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The effectiveness of chemotherapy in small cell lung cancer patients with *BRCA2* gene mutation and Schwartz-Bartter syndrome

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Oncology in Clinical Practice
 2019, Vol. 15, No. 2, 120–123
 DOI: 10.5603/OCP.2019.0008
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 ISSN 2450–1654

ABSTRACT

Small cell lung cancer (SCLC) currently comprises 15–20% of all lung cancers. It is characterised by rapid growth and early appearance of distant metastases. It is closely related to smoking. A characteristic feature of this type of cancer is the frequent coexistence of paraneoplastic syndromes (about 50% of patients). Paraneoplastic syndromes are clinically important because they can be the first sign of cancer. Early diagnosis of disturbing symptoms is an important factor in increasing the effectiveness of treatment and the patient's chance for longer survival. The most frequent and important paraneoplastic syndromes in the course of SCLC are primarily the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), paraneoplastic cerebellar degeneration, and Lambert-Eaton syndrome. This paper presents the case of a patient who came to the hospital with symptoms of hyponatraemia. Looking for the causes of hyponatraemia, the syndrome of abnormal secretion of antidiuretic hormone (Schwartz-Bartter syndrome) in the course of small cell lung cancer was confirmed. The fact that the patient was genetically burdened with the family history of breast cancer and was a carrier of the *BRCA2* gene mutation was also significant. According to the latest research, mutation in the *BRCA2* gene significantly affects the chemosensitivity of cancer cells, and thus increases the body's response to treatment. The patient received chemotherapy with carboplatin and etoposide, resulting in partial remission of cancer after two treatment cycles.

Key words: small cell lung cancer, *BRCA2* mutation, Schwartz-Bartter syndrome

Oncol Clin Pract 2019; 15, 2: 120–123

Introduction

Lung cancer is currently the most frequently diagnosed malignant tumour in the world. There are around 1.8 million new cases of disease per year, and this number is constantly increasing. In Poland, the incidence of lung cancer is estimated at approximately 23,000 new cases per year. Lung cancer is the leading cause of cancer deaths among men and women around the world. High mortality is caused by, among others, late diagnosis of the cancer process. Lung cancer does not show characteristic early-stage symptoms, and no effective screening methods have been developed so far that would reduce the number of deaths due to this

disease. Therefore, in the majority of patients at the time of qualification for oncological treatment, there are present features of significant advanced local or distant metastases. Another factor conditioning high cancer mortality is a relatively poor response to chemotherapy.

Small cell lung cancer (SCLC) accounts for 15–20% of lung cancer cases, but is characterised by an extremely aggressive course, the presence of metastases at the time of diagnosis, and the lack of surgical treatment options. The basic method of treatment of patients with small cell lung cancer is chemoradiotherapy or chemotherapy. Significant antitumour activity is demonstrated by alkylating drugs (cisplatin, carboplatin), anthracyclines (doxorubicin, epirubicin), topoisomerase in-

hibitors (etoposide, topotecan), followed by antimitotic drugs (vincristine, paclitaxel) and some antimetabolites (methotrexate). Higher efficacy of therapy was noted after the application of multidrug regimens. Response to treatment and its duration is still unsatisfactory. Median survival in patients with limited stage of small cell lung cancer (stages I–IIIA) is 14–20 months, and in patients in the generalised stage (stages IIIB–IV) it is 9–11 months. The search for new factors that influence the effectiveness of chemotherapy is ongoing [1–3].

Due to the development of genetic tests, it was observed that the presence of mutations in the *BRCA2* gene, in addition to an increased risk of breast and ovarian cancer, significantly contributes to the increase of chemosensitivity [4–6]. The subject of the study is the case of a 67-year-old patient with small cell lung cancer with *BRCA2* mutation and Schwartz-Bartter syndrome, in which a significant regression of advanced SCLC was obtained as a result of carboplatin chemotherapy with etoposide.

