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PRACA POGLĄDOWA
REVIEW

Long-term course of disease in 71-year-old patient with diagnosis of small cell lung cancer – case report and literature review

Wieloletni przebieg choroby u 71-letniego pacjenta z rozpoznaniem raka drobnokomórkowego płuca – opis przypadku i przegląd piśmiennictwa

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ABSTRACT

Small cell lung cancer is the most aggressive cancer that originates in the lung. Current treatment options are based on systemic treatment (chemotherapy, immunotherapy) and radiotherapy. Only in rare cases is it possible to perform surgical treatment. Despite its high sensitivity to chemotherapy and radiotherapy, only a small percentage of patients achieve long-term survival. The following case presents a patient after four lines of chemotherapeutic treatment and radiotherapy, which enabled 5-year disease control, along with an analysis of the available therapeutic options, their side effects and factors affecting the response to treatment.

KEYWORDS

small cell lung cancer, chemotherapy, radiotherapy, long-term survival

STRESZCZENIE

Rak drobnokomórkowy płuca jest najbardziej agresywnym nowotworem wywodzącym się z płuc. Obecne opcje leczenia opierają się na leczeniu systemowym (chemioterapia, immunoterapia) i radioterapii. Jedynie w rzadkich przypadkach możliwe jest wdrożenie leczenia chirurgicznego. Pomimo wysokiej wrażliwości na chemioterapię i radioterapię tylko niewielki odsetek pacjentów osiąga długoterminowe przeżycie. W pracy przedstawiono przypadek pacjenta po czterech liniach chemioterapii i radioterapii, które umożliwiły 5-letnią kontrolę choroby, wraz z analizą dostępnych opcji terapeutycznych, ich skutków ubocznych, a także czynników wpływających na odpowiedź na leczenie.

SŁOWA KLUCZOWE

rak drobnokomórkowy płuca, chemioterapia, radioterapia, przeżycie długoterminowe

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INTRODUCTION

Lung cancer remains one of the most frequently occurring cancers worldwide, ranking second in terms of incidence in both women and men, although first in terms of mortality [1]. The estimates are 2.2 million new cases and 1.79 million deaths per year due to lung cancer on a worldwide scale [2]. Histologically, lung cancer is divided into the non-small cell type (non--small cell lung cancer – NSCLC) and the small cell type (small cell lung cancer – SCLC). NSCLC is characterised by a higher incidence than other types of lung cancers and is categorised into several histological subtypes, of which adenocarcinoma is the most common, followed by squamous cell carcinoma and large cell carcinoma [3]. Nevertheless, SCLC, which represents approximately 10–15% of all lung cancers [4], is associated with a more aggressive course, a high growth rate, earlier metastasis and low survival rates.

SCLC is a cancer that correlates strongly with tobacco exposure [4], and to a lesser extent, radon exposure [5]. Patients with SCLC most commonly present with symptoms originating from the respiratory system such as cough, dyspnoea and haemoptysis, which may or may not be accompanied by systemic symptoms (e.g. weakness, weight loss) [6]. Of all the types of lung cancer, SCLC is the most frequently associated with paraneoplastic syndrome. Paraneoplastic syndrome represents a distant manifestation of malignant tumors that is not directly related to tumor invasion and metastasis [7].

Endocrine disorders (inadequate vasopressin secretion syndrome, ectopic Cushing's syndrome, acromegaly, malignant hypercalcaemia) and neurological disorders (the Lambert-Eaton syndrome, myasthenia gravis, limbic encephalitis, subacute sensory neuropathy), are most commonly reported in the course of SCLC. Of all those mentioned, the Lambert-Eaton syndrome and inadequate vasopressin secretion syndrome are the most frequent. The presence of paraneoplastic syndromes in undiagnosed patients enables early diagnosis and increases the chances of survival [8].

The estimated 5-year median survival rate in SCLC is 6.4% [9]. In assessing the stage of SCLC, a classification into limited (TNM I-III) and advanced (disseminated) stage disease (TNM IV) is used. Limited-stage SCLC (LS-SCLC) is characterised by the restriction of infiltrative lesions to one half of the thorax as determined by imaging, although it admits bilateral supraclavicular lymph node involvement and the possibility of treatment with a tolerable radiation field [9].

