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The results of first line systemic therapy of NSCLC in clinical practice

Krzysztof Adamowicz

Introduction. Lung cancer is the most common cancer in the world. Every year, there are over 1.4 million new cases and about 1.3 million deaths due to lung cancer. Data on the results of palliative treatment of patients with non-small cell lung cancer in Poland are scarce.

Methods. The results of first-line palliative chemotherapy in 204 lung cancer patients treated in the period 2011–2014 in two cancer centres were analysed.

Results. The mean age of the study group was 63.4 ± 8.3 years; 155 patients received chemotherapy with cisplatin, 33 — schemes containing carboplatin, 8 — inhibitors of *EGFR* tyrosine kinase, 8 — vinorelbine or gemcitabine monotherapy. Complete regression was observed in 2 patients, partial response — in 52 patients (25%), stable disease in 92 (45%) and 58 (28%) patients had progression. Median survival for the entire group of patients was 12 months. Multidrug chemotherapy with cisplatin compared with chemotherapy involving carboplatin monotherapy was associated with increased toxicity in total ($p = 0.04$). An increased toxicity concerned only to haematological complications and renal insufficiency expressed by the level of creatinine in blood serum. There was no apparent effect of chemotherapy on the overall quality of life.

Conclusions. The results of palliative treatment of non-small cell lung cancer in daily practice are comparable to those obtained in prospective clinical trials despite having a different population of treated patients. The use of palliative chemotherapy had no significant effect on quality of life.

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Key words: non-small cell lung cancer, chemotherapy, treatment outcomes

Introduction

Lung cancer is the most common cancer in the world. Each year, there are more than 1.4 million new cases and about 1.3 million deaths due to lung cancer are recorded [1]. Admittedly, in the case of men, these figures have ceased to grow for some time. That said, in many places of the world (including Poland), the number of cases of adenocarcinoma in both sexes and all types of lung cancer in women has been increasing. According to the National Cancer Register, in Poland about 21,000 new cases of lung cancer are diagnosed annually with almost 15,000 among men and more than 6,000 in women [2]. Non-small cell lung cancer (NSCLC) makes up about 80–85% of all primary cancers of the respiratory tract in Poland [2].

In spite of some improvements in early diagnostics and treatment in recent decades, the prognoses in lung cancer still remains poor. In Poland, only about 11.9% men and 16.9% women survive five years with the majority of them being treated only palliatively already from the moment of their diagnosis [2, 3]. In spite of significant development and progress in molecular therapies and new chemotherapeutic agents, patients with metastatic lung cancer practically cannot be cured. Patients with NSCLC with IIIB and IV have particularly poor prognoses. In the last decade, the me-

Regional Hospital in Wejherowo, Poland

dian overall survival of the patients with metastatic NSCLC treated systemically within clinical studies, have grown from a few months to more than 20 months as reported in some studies results [4–7]. This improvement was obtained thanks not only to the modification of the previous treatment regimens [8–11], but first of all thanks to the application of new drugs, such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) and ALK inhibitors [12–20].

The data concerning palliative treatment of lung cancer patients in Poland are scarce. The data concerning the toxicity of treatment and life quality of the patients are also missing. This study, comprising a large group of patients undergoing systemic treatment within everyday clinical practice, forms an attempt to evaluate the real efficiency of treatment within this population, taking into consideration the therapeutic possibilities within the reimbursement programme of the National Health Fund. An attempt to determine the factors affecting the overall survival of the patients was also made.

Material and methods

The study concerned 204 patient with non-resectable, metastatic NSCLC (ICD10 = C34), who, in the period between 2011 and 2014 were treated with first-line chemotherapy in the Specialist Hospital in Wejherowo and in the Regional Oncology Centre in Gdansk. This group was made up of patients with primary or secondary cancer spread, who were not qualified for an attempt at radical treatment. The clinical data was obtained from the source documentation — patient information charts. In total, the files of 210 were analysed, and the documents of 6 patients were excluded from further analysis on account of incomplete data.

The analysis concerned the age, gender, educational status, smoking and family history, body height and weight, pain intensity, histopathological diagnosis, *EGFR* evaluation and the treatment regimen applied. Smokers were defined as those who smoked at least one cigarette per day within 12 months. A positive family history in lung cancer was defined as lung cancer among the relatives with first and second degree of consanguinity. These data were obtained from patients on the basis of interviews. The body weight and height of each patient was registered at the moment of commencement of treatment. The response was evaluated with the RECIST 1.1 scale, always on the basis of CT examination.

