
pleural effusion		10 (12.5%)	2 (5.9%)	0.2922

In patients with pleural effusion at the first phase of RT, the PTV covered the pleural cavity and mediastinal nodes with adequate margins. The technique of two parallel anterior and posterior fields was used to administer a dose of 20 Gy to the pleural cavity, and then the PTV was reduced to a volume covering the GTV and the hilar and mediastinal nodes with adequate margins, thus continuing irradiation to a dose 45 Gy. The second phase of RT was the same as in patients without pleural effusion.

Supraclavicular nodes were irradiated in patients with infiltration of the upper bronchus and the presence of metastases into the mediastinal nodes located over the tracheal bifurcation, and in patients who had developed metastases to the supraclavicular nodes.

Prophylactic cranial irradiation (PCI)

PCI was performed during chemotherapy, between the fourth and fifth PE cycle. The PTV involved the whole brain. We employed a technique of two parallel opposing lateral fields with a total dose of 30 Gy in 15 fractions over 3 weeks.

Table III shows the treatment characteristics of 34 patients with LD SCLC treated with the "modified" schedule, as compared to the group of 80 patients treated with the "classical" schedule.

In the entire group of 34 patients, 24 (70.6%) received the complete treatment as planned. The remaining 10 patients were given less PE cycles (1-4). In this subgroup radiotherapy was terminated early in 3 patients, while 6 patients did not receive PCI.

The reasons for treatment discontinuation in the group of 10 patients were as follows: side-effects (8 patients), death due to cardiac failure (1 patient) and refusal of further treatment (1 patient).

In order to evaluate the efficacy of chemo-radiotherapy some diagnostic procedures were performed: radiological imaging (conventional chest radiograph, computerized tomography of the chest) and CBC and clinical chemistry tests.

During follow-up patients were seen every 2 moths during the first year after therapy, and every 3 months starting from 2 years after treatment.

The treatment results were evaluated as the frequency of complete remission obtained in the chest and the survival rates: overall, disease-free, and brain metastases-free. The survival rates were estimated using the Kaplan- Meier method.

The results in the group of patients who were treated according to the "modified" schedule were compared to the results obtained among patients treated with the "classical" schedule of concurrent chemo-radiotherapy. These comparisons were evaluated by the log-rank test (survival rates), and the Chi-square test (frequency of CR).

Results

In the analysed group of 34 patients with LD SCLC follow-up ranged from 4 to 23 months (mean: 13.7 months, median: 14 months).

During the follow-up period 10 patients (26.5%) died. The causes of deaths included progression of disease in the chest (1 patient), development of distant metastases (3 patients), lung haemorrhage (1 patient), cardiac failure (1 patient), in case of the remaining 3 patients the cause of death is unknown.

Twenty- four patients are alive, 14 of them (58.3%) with CR.

The treatment results were evaluated as the frequency of CR and survival rates: overall, disease-free, and brain metastases-free.

Table III. A comparison of treatment characteristics of concurrent chemo-radiotherapy according to the "classical" and "modified" schedules

Feature		„classical" schedule	„modified" schedule	P (Chi square test)
PE chemotherapy				
No of courses:	1	1 (1.3%)	1 (2.9%)	
	2	2 (2.5%)	1 (2.9%)	
	3	2 (2.5%)	4 (11.8%)	0.2299
	4	14 (17.5%)	4 (11.8%)	
	5	58 (72.5%)	24 (70.6%)	
	6	3 (3.8%)	-	
Chest radiotherapy total dose [Gy]	range:	29.4 – 69.6	18 – 54	
	mean:	53.9	52.4	0.1766
	median:	55	54	
Mediastinal dose [Gy]	range:	29.4 – 50.0	10.6 – 45.0	
	mean:	42.3	40.2	0.0130
	median:	43.2	41.4	
No of fractions	range:	18 – 50	10 – 30	
	mean:	29.3	29.1	0.8469
	median:	30	30	
Time of treatment [days]	range:	25 – 77	18 – 51	
	mean:	46	36.1	0.0000
	median:	45	37	
PCI		42 (52.5%)	28 (82.4%)	0.0027

Survival

Complete response was observed in 22 pts (64.7%), and the 1-year survival rates were: overall – 87.1%, disease-free – 49.5%, and brain metastases-free – 100%.

Table IV compares the efficacy of chemo-radiotherapy between the two groups of LD SCLC patients treated over two different periods: 1994-2002 (the "classical" schedule) and 2002-2004 (the "modified" schedule).