In more than two-thirds of patients, small cell carcinoma is detected at an extensive-stage (ES-SCLC) [4]. Thus, ES-SCLC is any case beyond the boundaries of the limited stage [9]. The most common sites of metastasis are the second lung, brain, liver, adrenal glands and bones [10]. In LS-SCLC, the basis of treatment is chemotherapy.

Radiotherapy and elective radiotherapy of the brain, and in a few limited cases, surgical intervention, are also used. In ES-SCLC, treatment consists primarily of chemotherapy, radiotherapy, and immunotherapy, which has been implemented in recent years [11] and has contributed to increased overall survival and progression-free time when combined with standard chemotherapy [12].

We present the case of a 71-year-old patient with LS-SCLC who achieved good disease control for 5 years after diagnosis with a 4th line of systemic treatment and radiotherapy.

CASE REPORT

A 66-year-old patient with a diagnosis of small cell carcinoma of the left lung was admitted to the pulmonology department in April 2019 to start systemic treatment. The infiltrative lesion was detected incidentally in February 2019 during a chest X-ray due to pneumonia. Subsequently, chest computed tomography (CT scan of the chest) confirmed the presence of a 35 × 44 × 24 mm tumor of the upper lobe of the left lung (Figure 1A), multiple fine nodule lesions (tree-in-bud-appearance) and infiltrative--atelectasis densities within the right lung, as well as fine nodule densities in the remaining lung parenchyma (Figure 1B). In the mediastinum, oval lymph nodes with a diameter of 11 mm in group IV R were visualised, otherwise not exceeding 10 mm in diameter in the short axis.

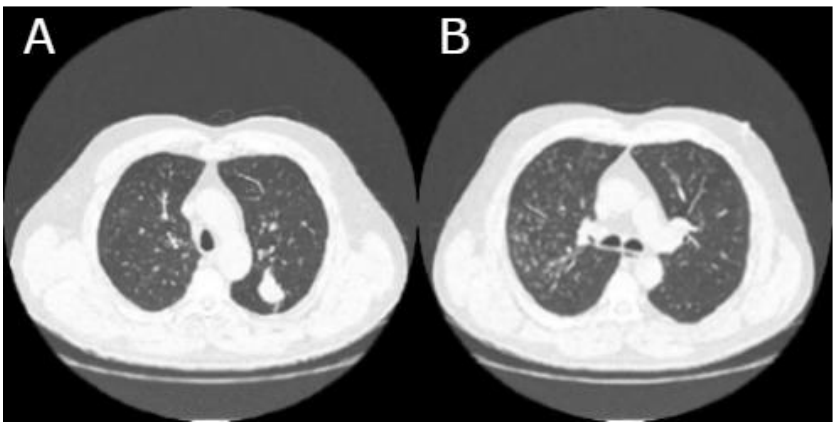

Fig. 1. Computed tomography of lung (02/2019): A – tumor of upper lobe of left lung measuring 35 × 44 × 24 mm; B – fine nodule lesions of budding tree type and infiltrative-atelectasis densities.

In the diagnostic pathway, bronchofiberoscopy was initially performed, in which no abnormalities were found. A precise histopathological diagnosis was made possible by fine-needle aspiration biopsy (FNA) under CT guidance in March 2019, in the department of thoracic surgery of the local hospital (Figure 2).

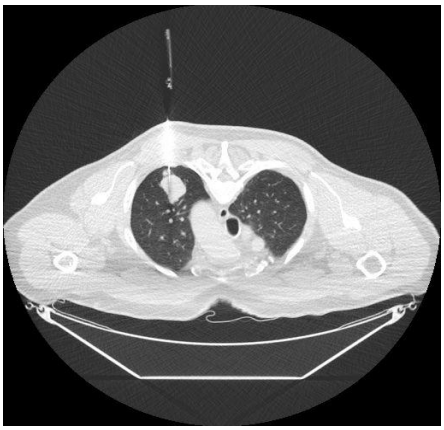

Fig. 2. Fine-needle aspiration biopsy under computed tomography guidance in prone position (03/2019).