The analysis also concerned the data on treatment toxicity classified according to WHO (World Health Organization) criteria, observed on the first day of the consecutive chemotherapy cycle, irrespectively of its regimen. Haematological toxicity was evaluated on the basis of the laboratory tests performed on the day of the planned administration of chemotherapy. Other adverse events were analysed on the basis of the medical records kept by a doctor in charge of a case.

The quality of life was evaluated on the basis of the EORTC QLQ-C30 questionnaire [21]. The questionnaires in the Polish language version were filled in by the patients on the last week preceding the commencement of chemotherapy and in the first week after its completion.

For the analysis of the results, some basic descriptive statistic techniques were used. Arithmetic means were compared with the use of the t-Student test in the case of two variables and on the basis of the ANOVA analysis for more than two variables. The evaluation of the relationship of the demographic and clinical data and the response to treatment was made with logistic regression. The influence of specific factors on the overall survival was evaluated with the use of Cox proportional hazard regression with the likelihood ratio test. A value below $p = 0.05$ was regarded as statistically significant.

In the evaluation of the quality of life, detailed instructions provided by EORTC were taken into consideration. The statistical processing was made with Microsoft Excel software and the PQSTAT software, version 1.4. The study received the consent of the directors of both institutions and the Ethical Committee at the Regional Medical Chamber in Gdansk. The condition to receive the consent was the presentation of the database observing the complete confidentiality of the patients' data.

Results

The patients' details are presented in Table I. The mean age of the study group was 63.4 ± 8.3 years, and the median age was 65 years; 13% of the patients was made up of patients above 70 years of age; 64% were men; 78% were patients with dissemination of the primary tumour; 90% of the groups were previous or current tobacco smokers. The most frequent histological subtype was adenocarcinoma (46.6%) and squamous cell carcinoma (41.6%). The *EGFR* mutation was determined in 98 cases and found in 10 of them.

In the first line of treatment, the therapy with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) was used in 8 cases, whereas, in the second line — in one case, whilst in another case, in spite of the identification of the *EGFR* mutation, this therapy was not applied on account of uncontrolled metastases to the central nervous system.

In 155 cases, chemotherapy regimens with cisplatin were used, and in 33 cases — with carboplatin, whereas in the remaining 8 cases — vinorelbine or gemcitabine in monotherapy. The applied treatment regimen had no relationship with the performance status ($p = 0.17$), sex ($p = 0.19$), patients' educational status ($p = 0.19$), place of residence ($p = 0.15$), smoking status ($p = 0.69$) and primary or secondary metastases of the tumour ($p = 0.97$). Some relationship was found between the choice of monotherapy and the choice of the carboplatin regimens and the age of the subjects ($p < 0.01$). Carboplatin was more frequently

Table I. Patient's details

Feature	Number
Performance score	
0	108 (53%)
1	80 (39%)
2	16 (8%)
Distant metastases	
yes	178 (87%)
no	26 (13%)
Age (years)	
41–50	19 (9%)
51–60	62 (30%)
61–70	96 (47%)
> 70	27 (13%)
Sex	
women	73 (36%)
men	131 (64%)
Histological type	
adenocarcinoma	93 (46.6%)
squamous cell carcinoma	85 (41.7%)
other	13 (6.4%)
unknown	13 (6.4%)
EGFR mutation	
present	10 (4.9%)
absent	88 (43.1%)
not checked	108 (53.0%)
Lung cancer in the family	
yes	18 (9%)
no	186 (91%)
Place of residence	
urban areas	135 (66%)
rural areas	69 (34%)
Smoking history	
yes	184 (90%)
no	20 (10%)
Educational status	
lower than secondary	70 (34%)
secondary	72 (35%)
higher	62 (30%)
Cancer spread	
primary	159 (78%)
secondary	45 (22%)

applied in the elderly patients. Monotherapy was used in all patients above 75 and whose performance status was = 2.

In the case of the adenoma diagnosis, giant-cell carcinoma of the lung (GCCL) or a cancer with the predominance of the above-named histological subtypes, treatment by pemetrexed in the first line of therapy was applied in 21 cases.

Complete regression was obtained in 2 cases (one case of chemotherapy based on cisplatin and one case of treatment with the tyrosine kinase inhibitor). A partial response was obtained in 52 cases (25.5%), stabilisation in 92 cases h (45.1%), whist in 58 cases (28.4%) progression of the disease was observed.

