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Evaluation of efficacy of combined chemoradiotherapy in locoregional advanced, inoperable Non-Small Cell Lung Cancer (clinical randomized trial)

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Aim. The aim of the study was comparison of the results of sequential and concurrent chemoradiotherapy in patients with advanced inoperable NSCLC.
Material and methods. Between 2001-2004 in the group of 173 patients with locally advanced, inoperable NSCLC the randomized, prospective clinical trial was conducted. The study group consisted of 2 arms: in 89 patients neoadjuvant chemotherapy plus teleradiotherapy was used; in 84 patients concurrent chemo- radiotherapy was given. In both groups conformal radiotherapy and 2-drug chemotherapy cisplatin and navelbine was given. The only difference between the two groups was the sequency of radiotherapy and chemotherapy.
Results. The similar benefit of both methods adding chemotherapy to radiation therapy was established. 2-year overall survival and disease free survival in sequential therapy arm was 25.8% and 11.2% and in concurrent therapy group 25.0% and 11.9% respectively. The rate of toxicity of treatment in concurrent therapy arm was statistically significantly higher; full treatment according to the plan was given to 96.7% patients treated sequentialy and to 75% in concurrently treated group.
Conclusion. The results of sequential and concurrent chemo- radiotherapy in locally advanced inoperable NSCLC are very much the same but the toxicity due to treatment was significantly higher in the latter group.

Ocena skuteczności skojarzonej chemio- teleradioterapii chorych na miejscowo zaawansowanego, nieoperacyjnego, niedrobnokomórkowego raka płuca (kontrolowane doświadczenie kliniczne)

Cel pracy. Celem badań było porównanie skuteczności sekwencyjnego i równoczesnego kojarzenia chemio- i teleradioterapii chorych na miejscowo zaawansowanego, nieoperacyjnego, niedrobnokomórkowego raka płuca.
Materiał i metody. W grupie 173 chorych na miejscowo zaawansowanego, nieoperacyjnego, niedrobnokomórkowego raka płuca przeprowadzono, w latach 2001-2004, prospektywne, kontrolowane doświadczenie kliniczne. Doświadczenie miało dwa ramiona: u 89 chorych zastosowano indukcyjną chemioterapię z następową teleradioterapią, u 84 chorych równoczesną chemio- teleradioterapię. W obu grupach chorych stosowano teleradioterapię konformalną oraz chemioterapię dwulekową (cisplatyna + nawelbina). Różnica obu schematów leczenia polegała wyłącznie na sekwencji stosowania chemio- i teleradioterapii.
Wyniki. Stwierdzono podobną skuteczność obu metod kojarzenia chemio- i teleradioterapii. 2-letnie przeżycia całkowite i bezobjawowe, w grupie chorych leczonych sekwencyjnie, wyniosły odpowiednio 25,8% i 11,2%, w grupie leczonej równocześnie – 25,0% i 11,9%. Toksyczność leczenia równoczesnego była znamiennie statystycznie wyższa; z tego powodu pełne zaplanowane leczenie przeprowadzono u 96,7% chorych leczonych sekwencyjnie, a tylko u 75% leczonych równocześnie.

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Wnioski. Skuteczność sekwencyjnej i równoczesnej chemio- teleradioterapii chorych na miejscowo zaawansowanego, nieoperacyjnego NKRP jest zbliżona, natomiast toksyczność tej drugiej, znamiennie wyższa.

Key words: locally advanced, nonresactable NSCLC, sequential and concurrent chemo- radiotherapy
Słowa kluczowe: miejscowo zaawansowany, nieoperacyjny NKRP, sekwencyjna i równoczesna chemio- teleradioterapia

The mainstay of treatment of locoregionally advanced [III°] nonresactable, Non-Small Cell Lung Cancer (NSCLC)is irradiation. The results of radiotherapy as a sole modality are nevertheless poor, especially in patients in grade IIIA (with the N2 feature) and IIIB (T4 and/or N3). Only a few percent of patients achieve a 5-year survival, while mean survival time ranges between a few months and two years [1-12]. A number of attempts have been made to alter this situation – these include increasing the total irradiation dose, using unconventional methods of fractioning (CHART, HART), administering radio-sensitising substances, 3D treatment planning, combining teletherapy and brachytherapy [1, 2, 5, 7, 8, 13-16]. However, over the last few years the most promising method appears to be the administration of conformal radiotherapy with intensity modulated radiotherapy (IMRT) [1, 5, 6, 8, 10].