The patient has a history of hypertension, ischaemic heart disease (post-PCI status), as well as post--cholecystectomy syndrome. The patient stopped smoking in February 2019. Prior to this, the patient smoked approximately 25 cigarettes per day for 30 years, which equates to 38 pack-years. A family history of cancer revealed a diagnosis of breast cancer in the patient's mother. The patient did not report symptoms originating from the respiratory system such as dyspnoea, haemoptysis or cough. The patient did not present with symptoms of paraneoplastic syndrome.

The Oncological Consilium decided to administer chemotherapy based on cisplatin and etoposide in four three-week cycles, which was started in April 2019. However, chemotherapy was complicated by neutropenia and anaemia, requiring a human granulocyte growth factor derivative. Consequently, from cycle 2 onwards, the treatment was modified by implementing carboplatin.

After completing chemotherapy, a follow-up CT scan of the chest was performed in August 2019. Compared to the scan performed 6 months earlier, it showed regression of the dimensions of the tumor structure to 13 × 21 mm in the upper lobe of the left lung. A fine nodular lesion and a band of atelectasis also appeared. There was also near-complete regression of the micronodular tree-in-bud type lesions and infiltrative--atelectasis lesions in the middle lobe of the right lung (Figure 3).

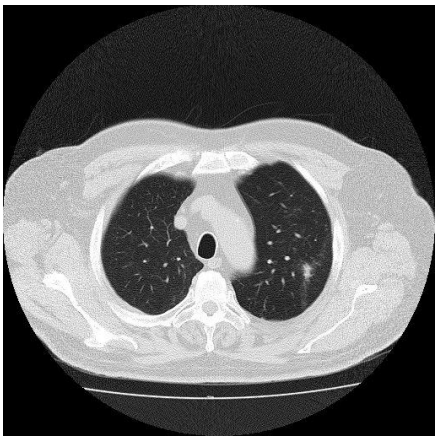

Fig. 3. Computed tomography scan of thorax (08/2019): regression in size of left upper lobe tumor to 13 × 21 mm, almost complete regression of tree-in-bud micronodular lesions and infiltrative-atelectasis lesions in middle lobe of right lung.

Subsequently, the patient was scheduled for radiotherapy of the thorax to the tumor area at a total dose of 56 Gy and radiotherapy to the hilar, mediastinal and supraclavicular nodes of the left side at a total dose of 40 Gy. Three weeks after the completion of thoracic radiotherapy, elective radiotherapy of the brain to a total dose of 30 Gy was performed.

As a radiological follow-up, a CT scan of the lumbar spine performed in February 2020 described a further reduction in the size of the nodular lesion (10 × 9 mm)

with a nodular band in the left peak and nodular lesions at the bronchovascular bundle in the posterior part of segment 1/2L, as well as regression of the nodular lesion in the anterior part of the upper lobe of the left lung.

Owing to the radiological progression found on the subsequent follow-up CT scan of the lung in May 2020, which described a small increase in the size (14 × 10 mm) of the infiltrative and banded atelectatic lesions in the top of the left lung (Figure 4), a second line of chemotherapeutic treatment based on etoposide in monotherapy (6 cycles) was administered, which was completed in September 2020.

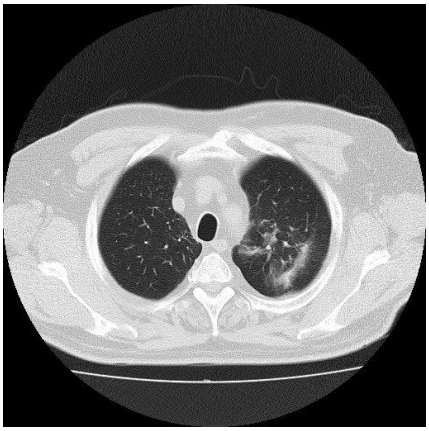

Fig. 4. Computed tomography scan of thorax (05/2020): enlargement of dimensions of infiltrative and banded atelectatic lesions in left lung apex.