In multiple factor analysis of variance (logistic regression), the response to treatment (complete and partial) with the use of cisplatin was not related to the analysed factors. However, a tendency towards higher probability of obtaining response to treatment was observed once pemetrexed was added to cisplatin (Tab. II). For carboplatin, the number of cases did not meet the statistical objectives for multiple factor analysis of variance.

Out of 204 analysed cases, 3 patients were still alive at the moment of the analysis. The median of overall survival in the entire group was 12.1 months. In the multiple factor analysis of variance, the overall survival period was affected by the performance status (PS = 0 contributed to a longer survival), treatment regimen (longer survival in cisplatin therapy) and the reported response to treatment (Tab. III). The median of overall survival for patients treated with cisplatin was 12.1 months (after the addition of pemetrexed — 12.7 months); for the patients treated with carboplatin — 10.6 months; for monotherapy — 10.2 months; the therapy with epidermal growth factor receptor tyrosine kinase inhibitors — 21.2 months. The median overall survival for adenocarcinoma was 12.6 months and did not differ significantly from the median overall survival for other types of non-small cell lung cancer (11.9 months; $p = 0.22$).

Second line therapy was applied in 139 subjects (68%). 35 patients did not receive the second line of chemotherapy on account of their poor general condition; 21 patients — on account of the fast progression and very short expected survival period, the further course of treatment of 8 patients remains unknown, whilst one of the patient refused further treatment. The second line of chemotherapy was used only in one patient who, in the first line, was treated with monotherapy. If, in the first line of chemotherapy, drugs with platin were used, the patients in the second line of treatment, received monotherapy with docetaxel (n = 89), pemetrexed (n = 18), gemcitabine (n = 19) and vinorelbine (n = 12) and anti-*EGFR* therapy (n = 1).

The survival period in the patients who received one line of treatment was shorter in comparison with those who received some consecutive lines of therapy (median survival: 9.9 and 12.9 months respectively; $p < 0.01$). The overall survival period in the case of patients receiving pemetrexed in the first or second line of treatment was similar in comparison with patients treated without this agent (median survival: 12.5 and 12.0 months respectively, $p = 0.33$). The median overall survival of the patients who, in the second line of treatment were receiving docetaxel was 12.1 months.

Table II. The impact of demographic and clinical factors on response to cisplatin (multivariate analysis)

	–95% CI	+95% CI	Statistical value	P value
Performance score	–0.89207	0.499571	0.305573	0.58041
Pemetrexed addition	–3.91701	0.324714	2.755215	0.096938
Age	–0.07819	0.021592	1.235977	0.266248
Sex	–0.81292	0.735198	0.009682	0.921616
Histopathological type	–0.43621	0.778585	0.305138	0.580679
Presence of distant metastases	–0.6217	2.253003	1.237026	0.266045

Table III. The impact of demographic and clinical factors on overall survival (multivariate analysis)

	–95% CI	+95% CI	stat. t	P value
Performance score	–2.82465	–0.79149	–3.50796	0.000562
Pemetrexed addition	–1.35659	2.973976	0.73663	0.462242
Age	0.054997	1.821152	2.095165	0.037461
Sex	–0.08897	0.068761	–0.25266	0.800799
Histopathological type	–0.81468	0.688952	–0.16491	0.869186
Presence of distant metastases	5.159973	8.092461	8.913318	<0.000001

Table IV. The frequency of side effects according to chemotherapy regimen. Significant differences marked in bold

Toxicity	The share of toxicity level 3. and 4.			
	erlotinib/gefitinib	cisplatin	carboplatin	monotherapy
Vomiting	0/8	22/155	2/33	1/8
Diarrhoea	1/8	15/155	3/33	1/8
Infections	0/8	6/155	1/33	0/8
Anaemia	0/8	34/155	1/33	0/8
Thrombocytopaenia	0/8	20/155	1/35	0/8
Neutropenia	0/8	51/155	3/33	0/8
Neuropathy	0/8	7/155	0/33	0/8
Nephrotoxicity*	0/8	19/155	1/33	0/8
Dermal toxicity and dry cornea	2/8	1/155	0/33	0/8
Ototoxicity	0/8	2/155	0/33	0/8