Another promising modality is combined radiochemotherapy. Theoretically, this method allows to increase the chances of local cure and to limit the frequency of distant metastases, which are usually the only or the main reason for treatment failure in some 75% of patients with NSCLC [1, 3, 5, 7, 8, 10, 17]. The results of controlled clinical trials and metaanalyses, which have been hitherto published stress the increased efficacy of combined treatment (radio- and chemotherapy) as compared to radiotherapy alone, although the improvement in long term survival does not exceed a few percent [1, 2, 7, 8, 10, 17-21]. A number of issues remain to be resolved, such as patient qualification for combined therapy, treatment toxicity, its impact on the quality of life, optimal radio- and chemotherapy treatment protocols and the economical aspects.

Some controversies are also evoked regarding the optimal sequence in which radio- and chemotherapy should be combined. Both these methods may be administered sequentially (in which case chemotherapy is usually administered as the first modality) or concurrently. Literature data suggests that induction chemotherapy, followed by radiotherapy is less toxic, but also less efficient than concurrent chemo- and radiotherapy [7, 8, 22-24]. The aim of this paper is to verify hypotheses derived from published data basing upon an analysis of the results of a randomized prospective trail performed at the Kraków branch of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology (COOK).

Material and methods

The prospective randomized trial was set according to the outlines presented by Bryse, Stagnet and Sylwester in their publication "Cancer Clinical Trials; Methods and Practice" (Oxford Medical Publ. 1992). We obtained the opinion of the Local Ethics Committee of the COOK. On entering the trial the patients were provided with all the information concerning its objectives and regulations and they all consciously gave signed consent. The study group was dichotomized into patients receiving induction chemotherapy followed by conformal teleradiotherapy and patients receiving concurrent chemotherapy and conformal teleradiothepay (details are provided in the treatment protocol).

Treatment protocol

1. On qualification the following procedures were performed: detailed case history, detailed physical examination, measurements of body weight, Karnofsky status, bronchoscopy followed by microscopic analysis of the cancer specimen, spirometry, blood gas analysis, PA and lateral chest X-ray, Computerised Tomography (CT) of the chest and ultrasonography and CT of the abdomen; CT of the brain, ECG, coagulology, blood cell count, biochemical analyses hepatic/renal function (transaminases, GGTP, bilirubin, creatinin and creatinin clearance, ureal nitrogen, glucose and LDH), serum protein with electrophoresis and the acid-base balance.

2. The inclusion criteria were:
   – microscopically confirmed NSCLC not qualifying for surgical treatment,
   – age below 70 years,
   – grade of malignancy III°A (N2 feature) and III°B acc. to TNM (UICC 1997), without pleural effusion,
   – Karnofsky status 70 points or over,
   – decrease in body weight not exceeding 5% of calculated body mass,
   – hemoglobin level >11 g/d; WBC >4000/mm^3; platelet count >150 000 mm^3,
   – no respiratory insufficiency: spirometry and blood gas analysis values as for radical radiotherapy (see [25]),
   – adequate hepatic and renal function (in biochemical analysis),
   – no circulatory insufficiency (on clinical examination and in ECG),
   – no previous history of malignancy,
   – no previous causative treatment.

3. Patients who fulfilled the inclusion criteria were randomly assigned to one of the two groups (acc. to randomization tables):
   a) patients treated with induction chemotherapy followed by external beam irradiation,
   b) patients treated concurrently with chemotherapy and external beam irradiation.