Table IV. The results of chemo-radiotherapy in patients with LD SCLC treated with the "classical" schedule, as compared to the "modified" schedule

Results	„classical" schedule	„modified" schedule	p
no of patients	80	34	
complete remission in chest			0.2797
no of pts	43	22	
%	53.8%	64.7%	
1-year survival rate (Kaplan-Meier method):			
overall	61.8%	87.1%	0.1077
disease-free	36.8%	49.5%	0.3824
brain metastases- free	68%	100%	0.0041

Failures

During follow-up, progression of disease in the chest was observed in 4 patients (11.8%). Distant metastases developed in 9 patients (26.5%) – in 6 pts with CR, and 3 pts with PR after chemo-radiotherapy. The metastases were localised in the brain (1 pt), the lymph nodes (4 pts), the bones (3 pts) and the liver (3 pts). Some patients developed metastases in several sites.

Patients with PR in the chest after treatment and with nodal disease progression received chemotherapy according to schedules containing Adriblastin.

The remaining patients received symptomatic therapy only.

Tolerance

Treatment tolerance was evaluated in respect to acute side effects observed during treatment or immediately after chemo-radiotherapy. These symptoms were divided into two groups: site effects related to radiotherapy (oesophageal reaction manifesting as dysphagia, and skin reaction), and symptoms associated with chemotherapy (renal function impairment and bone marrow depletion).

The grades of side effect intensity were estimated according to NCI and RTOG [27, 28].

Table V presents the frequency and the intensity of side effects associated with concurrent chemo-radiotherapy in a group of 34 patients with LD SCLC.

Table V. The symptoms and grade of intensity of the side-effects observed in the group of 34 patients with LD SCLC treated with the "modified" schedule of chemo-radiotherapy

Symptoms	Grade	No of pts.	%
leucopenia		28	82.4
	G1	6	
	G2	8	
	G3	7	
	G4	7	
thrombocytopoenia	G4	4	11.8
anaemia		31	91.2
	G1	14	
	G2	11	
	G3	4	
	G4	2	
dysphagia		17	50.0
	G1	16	
	G3	1	
nausea, vomiting		19	55.9
	G1	14	
	G2	4	
	G3	1	
biochemical symptoms of renal function impairment		18	52.9
	G1	17	
	G2	1	

Haematological complications were the most frequent, with anaemia in 31 patients (91.2%) and leucopoenia in 28 patients (82.4%). Twelve patients with anaemia required packed red blood cell transfusion and 3 patients received erythropoietin therapy. Of the 28 patients with leucopenia 13 developed fever, 18 received antibiotics, and granulocyte colony-stimulating factor was used in 4 patients.

Haematological complications of grade 3 or 4, and biochemical symptoms of renal insufficiency (elevated concentration of creatinine and urea) caused discontinuation of therapy in 8 patients. These patients received a lower number of PE chemotherapy cycles: 1 cycle in 2 pts, 3 cycles in 2 pts. and 4 cycles in 4 pts.

Oesophageal reaction manifested as dyphagia was observed in 17 patients (50%) while a reduction of body weight exceeding 5% was observed in 11 patients (32.4%).

Skin reactions (G2-3) related to radiotherapy developed in 4 patients. During chemo-radiotherapy 4 patients developed exacerbation of coexisting diseases: thrombophlebitis in 3 pts and cardiac dysrhythmia in 1 pt.

Discussion

Concurrent chemo-radiotherapy is considered the treatment of choice in patients with LD SCLC, and it offers increased ratios of complete regression in the chest, longer remission and overall survival and, simultaneously, a decrease in the frequency of locoregional failures [7-13].

The grounds for the administration of concurrent chemo-radiotherapy arise from the somatic mutation

theory of drug resistance occurring in the SCLC cells. This theory can be used as a conceptual model to divide LD SCLC patients into three groups. In the first group, the mutation accounting for chemotherapy resistance has not occurred in the primary tumour and in the subclinical metastases outside the chest. These patients may be cured with chemotherapy alone, and unfortunately, only about 5-10% of LD SCLC patient population fall into this category. The second group includes patients who have chemotherapy-resistant cells in the primary tumour, but chemotherapy resistance has not occurred in the subclinical metastases. This group encompasses some 30-40% of LD SCLC patients, and is the target group for the application of concurrent chemo-radiotherapy. Early administration of RT may eradicate the chemo-resistant clones before they spread outwards and reduce the probability that chemo-resistant or radio-resistant clones will evolve during treatment. The third group accounts for a majority of LD SCLC patients (50-60%), who not only have undergone mutation to chemo-resistance, but have also disseminated resistant clones to distant sites. In these patients chest RT may improve local control, but it cannot change the fatal outcome [14].