*defined as an increase of creatinine level above referential values

The most frequent adverse events in the chemotherapy group were haematological toxicity, including neutropenia, thrombocytopaenia and anaemia, as well as peripheral neuropathy, vomiting and diarrhoea (Tab. IV). Adverse events which occurred more rarely comprised infections, hair loss, fatigue and constipation. General toxicity was not related to the performance status ($p = 0.13$), sex ($p = 0.67$), educational status ($p = 0.25$), place of residence ($p = 0.76$), smoking status ($p = 0.17$), primary or secondary metastases ($p = 0.85$), diabetes ($p = 0.09$), arterial hypertension ($p = 0.35$) and response to treatment ($p = 0.89$). General toxicity depended on the type of chemotherapy (monotherapy in comparison with multi-drug regimens; $p < 0.01$) and age (above and below 70 years of age; $p < 0.01$). Also a significant difference in general toxicity was observed in the groups receiving chemotherapy based on varied platin derivatives (cisplatin vs carboplatin; $p = 0.04$). The risk of toxicity was higher in the group treated with cisplatin. Higher toxicity of chemotherapy based on cisplatin concerned solely haematological complications and an increase of creatinine level in blood serum. Moreover, in two cases, a deterioration in audiometric hearing was documented. Other toxicity profiles were observed in the case of inhibitors of *EGFR* tyrosine kinase (Tab. IV).

Table V. Results of palliative treatment of patients with NSCLC in phase III trials since 2000 (detailed data and references available from the authors)

The first author	Year	Primary endpoint	OS (months)	Number of patients
Sculier JP	2000	OS	8	297
Gatzemeier U	2000	OS	8.6	414
Ranson M	2000	OS	6.8	157
Frasci G	2000	OS	7	120
Fossella FV	2000	OS	8.5	373
Comella P	2000	OS	11.5	180
von Pawel J	2000	OS	8.5	438
Bonomi P	2000	QoI, OS	9.9	599
Shepherd FA	2000	OS	7	103
Sandler AB	2000	OS	9.1	522
Vansteenkiste JF	2001	RR	7.2	169
Kelly K	2001	OS	8	408
Smith IE	2001	OS	7	308
Souquet PJ	2002	OS	10	259
Scagliotti GV	2002	RR	9.8	607
Rosell R	2002	RR	9.8	618
Kosmidis P	2002	OS	10.4	509
Sculier JP	2002	OS	8.2	280
Socinski MA	2002	QoI, OS	8.9	230
Schiller JH	2002	OS	7.9	1155
Smit EF	2003	OS	8.9	480
Wachters FM	2003	OS	10.5	240
Belani CP	2003	RR, TTP	10.1	390
Danson S	2003	OS	8.8	372
Fossella F	2003	OS	11.3	1218
Gridelli C	2003	QoI	9.5	503
Gridelli C	2003	OS	9	707
Negoro S	2003	OS	12	398
Comella P	2004	OS	9.7	264
Georgoulias V	2004	OS	10.5	319
Stathopoulos GP	2004	OS	11	360
Laack E	2004	OS	8.5	300
O'Brien ME	2004	OS	8	419
Herbst RS	2004	OS	9.9	1037
Giaccone G	2004	OS	10.9	1093
Kubota K	2004	OS	11.3	302
Williamson SK	2005	OS	11	367
Sederholm C	2005	OS	10.3	325
Herbst RS	2005	OS	10.6	1059
Belani CP	2005	OS	9.8	369
Leighl NB	2005	OS	9.2	774
Pujol JL	2005	PFS	11.1	311
Georgoulias V	2005	OS	9.7	413
Bissett D	2005	OS	11.5	362
Lilenbaum RC	2005	OS	8.8	561
Rudd RM	2005	OS	10	422
Martoni A	2005	OS	11	272

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Table V. Results of palliative treatment of patients with NSCLC in phase III trials since 2000 (detailed data and references available from the authors)