   Conformal teleradiotherapy was applied in both groups, as was the cisplatin-navelbine chemotherapy regimen.. The difference between the two treatment protocols lay in fact only in the sequence of chemotherapy and radiotherapy administration.

4. Conformal teleradiotherapy was administered with the aid of a CT device (General Electric) used only for the purpose of treatment planning and a Varian therapeutic line. All basic conditions of conformal radiotherapy were maintained i.e. CT scanning for topographic data concerning the tumour

and the critical organs, image transfer from the CT device to the 3D treatment planning system, 3D reconstruction of the target volume and of the organs at risk, virtual simulation of the distribution of irradiation, 3D calculation of dose distribution with presentation, treatment planning and administration with the aid of a multileaf collimator (MLC), individual shields, dose-volume histograms, apparatus for patient positioning and immobilization in order to ascertain the identical conditions of irradiation, *in vivo* dosimetry.
Irradiation was performed using conventional fractioning (5 times a week, 1 fraction of 1.8 Gy per day). We administered a dose of 50.4 Gy in 28 fractions to the primary tumour site and the mediastinum (first stage of treatment) and, additionally, 19.8 Gy in 11 fractions to the primary tumor site and the macroscopically metastatic lymph nodes (i.e. lymph nodes of 2 cm or more in diameter) [GTV – gross tumor volume] (second stage of treatment). Altogether the GTV received a dose of 70.2 y in 39 fractions.
During the first stage of treatment we irradiated the primary tumour with a 2 cm margin and the mediastinum from the sternal incision to 6 cm below the bifurcation of the trachea (in case of tumours located in the superior or middle lobe) or to the level of the diaphragm (in case of tumours located in the inferior lobe). During the second stage of treatment the tumour and the macroscopically metastatic lymph nodes were irradiated with a 1 cm margin (to allow for respiratory movement). The target volume did not exceed 500 cm^3. In patients in whom we observed regression after induction chemotherapy the target volume was identical with that calculated at the onset of treatment.

5. The detailed outline of treatment was as follows:
Group A (induction chemotherapy followed by teleradiotherapy – sequential treatment) – 2 series of induction chemotherapy (cisplatin 100 mg/m^2 on day 1; navelbine 20 mg/m^2 on day 1 and 8; a 28 day gap between courses). Conformal radiotherapy began on day 8 of the second course.
Group B (concurrent chemotherapy and teleradiotherapy – concurrent treatment) – cisplatin 100 mg/m^2 administered on day 1 and 36 of irradiation, navelbine 20 mg/m^2 on day 1, 8, 36 and 43 of irradiation.
Supportive treatment was administered according to generally accepted indications (anti-emetics, growth fractors, hematopoesis stimulating drugs, antibiotics etc).

6. The first two follow up examinations were performed in the 6^{th} and 12^{th} week after the completion of treatment, the following – every 3 months. The follow-up examinations included physical examination, body weight, Karnofsky performance status, blood cell count, hepatic and renal function (biochemistry); chest X-ray (PA and lateral) and chest CT was performed every 3 months during the first year after treatment, and then every 6 months. Other examinations were performed only when recurrence or dissemination were suspected.

7. The degree of regression was evaluated according to chest imaging in accordance with the WHO criteria of response to chemotherapy [26] and the RTOG/EORTC criteria of response to radiotherapy [27].

8. The criterion appointed for the evaluation of treatment results was 2-year survival without symptoms of cancer (disease-free survival, DFS) calculating from the onset of treatment. All patients were followed-up for 12 months, unless death occurred. Mean duration of follow-up was 29 months. The probability of survival was calculated with the Kaplan-Meier method [28]. In order to evaluate the significance of the observed differences we used the log-rank test acc. to Peto [29]. Statistical significance level was set at p-value ≤0.05. In order to assess the impact of the assorted factors on patient survival we applied Cox's model of proportional hazard [30].