As a result of the administered treatment, radiological regression was again achieved in the form of a reduction in the volume of the infiltrative-atelectatic lesions in the left lung apex. A CT scan of the lung performed in November 2021 revealed radiological progression of lung cancer. Among the atelectatic band-like lesions a nodular lesion measuring 24 × 20 mm was discovered in segment 1+2 of the upper lobe of the of the left lung, which was not present on previous CT scans (Figure 5). Consequently, repeat radiotherapy of the area of recurrence in the left lung at a total dose of 24 Gy was administered in December 2021. A follow-up CT scan after radiotherapy revealed a slight reduction in the size of the tumor, measuring 22 × 22 × 14 mm in segment 1+2 of the upper lobe of the left lung.

In November 2021, a CT scan of the lung revealed the presence of an enlarged nodular lesion (37 × 30 × 20 mm) in the upper lobe of the left lung (Figure 6), indicating the progression of the neoplastic process. In addition, a suspicious single nodular lesion on the tract of the left oblique interlobar fissure was described, which potentially corresponded to the intrapulmonary lymph nodes.

A CT scan of the head with contrast was also performed, which did not reveal the presence of metastatic foci. Due to the local recurrence of small cell carcinoma of the lung left lung, the patient was qualified for repeat radiotherapy of the left lung lesion at a total dose of 30 Gy with respiratory gating.

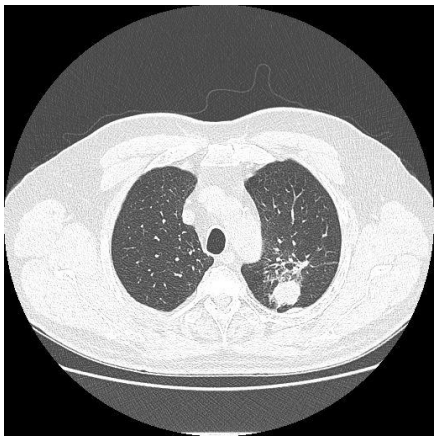

Fig. 5. Computed tomography scan of lung (11/2021) – new nodular lesion measuring 24 × 20 mm in segment 1+2 of upper lobe of left lung previously absent.

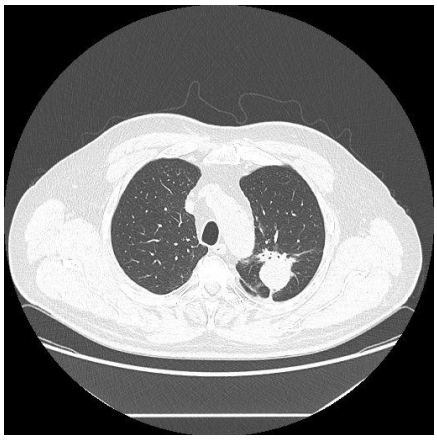

Fig. 6. Computed tomography scan of lung (11/2022) – re-enlargement of nodular lesion in upper lobe of left lung to 37 × 30 × 20 mm.

In April 2023, a follow-up CT scan of the lung once again revealed an enlargement (38 × 36 mm) and altered infiltrate morphology in the upper lobe of the left lung and significant progression of left hilar and mediastinal lymphadenopathy. As a result, 3rd line chemotherapy was immediately administered, comprising 6 cycles of carboplatin and etoposide. During the last cycle of chemotherapy, the dose of chemotherapeutics was modified because of severe anaemia. The applied treatment resulted in regression of the areas of ground glass around the tumor of the upper lobe of the left lung, with comparable dimensions of the tumor lesion. Regression of nodal lesions was also observed in the left hilar and mediastinum and along the left lung oblique fissure.

At the radiological follow-up in September 2023, the CT scan showed a stationary image of the tumor of the upper lobe of the lung left lung, a new nodular lesion in

segment 3 of the left lung and a fine nodular lesion 10 mm in diameter in segment 10 of the right lung (Figure 7). As a consequence of radiological progression, the decision was taken to qualify the patient for a 4th line chemotherapy scheme of topotecan in monotherapy (4 cycles). The treatment was complicated by anaemia and thrombocytopenia, requiring multiple transfusions of red blood cell (RBC) concentrates, the administration of steroid therapy and granulocyte colony-stimulating factors. At the end of the 3-month chemotherapy course, a head CT scan was performed, which described cortical-subcortical atrophy and retrograde vascular changes in the cerebral hemispheres, with no lesions suspected to be metastatic. A chest CT revealed a reduction in the diameter of the tumor of the upper lobe of the left lung, regression of the nodular lesions in segment 3 of the left lung and in segment 10 of the right lung. Progression of a predominantly budding tree type lesion at the base of the right lung was also described.