The first author	Year	Primary endpoint	OS (months)	Number of patients
Westeel V	2005	OS	11.9	566
Sandler A	2006	OS	12.3	878
von Plessen C	2006	Qol. OS	8	297
Kudoh S	2006	OS	14.3	180
Ramlau R	2006	OS	7.5	829
Booton R	2006	OS	9.5	433
Paz-Ares L	2006	OS	10.4	670
Paccagnella A	2006	OS. RR	10.8	319
Park JO	2007	OS	15.9	314
Hainsworth JD	2007	OS	8	345
Helbekkmo N	2007	OS	7.3	432
Gridelli C	2007	OS	11.5	240
Gatzemeier U	2007	OS	11	1159
Sculier JP	2007	OS	11.9	281
Novello S	2007	OS	13	250
Ohe Y	2007	OS	13.9	581
Comella P	2007	OS	10.7	433
Kosmidis PA	2008	OS	10.49	452
Kubota K	2008	OS	14.1	393
Scagliotti GV	2008	OS	10.8	1669
Ramlau R	2008	OS	12.3	623
Blumenschein GR Jr	2008	OS	12.4	612
Belani CP	2008	OS	9.5	444
Kosmidis PA	2008	OS	10.49	452
Reynolds C	2009	OS	6.7	170
Lee SM	2009	OS	8.9	720
Ciuleanu T	2009	PFS	13.4	663
Mok TS	2009	PFS	18.6	1217
Grønberg BH	2009	Qol	7.3	446
Pirker R	2009	OS	11.3	1100
Tan EH	2009	TTF	9.9	381
Takeda K	2009	OS	10.3	130
Fidias PM	2009	OS	12.3	309
Treat JA	2010	OS	8.7	1135
Reck M	2010	PFS	13	1043
Stathopoulos GP	2010	toxicity	10	236
Lee DH	2010	PFS	14.1	161
Takeda K	2010	OS	13.7	598
Lynch TJ	2010	PFS	9.69	676
Scagliotti G	2010	OS	10.7	926
Okamoto I	2010	OS	15.2	564
Maemondo M	2010	PFS	30.5	230
Kosmidis PA	2011	OS	11.1	398
Koch A	2011	OS	8.50	316
Gaafar RM	2011	OS	10.9	173
Hirsh V	2011	OS	10.0	828
Lara PN Jr	2011	OS	13.4	649

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Table V. Results of palliative treatment of patients with NSCLC in phase III trials since 2000 (detailed data and references available from the authors)

The first author	Year	Primary endpoint	OS (months)	Number of patients
Groen HJ	2011	OS	8.2	561
Quoix E	2011	OS	10.3	226
Coudert B	2012	PFS and TTP	11.9	889
Manegold C	2012	OS	11.0	839
Boni C	2012	OS	11.3	433
Fløtten Ø	2012	OS	7.0	444
Sun JM	2012	PFS	22.2	135
Han JY	2012	OS	22.9	309
Lee JS	2012	OS	8.5	924
Socinski MA	2012	RR	12.1	1052
Scagliotti GV	2012	OS	9.0	960
Scagliotti GV	2012	OS	13	1090
Gridelli C	2012	OS	11.6	900
Paz-Ares LG	2012	OS	12.5	904
Lee SM	2012	OS	3.7	350
Inoue A	2013	OS	27.7	228
Socinski MA	2013	RR	19.9	1052
Yoshioka H	2013	OS	15.2	564
Karampeazis A	2013	TTP	ND	357
Zukin M	2013	OS	9.3	205
Sequist LV	2013	PFS	16.6	1269
Paz-Ares LG	2013	PFS	13.9	939
Barlesi F	2013	PFS	12.8	376
Johnson BE	2013	PFS	14.4	1145
Patel JD	2013	OS	13.4	939
Wu YL	2013	PFS	18.3	451
Barlesi F	2014	PFS	17.1	376
Alfonso S	2014	OS	8.23	176
Laurie SA	2014	OS	13.1	306
Yang JC	2014	PFS	27.9	253
Langer CJ	2014	OS	9.8	681
Zhou C	2015	OS	29.7	165
Wu YL	2015	PFS	26.3	217
Kubota K	2015	OS	17.1	608
Kubota K	2015	OS	20.9	227
Langer CJ	2015	RR	13.8	546
O'Brien ME	2015	OS	17.4	600
Giaccone G	2015	OS	20.3	332
Abe T	2015	OS	14.8	276
Zhou C	2015	PFS	24.3	276
Shukuya T	2015	OS	13.6	355
Thatcher N	2015	OS	11.5	1093
Paz-Ares L	2015	OS	11.5	633
Yang JC	2015	OS	33	709

OS — overall survival; PFS — progression-free survival; TTP — time to progression; RR — response rate; QoI — quality of life; ND — no data