Results

Between January 1^{st} 2001 and December 31^{st} 2004 we had enrolled and observed 173 patients in the course of the described trial, all with locoregionally advanced nonresactable NSCLC. Sequential chemo-teleradiotherapy was administered to 89 patients (group A) and concurrent treatment – to 84 patients (group B).

Patient characteristics and microscopic/clinical data of both the groups have been presented in Table I.

Table I. Patient characteristics and microscopic/clinical data of patients treated with sequential (group A) and concurrent (group B) chemo-radiotherapy

Patient characteristics & microscopic + clinical data	Group A No. of pts.	%	Group B No. of pts.	%
Age:				
≤58	37	41.6	35	41.7
>58	52	58.4	49	58.3
Gender:				
m	64	71.9	60	71.4
f	25	28.1	24	28.6
Microscopic tumour type:				
Ca. planoepitheliale	61	68.5	56	66.7
Ca. glandulare	28	31.5	27	32.1
Ca. gigantocellulare	–	–	1	1.2
Karnofsky performance status:				
70-80	75	84.3	71	84.5
90	14	15.7	13	15.5
Malignancy advancement:				
IIIA	29	32.6	28	33.3
IIIB	60	67.4	56	66.7
Total	89	100.0	84	100.0

Data from Table I shows that the two patient groups did not differ as to their characteristics.

The course of treatment has been presented in Table II.

Complete combined modality treatment had been administered to 86/89 patients (96.7%) from group A and 63/84 (75%) of patients from group B. This difference achieves extreme statistical significance (log-rank test $p<0.01$). In all patients from both the groups we observed inflammation of the oesophageal mucosa (grade 1 or 2), moderate nausea and vomiting and myelosuppression of a different degree. In 6.8% of patients undergoing sequential treatment and 14.3% of patients undergoing concurrent treatment the above-mentioned complications enforced breaks in irradiation, lasting some 8-10 days, after which treatment was resumed and completed.

In the sequential treatment group two patients died due to treatment complications in the form of acute inflammation of pulmonary tissue or sepsis in the course of neutropoenia. In 1 patient treatment was discontinued

Table II. The course of treatment of patients treated with sequential (group A) and concurrent (group B) chemo-radiotherapy

Treatment course	Group A		Group B	
	No. of pts.	%	No. of pts.	%
Complete treatment administered as scheduled over the intended time	80	89.9	51	60.7
Complete treatment administered over an elongated treatment time	6	6.8	12	14.3
Treatment not completed due to:				
excessive toxicity	2	2.2	18	21.4
cancer progression	1	1.1	2	2.4
consent withdrawal	–	–	1	1.2
Total	89	100.0	84	100.0

due to the diagnosis of metastases to the central nervous system in the course of teleradiotherapy.

In the concurrent treatment group in 2 cases treatment was discontinued due to cancer progression (metastases to the bones, the liver and the brain), 1 patient withdrew consent in the course of the trial, in 18 cases (21.4%) treatment was discontinued due to its excessive toxicity taking the form of severe (grade 3 and 4) inflammation of the oesophageal mucosa in 7 cases, severe inflammation of the pulmonary tissue with respiratory insufficiency in 5 cases, leucopoenia and thrombocytopoenia in 4 cases and significant alterations in hepatic and renal function in 2 cases. Two patients died due to these complications, one in the course of acute pneumonia and the other due to the generalized sepsis.

The degree of tumour regression was evaluated 6 weeks after treatment completion and has been presented in Table III.

Table III. The degree of tumour regression 6 weeks after treatment completion

Degree of radiological tumour regression	Group A		Group B	
	No. of pts.	%	No. of pts.	%
Complete regression	12	13.5	11	13.1
Partial regression	48	53.9	46	54.8
Regression <50% or lack of regression	18	20.2	17	20.2
Progression	11	12.4	10	11.9
Total	89	100.0	84	100.0

As may be derived from Table III no statistically significant differences have been found between the two groups regarding early tumour regression – 6 weeks after treatment completion. Complete or partial radiological regression (>50%) was observed in 67.4% of patients from group A and 67.9% of patients from group B.