Case report

The 67-year-old patient had been under the care of the oncological surgery clinic for many years due to the presence of breast cancer in the family (her mother was ill). At one of the follow-up visits, the need for genetic testing for the possible presence of mutations in the *BRCA1* or *BRCA2* genes was suggested. In December 2016, confirmation of the presence of the N372H mutation in the *BRCA2* gene was obtained. The patient was informed about the increased risk of cancer, followed the doctor’s instructions, and set the time limits for periodic examinations.

In March 2018, the patient came to the hospital because of severe weakness, nausea, and dizziness, which had been intensifying for several days. After the basic tests, hyponatraemia was found. The serum sodium level was 116 mmol/l. No abnormalities were observed in the X-ray of the chest (Fig. 1). After symptomatic treatment, the patient was referred for further ambulatory diagnosis.

Two weeks later, the diagnostics of electrolyte disturbances began. During hospitalisation, moderate hyponatraemia was observed despite the treatment being used. Adrenal insufficiency and inadequate substitution of thyroid hormones was excluded (the patient suffered from post-operative hypothyroidism). The study revealed reduced osmolality of the plasma with normal osmolality of urine, and the urinary excretion of sodium remained > 30 mmol/l. In addition, normal daily diuresis, and decreased urea and uric acid levels were found. The overall clinical picture indicated a syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH). The occurrence

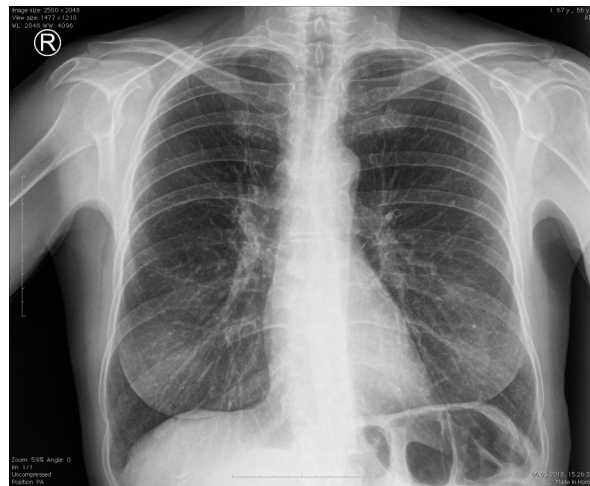


Figure 1. Chest review picture taken in March 2018. No irregularities were found

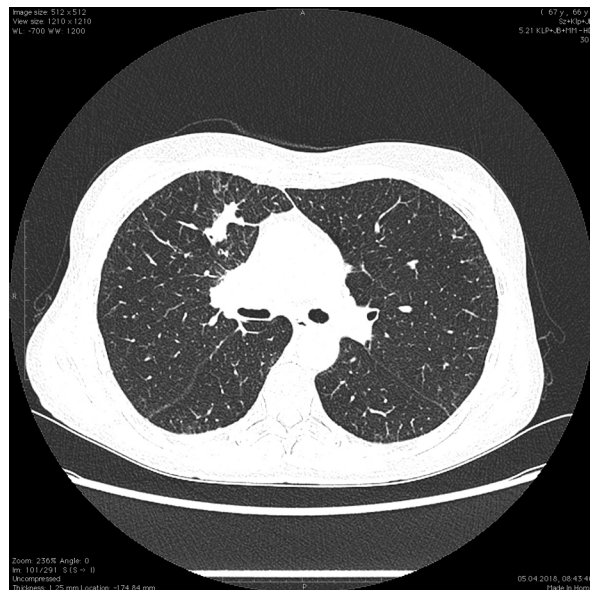


Figure 2. Infiltrative changes of the right lung (April 2018)

of Schwartz-Bartter syndrome, or syndrome of inadequate secretion of vasopressin, without any underlying cause, should always arouse oncological alertness, especially in smokers. This patient had smoked cigarettes for over 30 years. Paraneoplastic syndromes sometimes precede the symptoms of the cancer that they accompany. That was also the case with this patient. The diagnosis of computed tomography of the neck, chest, and abdomen was extended, which revealed the presence of infiltrative changes in the upper lobe of the right lung (Fig. 2) as well as the presence of a mediastinal lymph node with 20–30-mm disintegration with right bronchus pressure, causing a significant obstruction of the high-lobe bronchi (Fig. 3).