The average number of chemotherapy cycles in the entire group was 3.65 (the scope was from 2 to 6 cycles). Only in 15 cases were more than 4 cycles were administered. The number of cycles was not related to the treatment regimen ($p = 0.67$). No toxic death occurred during the therapy. On account of toxicity, chemotherapy was postponed 105 times (14.9% of administrations). The most frequent causes of chemotherapy postponement were: neutropenia (85.3% postponements, including neutropenic fever 1.3%), anaemia (6.5%), thrombocytopaenia (4.7%) and diarrhoea (3.5%). In 21 patients the chemotherapy dose was reduced (all the patients were treated with cisplatin; not counting the carboplatin reduction within the calculation of the area under the curve after an increase of creatinine levels). In 12 patients the treatment was discontinued on account of toxicity (11 subjects treated with cisplatin and 1 patient treated with carboplatin). The intensity of pain before and after treatment did not differ significantly ($p = 0.19$) and was not related to the response to treatment ($p = 0.27$).

As the quality of life questionnaires were distributed among patients from January 2013 onward, this aspect was taken into consideration solely in 129 patients. The mean age in this group was 64 ± 7.9 years. The quality of life was not related to age, sex, place of residence or the treatment response. With regards to the small number of the subjects within the study group, the quality of life was not analysed separately in the subgroups receiving specific chemotherapy regimens. With regards to the entire group, during the treatment only an exacerbation of nausea and vomiting ($p = 0.02$), constipation ($p < 0.01$) and decrease of dyspnoea ($p < 0.01$) were observed.

Discussion

We searched the PubMed database using such medical headlines as "lung tumours" and "pharmacological treatment" and with the following filters: "with randomisation" and "third phase trial" in order to find the studies presented in Table V. Then we limited the search results to the period between 1st January 2000 and 31st December 2015 in 10 leading journals (*Annals of Oncology*, *British Journal of Cancer*, *Cancer*, *Clinical Cancer Research*, *European Journal of Cancer Journal of Clinical Oncology*, *Journal of National Cancer Institute*, *Lancet Oncology*, *The Lancet* and *The New England Journal of Medicine*). The documents concerning biological and other prognostic factors in separation from the main study results were excluded from the cumulative breakdown, and the same concerned the trails with randomisation of the second phase and those based on adjuvant treatment. The mean survival in all listed studies was 12.8 months. This mean value is lower, being 9.9 months for the studies with the evaluation of classical chemotherapy (after the exclusion of the studies with inhibitors of EGFR tyrosine kinase inhibitors and ALK). In the material presented in this paper, the median overall survival was 12 months. The treatment results measured with the overall survival period in everyday clinical practice thus seem to be comparable with the results currently obtained in the prospective third phase studies.

However, these median values cannot be directly compared to other patient populations. On the other hand, though, the majority of incidence of malignant lung cancers occurs after 50 years of age (96% morbidity in men and 95% morbidity in women), and about 50% morbidity in both sexes occurs in groups above 65 years of age [2]. The risk of lung cancer increases with age, reaching its peak in men in the eighth decade of life and in women at the turn of their sixth and seventh decade of life. The situation was very similar in our population in which the mean age of patients was 63 years. The number of patients above 75 years, much lower than the number of patients below 75, is probably the result of withholding the toxic oncological treatment and replacing it with palliative care in this group. Also the predominance of male subjects and smokers was typical for this type of cancer and compliant with the published data.

Our study, however, casts some light on a few problems which are significant in everyday clinical practice. The evaluation of our results should thus take into consideration some factors. First of all, the decision concerning the commencement of treatment was always taken by specialists in clinical oncology. Their decision could have been subjective, but some tendencies can be observed. In the study group there were 27 patients above 70 years of age, including nine patients above 75; eight patients out of this group were treated with monotherapy without platin derivatives. A clear tendency to use monotherapy in elderly subjects is seen. On the other hand, though, in all these patients, the doctors in charge, defined the performance score as 2, and 90% of these patients had at least two clinical burdens with other serious internal diseases. Therefore, it is not very clear whether the decisive factors determining the choice of monotherapy are just the age, performance score or other burdens. Secondly, varied chemotherapy regimens were used in monotherapy: based either on cisplatin or carboplatin (with a significant predominance of the former). In a separate analysis, a significant difference with regards to overall survival in favour of cisplatin was shown. A limitation of this comparison is the relatively low number of patients receiving various treatment regimens based on carboplatin ($n = 33$). Thirdly, the analysis showed the significant influence of the performance status and the age of patients on their overall survival, which was also observed in the clinical studies addressed for the patients in older age groups [22, 23]. Our study also has a few potential drawbacks. The most important one is its retrospective character. The lack of significant differences in the overall survival period for diverse histological subtypes of non-small cell lung carcinoma