As may be derived from Table IV no statistically significant differences have been found between the two groups regarding the treatment results. In the sequential treatment group 2-year overall survival was 25.8%, with 11.2% of disease-free survival; in the concurrent treatment group these values were 25% and 11.9% respectively. Table V presents the treatment results observed in patients who had completed the treatment, i.e. 86 patients from group A and 63 patients from group B.

Table IV. Prognosed survival of patients treated with sequential (group A) and concurrent (group B) chemo-radiotherapy

2-year survival	Group A [89 pts.]		Group B [84 pts.]	
	No. of pts.	%	No. of pts.	%
overall	23	25.8	21	25.0
disease-free	10	11.2	10	11.9

When analyzing the contents of Table V one may notice that if a patient had completed treatment according to the concurrent treatment protocol he or she had a higher (though not statistically significant) chance of surviving 2 years, both as overall survival and as disease-free survival (33.3% vs. 26.7% and 15.9 vs. 11.6%), as compared to patients treated according to the sequential protocol. However, in our material, this effect is nullified by the higher toxicity observed in the concurrent treatment group.

Table V. Survival of patients treated with sequential (group A) and concurrent (group B) chemo-radiotherapy who had completed treatment

2-year survival	Group A [86 pts.]		Group B [63 pts.]	
	No. of pts.	%	No. of pts.	%
overall	23	26.7	21	33.3
disease-free	10	11.6	10	15.9

We did not observe differences in the treatment results regarding patient gender, age, the microscopic form of the tumour and Karnofsky status within the 70-90 point range. The correlation between 2-year survival and the advancement of the malignancy is presented in Table VI.

Both in univariate and multivariate analysis the only prognostic factor (which as such was noticeable in both groups) was the advancement of the malignancy. Patients in stage III°A had a statistically significantly higher chance

Table VI. Correlation between 2-year overall survival and the advancement of the malignancy

Advancement of malignancy	Group A			Group B		
	No. of pts. treated	2-year survival		No. of pts. treated	2-year survival	
		No. of pts.	%		No. of pts.	%
III°A	29	13	44.8	28	13	46.4
III°B	60	10	16.7	56	8	14.3
Total	89	23	25.8	84	21	25.0

of achieving 2-year overall survival as compared to patients with stage III°B tumours (log-rank test, $p<0.02$).

Discussion

There is no doubt as to the fact that in case of patients with locoregionally advanced, nonresactable NSCLC the treatment of choice is, at present, combined radio- and chemotherapy. It allows to achieve slightly better results than radiotherapy applied as a sole modality [1, 5, 8, 10, 20, 31-36].

The study, which we present here – a prospective randomized trial – has provided us with data which enables us to participate in the discussion concerning the optimal method of combining chemotherapy and teleradiotherapy in this particular group of patients. 173 patients with locoregionally advanced, nonresactable NSCLC were enrolled into the study; they were randomly assigned to receive either induction chemotherapy followed by conformal teleradiotherapy (n=89; group A – sequential treatment) or concurrent chemotherapy and teleradiotherapy (n=84; group B – concurrent treatment). Both chemotherapy (cisplatin and navelbine) and teleradiotherapy (conformal) were identical in both groups – the only differences arose from the sequence according to which the two modalities were administered.

We observed statistically significantly higher toxicity of concurrent treatment as compared to sequential treatment. Due to this toxicity the treatment was not completed in 21.4% of patients from the concurrent group and in 2.2% of patients from the sequential group. These results remain in accordance with literature data [1, 3, 5, 7, 8, 10, 28].

Acute inflammation of the oesophageal mucosa was the reason for treatment discontinuation in 7/84 patients (8.3%) treated according to the concurrent treatment protocol; it was the most frequent complication in this patient group. In none of the patients treated sequentially was it necessary to discontinue treatment due to this particular complication. Literature data, including the results of three controlled clinical trials, confirms that oesophageal mucositis is the main complication of concurrent treatment [5, 10, 17, 37-40]. Curran et al. report acute oesophagitis (3°) in 5% of patients treated sequentially, as compared to 26% in the case of patients treated according to the concurrent protocol [37], and, in the next study, 4% and 21% respectively [38].