The patient's last hospitalization was in April 2024. A CT scan of the thorax was performed (Figure 8), which demonstrated marked progression of the left upper lobe tumor (to a dimension of 54 mm in the transverse plane) with infiltration of the vascular structures of the left hilum compared with the earlier study. A CT scan of the brain did not show foci with an image typical of metastasis. Resulting from the progression of the disease, the patient's history of treatment, and his general status (ECOG 3 – Eastern Cooperative Oncology Group performance scale), the patient was disqualified from continuing systemic treatment. The patient was discharged from the hospital in a stable condition and referred to the hospice for further symptomatic treatment.

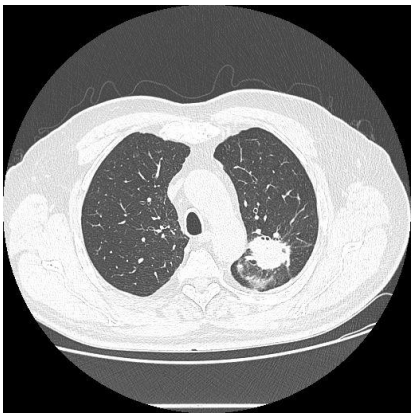

Fig. 7. Computed tomography scan of lung (09/2023): stationary left upper lobe tumor, appearance of new nodular lesions in segment 3 of left lung and fine nodular lesions in segment 10 of right lung.

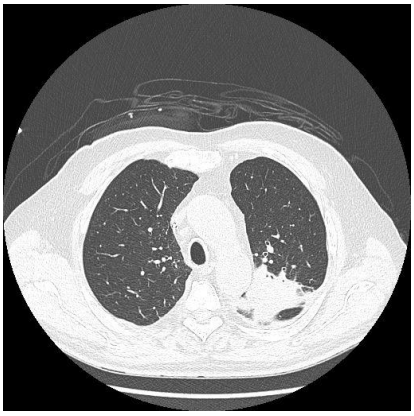

Fig. 8. Computed tomography scan of thorax (04/2024): progression of left upper lobe tumor to 54 mm in transverse plane, with infiltration of vascular structures of left lung hilum.

The exact clinical course of the disease is shown in Figure 9.