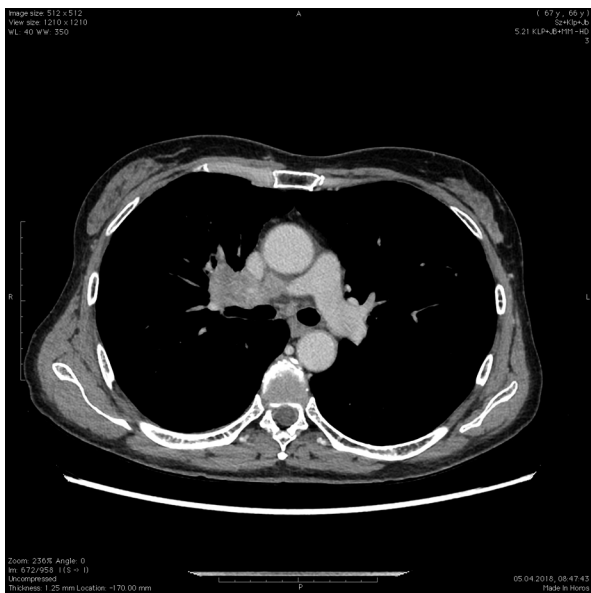


Figure 3. Lymph node pack with disintegration (April 2018)

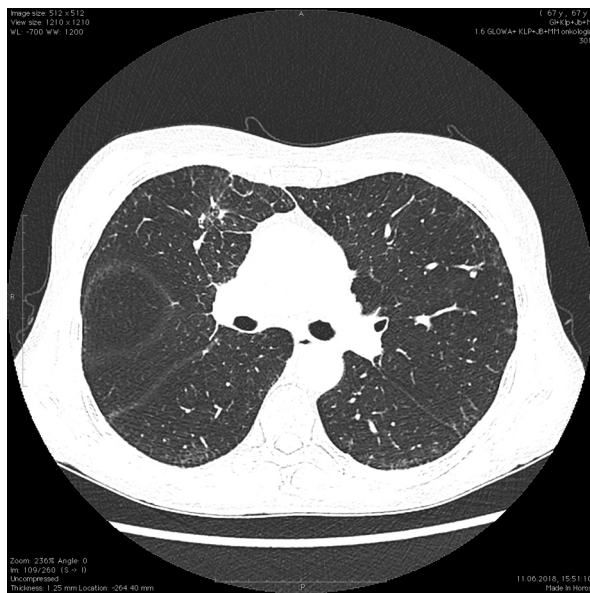


Figure 4. Regression of infiltrative changes of the right lung (June 2018)

In addition, the presence of the node of supra and subclavian nodes was revealed.

Oncological diagnostics of the disclosed changes has begun. Bronchofiberoscopy and endobronchial ultrasound — thin needle aspiration (EBUS-TNA) — were performed, collecting a fragment of bronchi and lymph nodes for pathomorphological examination. From the collected material a diagnosis of small cell carcinoma with expression of Ki-67 in 90% of tumour cells (high mitotic capacity) was obtained.

Due to the advanced degree of SCLC, the patient was qualified for chemotherapy. The need to reduce the amount of fluids taken (SIADH syndrome) led to the selection of chemotherapy with carboplatin (instead of cisplatin) and etoposide. The patient tolerated the treatment well (no side effects were reported). During oncological treatment, the patient required periodic sodium supplementation. After two treatment cycles, the response to treatment was assessed. In computed tomography, a significant regression of pathological lymph nodes of the mediastinum was observed (maximum size up to 13 mm within the lymph node bundle of the right cavity, the size of the remaining nodes did not exceed the limit values, Fig. 4). In addition, there was almost complete regression of pathological foci in the upper right lobe (only residual lesions with fibrotic features were visualised, Fig. 5). There were no metastases to the central nervous system.