may be explained by the lack of administration of different treatment schemes for adenocarcinoma. In our case, only 21 subjects in the first line of chemotherapy were treated with pemetrexed and 8 with *EGFR inhibitors*. This was partly the result of the period in which the studies were carried out, as, at this point, pemetrexed was refunded only in the second line of treatment (in this period, 34 patients with a diagnosis of adenocarcinoma began the first line of therapy). Moreover, a large group of patients did not meet the criteria of the National Health Fund Programme. In the analysed population, out of the patients qualified for treatment with the use of pemetrexed, as many as 12 patients had contraindications for cisplatin, 7 patients refused to commute 35 kilometres to the centres which had the possibility of administering cisplatin, 5 patients had brain metastases and in 3 cases some abnormalities in laboratory tests were found, which did not meet the criteria for the inclusion to the therapy; in 2 cases the performance score was PS = 2, in 2 other cases, there were cardiovascular contraindications and in 1 case the cause remained unknown. A low share of the patients with the *EGFR* gene mutation is also surprising (10 cases out of 204 patients — less than 5%). In the Polish population, the rat of this mutation carriers is about 8.4% [24]. The causes for this phenomenon, and especially discrepancies between the centres remain unknown (for Wejherowo, this share was only 3.2%). This may be the outcome of the different population profile of patients treated there, as in that centre the dominating group of patients were men, smoking cigarettes or other forms of tobacco users (this was pipe smoking or snuff usage, characteristic for Kashubia). The outcome of this fact may be a low rate of patients treated with anti-*EGFR* therapies which could affect the obtained results.

In the discussed material, in 5.8% cases, the treatment was discontinued on account of toxicity and in 10.3% the chemotherapy doses were reduced. In 33 cases at least two serious toxicity complications were found. The toxicity data presented here may be, however, underestimated, with regards to the retrospective character of the study. Only in 8 patients (3.9%) was hospitalisation during the therapy necessary. In all the cases this was connected with anaemia requiring the transfusion of packed red blood cells. These results show that palliative chemotherapy in lung cancer patients may be carried out on an outpatient basis in the majority of cases. It must be stressed that in the majority of patients, the secondary prophylaxis was applied with the use of granulocyte growth factors, which decreased the risk of clinically significant neutropenia after the first incident of this type of complication

The larger toxicity of cisplatin-based chemotherapy is complaint with the published data [25, 26]. Carboplatin was introduced into clinical studies at the beginning of the 1980s as an agent with a similar activity to cisplatin, yet with a different toxicity profile, comprising bone marrow suppression but with a significantly lower nephrotoxicity and neurotoxicity and much less emetogenic [25]. There is a widely held conviction that carboplatin is better tolerated than cisplatin. The presented data and their interpretation confirm our hypothesis that the toxicity of treatment observed in everyday clinical practice may be higher than the results obtained in the clinical studies; doctors, fearing this toxicity, may decide to choose carboplatin, which, in our study turned out to be the agent with a smaller share of serious toxicities. Those results, however, cannot be compared, as the populations of patients treated with cisplatin and carboplatin did not differ significantly from one another. In the population treated with carboplatin, the mean age was higher and the co-morbidities were more frequent. This does not change the fact that carboplatin was a drug that was better tolerated, with a smaller emetogenic and nephrotoxic potential, yet it was also less effective with regards to the treatment response and overall survival.

In our material the first line of palliative chemotherapy in lung cancer did not have any significant influence on the general quality of life. We have already shown in previous studies that the systemic treatment frequently does not affect the quality of life of the patients with NSCLC [27]. Moreover, during the therapy, in the entire group of patients, an increase of nausea and vomiting and constipation cases was observed, yet also a reduction of dyspnoea.

Conclusions

The presented conclusions suggest that the efficiency of palliative treatment of the patients with non-small cell lung carcinoma in everyday clinical practice may be comparable with the efficiency obtained in the clinical studies with classical chemotherapeutic agents and platin derivatives differ from each other not only with their toxicity profile, but also with clinical efficiency. This conclusion, however, should be verified in a well-designed observational trial.