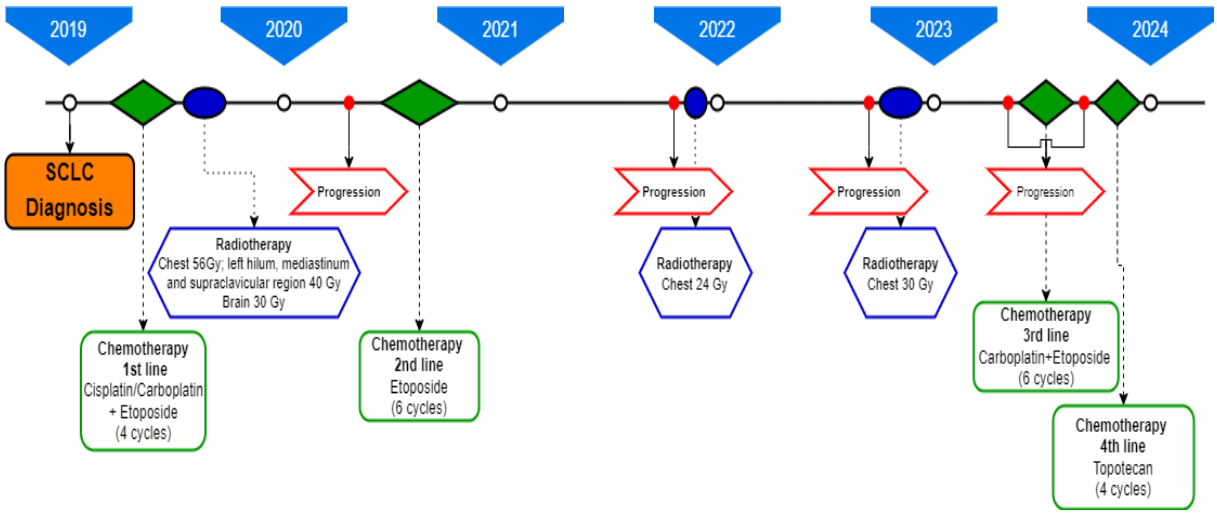

Fig. 9. Course of disease and treatment.

DISCUSSION

A comprehensive analysis of the SCLC genome has revealed a high degree of genetic instability, with a near-universal inactivation of the tumor suppressor genes *TP53* and *RB1*, as well as a high mutation burden [13]. The *TP53* gene is involved in a remarkable number of biological processes, such as DNA repair, cell cycle inhibition, apoptosis and autophagy [14]. In contrast, the *RB1* gene is primarily responsible for cell cycle blockade [15]. The fact that *TP53* and *RB1* are mutated in almost all SCLC cases may provide insight into the characteristics of this tumor that are commonly observed in clinical practice. The tumor lesion demonstrates both rapid and aggressive growth, while the initial response to chemotherapy and radiotherapy is notably favourable [16]. In consideration of the above, a diagnosis of SCLC is associated with an extremely poor prognosis. Furthermore, only in rare cases does systemic treatment enable long-term control of the disease. The presented case of a patient with SCLC remaining on treatment for 5 years is an extremely rare occurrence.

The long-term survival of a patient diagnosed with SCLC is defined as a period exceeding 24 months, in both the limited and disseminated stages [17]. The median overall survival of a patient with LS-SCLC is 17 months [18]. In the case presented above, the patient's 5-year survival is significantly beyond this limit.

As previously stated, surgical treatment of LS-SCLC is undertaken in a few cases. According to scientific societies, only 5% of patients qualify for radical treatment [19]. Due to the diagnosis and extent of the cancerous process, the patient was disqualified from surgery. Only a small group of patients with limited--stage SCLC are eligible for surgery. The primary treatment of SCLC is systemic chemotherapy, with platinum-based therapeutic agents (cisplatin, carboplatin) in combination with topoisomerase inhibitors (such as etoposide, topotecan, irinotecan) representing a crucial component. The combination of this treatment with or without other therapies, such as radiotherapy, has been demonstrated to be both effective and safe [13]. According to the guidelines, in the 1st line of treatment the patient received chemotherapy based on a platinum derivative and etoposide, supplemented with thoracic radiotherapy and elective radiation of the brain.

It is of significant importance to note that following the achievement of remission or stabilization, the patient is required to undergo periodic radiological follow-up. According to the recommendations of the National Comprehensive Cancer Network (NCCN), a follow-up CT scan every 2–6 months is recommended for cancer patients [20]. In the presented case, the patient therefore underwent a follow-up radiological examination at approximately three-month intervals.

Although SCLC is a highly chemotherapy-sensitive cancer, with an 80% response rate to chemotherapy, recurrence occurs within 6 months in the majority of patients [21]. In the case presented here, when disease progression was detected, systemic treatment was reintroduced with good results. The decision regarding the 2nd line chemotherapy and subsequent lines is determined by the response to previous treatment and the time over which progression occurred. In patients who have demonstrated sensitivity to platinum-based therapies and have had a treatment-free interval exceeding 3 months, it is possible to undertake a second round of platinum-based chemotherapy in combination with etoposide [22]. Therefore, the second line of treatment in the presented case was etoposide in monotherapy (6 cycles), followed by repeat radiotherapy to the tumor area. In addition, disease dissemination to the brain was excluded. In the third line of treatment, implemented after a further 5 months of prior therapy, 6 cycles of carboplatin and etoposide were administered, where the doses were reduced in the last cycle because of increased anaemia. After recurrent radiological progression, fourth-line treatment based on topotecan in monotherapy was implemented. Currently, topotecan is the only drug approved for the treatment of patients with SCLC who experience a relapse after treatment with prior agents [6]. In the reported case, complications after topotecan treatment in the form of anaemia and thrombocytopenia demanded the use of RBC transfusions, steroid therapy and epoetin alfa.

