

## The results of chemotherapy in 976 patients with non-small lung cancer

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*Introduction.* There are substantial changes in the achieved chemotherapy response rate in non-small lung cancer (NSCLC) from 4.7% in the years 1960–1970, to 48% in the period 1993–1998. The aim of this study is to evaluate retrospectively the efficacy of NSCLC palliative therapy in regard to the modifications of chemotherapy schedule within the last 40 years. *Material and methods.* In years 1960–1998, 976 patients with NSCLC, not suitable for surgery or/and radiotherapy, received palliative chemotherapy in the Cancer Center, Krakow, Lung Diseases Department, John Paul II Hospital, Kraków, and Lung Diseases Department, Hospital in Czerwona Góra. Different chemotherapy regimens were used in subsequent periods of time.

*Results.* The remission rate, mean survival time and one-year survival were used to evaluate the efficacy of chemotherapy. The constant increase in remission rate and increasing trends in mean survival time in subsequent periods of time were observed. The most spectacular result was an increase of one-year survival from 10% in 1971–1980 to 41% in years 1993–1998. The number of severe toxicity cases (G3 – G4) was diminished, despite the increasing intensity of treatment. Almost 30% improvement of the quality of life was seen.

*Conclusion.* The data presented show the increased remission rate in NSCLC when using modified chemotherapy regimens. These results may be compared with the results in those cancers which are commonly treated with chemotherapy. This suggests to introduce chemotherapy to all NSCLC patients who are not suitable for surgery or/and radiotherapy. However, such an intensive, toxic and very expensive treatment, required to produce a clinical benefit, must be offered to the carefully selected patients and delivered only in reference cancer centers.

### Wyniki leczenia cytostatykami 976 chorych na niedrobnokomórkowego raka płuca

*Wstęp.* Na przestrzeni ostatnich czterdziestu lat zmieniają się odsetki remisji uzyskanych w niedrobnokomórkowym raku płuca (ndrp) chemioterapią: od 4,7% w latach 1960–1970 do 48% w latach 1993–1998, a wraz z nimi – opinie na temat zasadności stosowania tej chemioterapii. Do końca lat siedemdziesiątych uważano, że niedrobnokomórkowy rak płuca jest modelem przykładem nowotworu niewrażliwego na chemioterapię. Obecnie przedmiotem kontrolowanych badań klinicznych są próby zarówno sformułowania wskazań do leczenia paliatywnego, uwzględniających również (poza zaawansowaniem i stanem ogólnym pacjenta) czynniki biologiczne nowotworu, oraz próby kojarzenia metod leczenia miejscowego, zwłaszcza chirurgii w z chemioterapią. Podstawowym pytaniem pozostaje nadal: który z dostępnych schematów leczenia jest najskuteczniejszy, w jakim stopniu leczenie wpływa na przedłużenie życia i czy rzeczywiście wprowadzenie nowych leków wpłynęło na zwiększenie odsetka remisji i czasu przeżycia. Celem prezentowanej tu analizy jest retrospektywna ocena skuteczności leczenia paliatywnego ndrp, w zależności od zmieniających się metod leczenia cytostatykami.

*Materiał i metoda.* W latach 1960–1998 w Centrum Onkologii w Krakowie, w III Oddziale Chorób Płuc Szpitala im. Jana Pawła II w Krakowie oraz w III Oddziale Chorób Płuc w Czerwonej Górze, leczono 976 chorych na ndrp, zdyskwalifikowanych od leczenia operacyjnego i/lub radioterapii. Chorzy byli leczeni według jednolitych protokołów terapeutycznych, a wyniki leczenia oceniano kolegialnie.

*Wyniki.* Wyniki leczenia oceniano na podstawie odsetka remisji, średniego czasu przeżycia oraz odsetka przeżyć jednorocznych. Zaobserwowano stały wzrost odsetka remisji i średniej czasu przeżyć w poszczególnych przedziałach czasowych. Najbardziej spektakularny wydaje się wzrost odsetka przeżyć jednorocznych z 10% w latach 1971–1980 do 41% w latach 1993–1998. Mimo zwiększenia agresywności leczenia obniżył się odsetek poważnych działań niepożądanych (G3 – G4). Indeks jakości życia poprawiał się aż o 30%, po właściwie stosowanej chemioterapii i przy prawidłowym doborze chorych do leczenia.