Conflict of interest: none declared

Krzysztof Adamowicz, PhD
Regional Hospital in Wejherowo
Department of Oncology
Jagalskiego 10
80–200 Wejherowo, Poland
e-mail: krzys.adamowicz@gmail.com

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References

1. Ferlay J, Soerjomataram I, Ervik M et al. *GLOBOCAN 2012 v 1.0. Cancer incidence and mortality worldwide*: IARC CancerBase No. 11 [Internet]. Lyon: International Agency for Research on Cancer, 2013 (http://globocan.iarc.fr).
2. Wojciechowska U, Didkowska J, Zatoński W. *Nowotwory złośliwe w Polsce*. Warszawa: Centrum Onkologii — Instytut, 2012.
3. De Angelis R, Sant M, Coleman MP et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE–5-a population-based study. *Lancet Oncol* 2014; 15: 23–34.
4. Kubota K, Ichinose Y, Scagliotti G et al. Phase III study (MONET1) of motesanib plus carboplatin/paclitaxel in patients with advanced nonsquamous non-small-cell lung cancer (NSCLC): Asian subgroup analysis. *Ann Oncol* 2014; 25: 529–536.
5. Wu YL, Zhou C, Liam CK et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced *EGFR* mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol* 2015; 26: 1883–1889.
6. Inoue A, Kobayashi K, Maemondo M et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013; 24: 54–59.
7. Maemondo M, Inoue A, Kobayashi K et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; 362: 2380–2388.
8. Fidias PM, Dakhil SR, Lyss AP et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 2009; 27: 591–598.
9. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008; 26: 3543–3551.
10. Kubota K, Kawahara M, Ogawara M et al. Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study. *Lancet Oncol* 2008; 9: 1135–1142.
11. Kosmidis PA, Fountzilas G, Eleftheraki AG et al. Paclitaxel and gemcitabine versus paclitaxel and vinorelbine in patients with advanced non-small-cell lung cancer. A phase III study of the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol* 2011; 22: 827–834.
12. Mok TS, Wu YL, Thongprasert S. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; 361: 947–957.
13. Treat JA, Gonin R, Socinski MA et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. *Ann Oncol* 2010; 21: 540–547.
14. Lee SM, Khan I, Upadhyay S et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2012; 13: 1161–1170.
15. Boni C, Tiseo M, Boni L et al. Triplets versus doublets, with or without cisplatin, in the first-line treatment of stage IIIB–IV non-small cell lung cancer (NSCLC) patients: a multicenter randomised factorial trial (FAST). *Br J Cancer* 2012; 106: 658–665.
16. Han JY, Park K, Kim SW et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol* 2012; 30: 1122–1128.
17. Wu YL, Lee JS, Thongprasert S et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. *Lancet Oncol* 2013; 14: 777–786.
18. Sequist LV, Yang JC, Yamamoto N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; 31: 3327–3334.
19. Zhou C, Wu YL, Chen G et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann Oncol* 2015; 26: 1877–1883.
20. Yang JC, Wu YL, Schuler M et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; 16: 141–151.
21. http://groups.eortc.be/qol/eortc-qlq-c30.
22. Hainsworth JD, Spigel DR, Farley C et al. Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced non-small cell lung cancer: a randomized phase 3 trial of the Minnie Pearl Cancer Research Network. *Cancer* 2007; 110: 2027–2034.
23. Comella P, Frasci G, Carnicelli P et al. Gemcitabine with either paclitaxel or vinorelbine vs paclitaxel or gemcitabine alone for elderly or unfit advanced non-small-cell lung cancer patients. *Br J Cancer* 2004; 91: 489–497.
24. Krawczyk P, Reszka K, Ramlau R et al. Prevalence of rare EGFR gene mutations in non-small-cell lung cancer: a multicenter study on 3856 Polish Caucasian patients. *Ann Oncol* 2016; 27: 358–359.
25. Canetta R, Goodlow J, Smaldone L et al. Pharmacologic characteristic of carboplatin: Clinical experience. In: *Carboplatin (JM-8): Current perspectives and future directions*. Bunn PA, Canetta R, Ozols RF et al. (eds.). Philadelphia: WB Saunders, 1990: 19–38.
26. Klastersky J, Sculier JP, Lacroix H. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced stage non-small cell lung cancer: European Organization for Research and Treatment of Cancer. Protocol 07861. *J Clin Oncol* 1990; 8: 1556–1562.
27. Saad ED, Adamowicz K, Katz et al. Assessment of quality of life in advanced non-small-cell lung cancer: an overview of recent randomized trials. *Cancer Treat Rev* 2012; 38: 807–814.