The case history allows longitudinal observation of the patient over time, with assessment of the effects of the treatment and the potential side effects of the therapy. Thus, the systemic treatment implemented in the patient was not without side effects. The treatment was modified (e.g. by implementing carboplatin in place of cisplatin) or the drug doses were reduced due to the observed haematological disorders (neutropenia and anaemia) [13]. The occurrence of adverse effects associated with chemotherapy is not uncommon. According to reports, chemotherapy used in SCLC is complicated by a range of side effects such as nausea and vomiting (65%), alopecia (25%), infection (36%), anaemia (37%), leukopenia (42%), thrombocytopenia (54%), and granulocytopenia (22%) [23]. The patient exhibited signs of hair loss throughout the course of chemotherapy in the described case, while the occurrence of myelotoxicity may be attributed to the administration of platinum derivatives [13]. In the case above, the patient tolerated the chemotherapeutic treatment well. Apart from haematological disorders, the chemotherapy did not significantly impact the patient's quality of life. Five years after treatment, the

patient remained in good health and was able to perform basic daily activities (ECOG 0).

Radiotherapy also plays a significant role in the treatment of SCLC. The evidence gathered in studies to date suggests that initiating radiotherapy at the earliest possible stage, preferably during the first or second cycle of chemotherapy, is optimal. Nevertheless, there is the possibility of sequential radiotherapy in frail or elderly patients [10]. In the discussed case, sequential radiotherapy of the thorax and elective radiotherapy of the brain were used. Elective brain radiotherapy in SCLC was demonstrated to reduce the incidence of brain metastases and improve overall survival in patients who respond to initial treatment [24].

Given the unfavourable prognosis, there is considerable anticipation surrounding the introduction of immunotherapy. From July 2021, patients with advanced SCLC in Poland, meeting the eligibility criteria for the program, have the opportunity to receive immunochemotherapy as 1st-line treatment. Atezolizumab is a fully humanised anti-PD-L1 monoclonal antibody that inhibits PD-L1 and B7-1 signaling, thereby restoring tumor-specific T1 lymphocyte immunity. In combination with carboplatin and etoposide, it has been approved for first-line treatment in ES-SCLC in the EU, USA, China, and other countries [25]. Studies have demonstrated improvement in overall survival with the combination of atezolizumab and chemotherapy. A 12-month and 18-month follow-up period revealed that 13% more patients were alive in the group treated with atezolizumab and chemotherapy than in the group receiving a placebo and chemotherapy [26]. The combination of atezolizumab and chemotherapy is associated with a higher incidence of adverse events due to chemotherapy itself (58–82% compared with 50–70% for chemotherapy alone) and additional adverse effects of an immunological origin (such as rash, hypothyroidism, hepatitis). Nonetheless, in the final conclusion, the clinical benefits outweighed the minimal increase in adverse effects, as these, especially those of immunological origin, were of low severity and manageable with appropriate treatment [27]. Due to the availability of the aforementioned programme only in 1st-line treatment, it was not possible to add immunotherapy to the treatment plan for the patient in the presented case after the diagnosis and initiation of treatment.

This raises the question of what determines the response to systemic treatment in SCLC patients. In other words, why will one patient respond to systemic treatment with long-term remission, while another will not have a positive response? The factors influencing the clinical course of SCLC include age, gender, and various laboratory tests, such as baseline lactate dehydrogenase (LDH), sodium, serum creatinine or a baseline neutrophil-to-lymphocyte ratio, as well as the patient's performance status [6]. Analysing sequentially, in LS-SCLC, age below 70 years, female sex and good patient status (ECOG 0–1) are associated with a better prognosis, and normal baseline LDH levels are associated with better organ function [28,29]. In contrast, baseline low sodium levels, high creatinine levels [30] and a high neutrophil--to-lymphocyte ratio (> 4.15) [31] are indicative of worse organ function in SCLC. The patient in the presented case, aged 66 at the time of diagnosis, exhibited normal levels of LDH (169 IU/L), sodium (141 mmol/l) and creatinine (78 μmol/l), along with a baseline neutrophil-to-lymphocyte ratio of 1.77. All the laboratory parameters and age, as well as the patient's performance status (at ECOG diagnosis 0), were favourable prognostic factors. Only male sex remained an unfavourable prognostic factor.