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*Podsumowanie. Przedstawione wyniki mogą dowodzić, że zwiększenie odsetka remisji, uzyskiwanych w kolejnych modyfikacjach leczenia cytotatykami, doprowadziło do stanu, w którym uzyskane rezultaty są zbliżone do wyników paliatywnej, stosowanej obecnie rutynowo chemioterapii nowotworów. Można to uznać za argument w podejmowaniu leczenia u chorych na ndrp nieoperacyjnych i nie kwalifikujących się do radykalnej radioterapii. Wniosek ten nie może być jednak przyjęty automatycznie i bez zastrzeżeń. Intensywne, toksyczne i kosztowne leczenie chemiczne, a takie musi być, o ile ma przynieść kliniczne korzyści, powinno być oferowane chorym wyłonionym drogą starannego doboru, uwzględniającego m.in. aktualny stan sprawności organizmu, wydolność narządową, jakość przeżycia itd. Tego typu leczenie powinno być prowadzone w wyspecjalizowanych ośrodkach referencyjnych, biorąc pod uwagę możliwości zarówno logistyczne, jak i finansowe.*

**Key words:** non-small lung cancer, chemotherapy, treatment efficacy

**Słowa kluczowe:** niedrobnokomórkowy rak płuca, chemioterapia, skuteczność leczenia

## Introduction

There are substantial changes in the achieved chemotherapy response rate in non-small lung cancer (NSLC) – from 4.7% in the years 1960-1970, to 48% in the period 1993-1998. Subsequently, the opinions on the usefulness of chemotherapy in NSCLC change. This cancer was thought to be chemotherapy-resistant till the end of the seventies.

Recently, some monitored clinical trials appeared, searching for indications to palliative treatment, with regard to clinical stage, patient performance status and biologic factors of cancer. Other interesting studies are focused on combining surgery and chemotherapy. The basic questions are: which chemotherapy regimen is most effective? Does chemotherapy prolong survival? Does the introduction of new generation of cytostatic drugs bear an impact on the response rates and survival time? The aim of this study is to analyze retrospectively the efficacy of NSCLC palliative therapy in regard to changing chemotherapy schedules within the last 40 years.

## Material and methods

Nine hundred seventy six patients with NSCLC, not suitable for surgery or/and radiotherapy, were treated with palliative chemotherapy in the Cancer Center Krakow, Lung Diseases Department, John Paul II Hospital, Kraków and Lung Disease, Department Hospital Czerwona Góra, in the years 1960-1998. Different chemotherapy regimens were used in subsequent periods of time. The treatment was based on uniform clinical protocols [1-9]. All analyzed patients were not eligible for surgery and these refusing surgery were referred to radiotherapy. Patients suitable for the primary combined treatment (chemotherapy and radiotherapy) and those who received less than 2 chemotherapy cycles, were excluded from the analysis. At least one-year follow-up was required. The quality of life assessment was included to the study in all patients treated since the end of eighties. The EORTC standard quality of life questionnaire was used. The clinical set of patients is presented in Tab. I.

## Results

The remission rate, mean survival time and one-year survival were used to evaluate the efficacy of chemotherapy.

**Tab. I. Clinical subset of patients**

|   |            |  |          |
|---|------------|--|----------|
| 882 male 54 female                                      |            |  |          |
| age 18–75 yr  | 59 yr      |  |          |
| Disease stage   |            |  |          |
| II A i III A -10%                                       | IIIB – 27% |  | IV – 49% |
| Microscopic diagnosis                                   |            |  |          |
| sqamous cell carcinoma                                  |            |  | 716      |
| adenocarcinoma  |            |  | 216      |
| large-cell carcinoma                                    |            |  | 36       |
| unspecified non-small cell lung cancer                  |            |  | 8        |
| Percentage of untreated patients in subsequent periods: |            |  |          |
| 1960–1970:  | 78%,       |  |          |
| 1971–1980:  | 62%,       |  |          |
| 1981–1992:  | 39%,       |  |          |
| 1993–1998:  | 38%        |  |          |
| Primary treatment                                       |            |  |          |
| chemotherapy naive                                      | 76%        |  |          |
| primary radiotherapy                                    | 12%        |  |          |
| primary surgery   | 7%         |  |          |
| previous chemotherapy                                   | 5%         |  |          |

The constant increase in the remission rate and increasing trends in mean survival time in some periods were observed. The most spectacular result was an increase of one-year survival from 10% in 1971–1980 to 41% in years 1993–1998.