Our results from a group of 34 patients with LS SCLC confirm the efficacy of concurrent chemo-radiotherapy regarding the immediate effect of therapy and the survival rates: overall, disease-free, brain metastases-free.

The studies on LD SCLC carried out to improve the treatment effects have referred to some aspects of combined treatment, such as the total dose, starting time of radiotherapy in relation to chemotherapy, and intensification of treatment [17].

Jeremic et al. have shown the relationship between the efficacy of treatment and the use of the total dose, the timing of radiotherapy, and the schedule of fractionation dosing in patients with LD SCLC [16]. The 2-year local control rates were 40-50% (for a total dose of 45 Gy), and 70% when the total dose was 54 Gy. Better results were observed, particularly, when RT was administered as initial therapy at the beginning of chemotherapy [15, 16, 18, 29].

The administration of radiotherapy with the use of accelerated hyperfractionation dose seems to produce better results, with an increasing rate of complete regression and decreases in locoregional and distant failures [15-19, 29, 31].

Turrisi et al. have performed a study to compare the efficacy of two schedules of dose fractionation: conventional (45 Gy in 25 fractions given over 5 weeks), and accelerated hyperfractionation (45 Gy in 30 fractions given over 3 weeks) which were given concurrently with chemotherapy. Patients who received hyperfrationated RT achieved better results. In this group both complete regression and a higher survival rate were observed more often, whereas, locoregional failures and the development of distant metastases were more rare [17, 18].

On the other hand, higher dose and accelerated hyperfractionation RT caused higher treatment toxicity, especially if it was a concurrent chemo-radiotherapy schedule. The most frequent side effects were dysphagia and haematological complications. Dysphagia in grade 3 and 4 has been observed in 43-49% patients who have been receiving concurrent chemo-radiotherapy [29, 30, 32, 33].

Our observations confirm the increase of haematological complications (leucopenia in 82.4% pts, anaemia in 91.2% pts) and dysphagia (in 55.9% pts) in patients treated with concurrent chemo-radiotherapy.

Other studies on the treatment of LD SCLC explored the influence of the onset of radiotherapy in relation to chemotherapy, revealing a higher efficacy of initial radiotherapy, as compared to delayed radiotherapy. This observation refers to the local control rate and the overall survival rate. Moreover, initial radiotherapy reduces the risk of locoregional failure and brain metastases [11, 14-17, 34].

Our earlier observations also confirm the higher efficacy of initial radiotherapy [24, 25]. However, these observations have also shown that the most frequent cause of failure after the therapy used for SCLC was the development of distant metastases, especially to the brain.

To minimize the risk of dissemination into the brain in patients with LD SCLC PCI is performed. The target group for this strategy are patients who develop complete regression after chemo-radiotherapy [15, 16, 35].

The results of randomized trials and of meta-analyses have shown that PCI positively influences the decrease in brain metastases and increases the survival rate [5, 6, 20].

The results of a randomized trial presented by Gregor et al. show that in PCI patients the rate of brain metastases falls by about 24%, and the rate of overall survival increases [21].

Our previous observation are in keeping with these data. The probability of developing brain metastases was lower among patients who had received PCI as compared to those, who did not receive PCI (15.4% versus 61.5% 1 year after therapy, 25.7% versus 61.5% 2 years after therapy) [25].

The controversies associated with PCI refer to its potential neurotoxicity, the value of the total dose and the time of its administration in relation to chemo-radiotherapy [5, 22].

A relationship can be observed between the total dose and avoiding brain metastases, where higher protection is associated with higher doses. However, when considering the dependence of neurotoxicity on the total dose, the authors recommend a conventionally fractionated dose of 30-35 Gy [5, 20, 23, 35].

The results of a meta-analysis performed by Auperin et al. and the data presented by Suwinski et al. show that early administration of PCI results in a more efficient reduction of brain relapses [20, 23].

The published data and our experience lie behind the introduction of changes in the previously administered chemo-radiotherapy regime. Preliminary results of the new schedule show the high efficacy of this therapy.

However, at the same time, its higher toxicity is also observed.

We must stress that these preliminary observations were performed in a group of 34 patients, and the duration of follow up was between 4 and 23 months.

Conclusion

The "modified" schedule of concurrent chemo-radiotherapy (conformal technique of chest radiotherapy with accelerated dose hyperfractionation and the early administration of prophylactic cranial irradiation) appears to improve the treatment results of patients with LD SCLC. The preliminary results show an increase of complete regression in the chest and a lower frequency of brain metastases. Complete response in the chest was observed in 64.7% patients.

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