A further significant issue is the patient's body mass index (BMI) and weight loss over the course of the disease or treatment. A strong association has been demonstrated between BMI (> 28) and weight loss (< 5%) and overall survival in patients with lung cancer. However, this association is more pronounced in cases of advanced NSCLC than in those of SCLC [32]. In accordance with the aforementioned findings, weight loss is associated with reduced survival rates, whereas obesity is correlated with prolonged survival. In the case under discussion, the patient's BMI at the commencement of treatment was 31.9 kg/m^2, which may be regarded as a favourable prognostic factor. Furthermore, no significant weight loss was observed over the course of subsequent years.

Another negative prognostic factor in SCLC is cigarette smoking. A Chinese institution has reported that nicotinism is an unfavourable independent prognostic factor for overall survival and progression-free survival [33]. It is noteworthy that the patient had been a long--standing smoker and had quit a year before his cancer diagnosis. According to reports, the risk of lung cancer does not decrease until 10–15 years after smoking cessation [34].

The case presented above for the long-term treatment of SCLC is not isolated. Tartarone et al. [35] presented the case of a patient with LS-SCLC who was treated seven years after the diagnosis of SCLC. A similar case of 7-year survival in SCLC was described by Rafei et al. [36]. A Chinese institution documented a case of 9-year patient survival from the moment of SCLC diagnosis [37]. A case in which a patient was treated successfully with several cycles of chemotherapy for 36 months was described in ES-SCLC [38]. It is noteworthy that a similar case of 8-year survival in stage IV SCLC was described in a patient with a diagnosis dating back to 1987, which was long before the implementation of immunotherapy [39]. Long-term survival is also achievable in young patients, as documented in a 41-year-old female patient with

ES-SCLC treated for 6 years [40]. Of particular interest is the case of a 62-year-old man with a diagnosis of ES-SCLC with synchronous brain metastases, who received radiotherapy to the brain, chest and chemotherapy as part of his treatment plan. Subsequent to this, he was diagnosed with two intracranial recurrences 3.5 years and 6 years after his initial diagnosis. In both instances of recurrence, the patient underwent stereotactic radiotherapy and exhibited no physical decline. At the time of the case report, the patient was alive 6 years and 4 months from the moment of diagnosis and demonstrated functional independence throughout [41].

The above cases illustrate that patients of varying ages and clinical presentations may exhibit unexpectedly prolonged survival times. This discovery offers the tantalising prospect that in the future the survival of patients diagnosed with SCLC will become a matter of routine.

CONCLUSIONS

At this time, the long-term treatment of SCLC is an isolated phenomenon. Owing to the aggressive nature of the disease, metastases to distant organs are observed at an early stage. Although SCLC is a chemosensitive cancer, the responses are typically observed to be of a relatively short duration.

In the light of the aforementioned characteristics, the regular radiological follow-up of patients during the observation period and the implementation of systemic treatment or radiotherapy in the event of disease progression is crucial. Nevertheless, the observed isolated cases of long-term treatment of SCLC instill optimism that the disease will eventually become a chronic condition and that the implementation of appropriate therapy will enable progression-free time to be gained and overall survival to be prolonged for patients.

Authors' contribution

Study design – S. Kostorz-Nosal, P. Kalisz, B. Gałuszka, S. Skoczyński
Data collection – P. Kalisz, S. Kostorz-Nosal, I. Zielińska-Leś, D. Jastrzębski
Manuscript preparation – P. Kalisz, B. Gałuszka, S. Kostorz-Nosal, I. Zielińska-Leś
Literature research – P. Kalisz, D. Jastrzębski, D. Syguła, D. Ziora
Final approval of the version to be published – S. Skoczyński, D. Jastrzębski, D. Ziora, S. Kostorz-Nosal

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