The number of severe toxicity cases (G3 – G4) was diminished, despite increasing nowadays of the treatment intensity. The toxicity was assessed using the four grade scale. A reclassification was necessary in some cases due to the three grade scale used previously. This reclassification might not be complete because of the less number of tests evaluating the toxicity, used earlier.

An almost 30% improvement in the quality of life, and 79% reduction of dyspnea were seen in patients carefully selected to treatment, and receiving proper procedures.

440 of our patients were enrolled to the clinical studies in the years 1971-1980. In our previous study [3] we concluded that the mean survival time in untreated patients with NSCLC was 3.7 months. In comparison our recent results are very satisfactory. We noted a high percentage of very advanced stage (IV) of the disease among

**Tab. II. NCCLC chemotherapy results in 976 patients treated in the years: 1960–1998**

| Years                        | 60–70            | 71–80             | 81–92                         | 93–98             | 93–98                  |
|------------------------------|------------------|-------------------|-------------------------------|-------------------|------------------------|
| Drugs                        | HN 2             | ADR<br>MTX<br>LDN | CDDP<br>CBDCA<br>VP-16<br>VDS | IFX<br>MTC<br>CTX | NVB<br>+CDDP           |
| No of pts                    | 42               | 448               | 193                           | 161               | 92                     |
| % pts w III°                 | 68%              | 54%               | 49%                           | 47%               | 48%                    |
| % pts w IV°                  | 32%              | 46%               | 51%                           | 53%               | 52%                    |
| Remission rate               | 4.7%             | 19%               | 27%                           | 29%               | 48.8%                  |
| Mean survival time<br>> 1 yr | 2.6<br>-         | 7.1<br>10%        | 7.9<br>19%                    | 6.9<br>21%        | 12.2<br>41.0%          |
| Toxicity<br>G 3–4            | 29%<br>1960-1970 | 21%<br>1971-1980  | 19%<br>1981-1992              | 14%<br>1993-1998  | 16.7-2.4%<br>1993-1998 |

analyzed patients which were not offered to be treated in the past decades.

### Discussion

The increased remission rate obtained with the use of modified chemotherapy regimens allows to compare these results with the palliative treatment of other cancers. It seems reasonable to offer chemotherapy to all NSCLC patients who are not suitable for surgery or/and radiotherapy. However this conclusion cannot be accepted without any conditions. Such an intensive, toxic and very expensive treatment should be offered only to the carefully selected patients. It should be delivered only in highly qualified reference cancer centers which have both the logistic and financial possibilities to do it.

A very careful selection of patients is required in the group with distant metastases and poor performance status, due to unsatisfactory results and high severe toxicity rate. High costs of treatment and hospitalization, raise questions about pharmacoeconomic analyses [10, 11]. High costs are also generated by the subsequent treatment of side effects resulting from new drug combinations e.g. platinum compounds, vinorelbine and gemcytabine or taxans. The specific palliative aim of the treatment must be clearly defined before the introduction of chemotherapy. The reduction of dyspnoe and symptom control in Pancoast syndrome appear to be the main goals of treatment. An acceptable quality of life, with the chance of life prolongation may be offered to patients with other than pulmonary location of the disease.

The differences in the results of treatment and in the therapy associated toxicity may be partially related to the improvement of diagnosis and supportive care.

The results of combined cisplatin, gemcytabin and paclitaxel were not included in our study because this regimen is still under investigation.

However, our present results suggest that selected chemotherapy regimens should be investigated not only as

a single treatment, but also in combination with other modalities (surgery, radiotherapy). This may result in further improvement in the treatment of NSCLC.

Our results are comparable with those presented in the literature, however, such great number of patients enrolled by one therapy team is uncommon and should be stressed.

We do recommend chemotherapy in NSCLC, particularly in two clinical situations. Chemotherapy and concomitant radiotherapy should be offered to patients with non operable, locally advanced cancer. Palliative chemotherapy may be employed in the group of patients with massive local involvement, with the dissemination of the disease, and after very careful selection (i.e. performance status, metastases location, exclusion of cachexia, satisfactory results of blood tests). In this way, a satisfactory palliation and even occasional survival benefit may be obtained in properly selected patients with NSCLC.

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