The remaining severe complications caused by concurrent treatment, i.e. granulocytopoenia and thrombocytopoenia and acute inflammation of pulmonary tissue are also reported by other authors [17, 41].

The results of treatment were found not to differ between the two groups. Complete radiological regression evaluated 6 weeks after treatment completion was observed in 13.5% of patients treated sequentially and in 13.1% of patients treated concurrently. Partial regression (>50%) was observed in 53.9% and 54.8% of patients, respectively. Altogether the >50% regression index was found to be 67.4% and 67.9%, respectively. In the study of Furuse et al. the total regression ratio ranged between 66% and 84%, in the study of Winterhalder et al. it was 65% (CR-12%) and in the study of Vokes et al. – 66-69% (CR-8-19%) [17, 39, 41].

The results of 2-year overall survival were also similar: 25.8% in the sequential treatment group and 25% in the concurrent treatment group, as was the 2-year disease-free survival – 11.2% and 11.9%, respectively. These results are also similar to those reported in literature, where 2-year survivals vary from 13% to 27% [7, 33, 35, 41-46%].

Our results have not shown the concurrent treatment regime to be superior to sequential treatment. Although, when comparing the results achieved by patients who had managed to complete the planned treatment concurrent therapy did appear more effective (although this failed to reach statistical significance), yet this gain was completely overruled by the significantly higher treatment toxicity. Literature reports maintain that concurrent treatment is more effective than sequential treatment [1, 5, 7, 8, 10, 17, 37-41, 47, 48]. This also appears to be the conclusion of 4 controlled clinical trials [37, 39, 47, 48].

In the RTOG 94-10 study, in the course of which 611 patients had been randomized, mean survival in the concurrent treatment group was 17 months, while in the sequential treatment group it was only 14.6 months ($p=0.08$) [37]. In a Japanese trial involving 320 patients the response ratio was significantly higher in the concurrent treatment group, as compared to the sequential treatment group (84% vs. 66%), as was the mean survival (16.5 months vs. 13.3 months) ($p=0.04$) [39]. In both of these studies treatment toxicity was greater in the concurrent treatment group.

In our material, in both the patient groups the only prognostic factor was the degree of disease advancement – in patients with III°A tumours the chances of 2-year survival were significantly higher than in patients with III°B tumours. Careful patient qualification made it

impossible for the other prognostic factors, such as the performance status, weight loss and gender etc. [1], to render their impact.

In the recent years attempts have been made at performing phase II trials aimed at increasing the efficacy of combined chemotherapy and radiotherapy in patients with advanced NSCLC. The evaluated modalities include:

- new drug combinations eg. carboplatin + paclitaxel, cisplatin + paclitaxel, cisplatin + carboplatin, cisplatin + etoposide, cisplatin + gemcytabin etc [1, 3, 5, 8, 10, 17, 36, 46];
- combining sequential and concurrent treatment [1, 17, 49, 50];
- combining chemotherapy and radiotherapy using unconventional methods of dose fractionation (hyperfractionation, accelerated hyperfractionation, irradiation with planned interval) [22, 24, 36, 46];
- combining induction treatment with concurrent treatment with radiation dose escalation using 3D planning [10].

Generally, a number of studies have failed to improve the results of treatment [8, 17, 22, 24, 41, 49, 50], while some provide only minor improvement [17, 36, 46, 51, 52]; phase III trials are a necessity. At present it is certain that only patients with a good performance status and without significant weight loss may be qualified for combined chemotherapy and radiotherapy, especially administered concurrently [1, 5, 8]; sequential regimes are safer [8, 31].

Conclusion

The efficacy of sequential and concurrent chemotherapy and teleradiotherapy in patients with locoregionally advanced nonresactable NSCLC is comparable, while the toxicity of concurrent treatment is significantly higher.

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