Anxiety was, however, caused by two osteosclerotic lesions visible in the thoracic vertebrae 3 and 11, not described in the previous study. Bone scintigraphy was performed, which revealed increased bone metabolism within the thoracic vertebra of the third, which may raise suspicion of a metastatic focus. It should be noted,

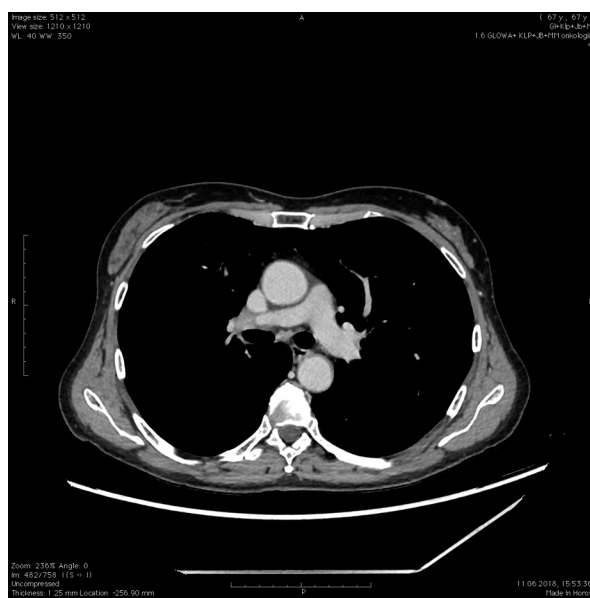


Figure 5. Regression of mediastinal node changes (June 2018)

however, that bone metastases are often unnoticed in radiological descriptions because of their initially osteolytic nature. Only the action of chemotherapy or molecular-targeted therapies leads to osteosclerotic outbreaks visible in computed tomography.

Oncological treatment continued. The patient received another two cycles of chemotherapy with carboplatin and etoposide. Due to CTC (common toxicity criteria) and CTC grade III thrombocytopenia after the fourth cycle of chemotherapy, filgrastim injections, fludrocortisone, and antibiotic cover were used.

An imaging assessment was made after the fourth cycle of treatment. In computed tomography, the changes were stationary and were comparable with the previous study. Stability of the disease was obtained.

Summary

BRCA2 is a suppressor gene that acts as a negative regulator of the cell cycle and has an effect on maintaining the stability of genetic material. The *BRCA2* gene encodes the BRCA2 protein, whose main function is to participate in DNA repair. BRCA proteins (the most important of them is the BRCA1 protein) together with the protein kinase associated with ataxia-telangiectasia and Rad family proteins are involved in the repair of single-strand DNA damage (caused by the formation of platinum compounds adducts to DNA) and damage to both DNA strands (caused *inter alia* by radiotherapy). If immediate DNA repair is not possible due to the extent of damage, BRCA proteins participate in the activation of cell cycle checkpoint kinase 1/2, which results in cell cycle arrest and prolongation of the time necessary for DNA repair. This effect is enhanced by the involvement of BRCA proteins in the process of activating transcription of other genes related to DNA repair and cell cycle control and cell direction on the pathway of apoptosis [4–6].

Accordingly, cells with a mutation causing loss of BRCA1 or BRCA2 protein activity have increased sensitivity to DNA damaging agents, e.g. ionising radiation or cytostatic drugs that cause DNA strand breaks. The basic DNA repair process is stopped, and the cell enters the alternative DNA repair pathways [4–6].

Previous observations and studies reveal the dual nature of the *BRCA2* gene mutation. On the one hand, mutations in the *BRCA2* gene significantly increase the risk of breast cancer (up to 56%) and ovarian cancer (up to 27%). At the same time, other studies based on the evaluation of the effectiveness of oncological treatment reveal a significant effect of the presence of mutations in the *BRCA2* gene on positive response to chemotherapy, especially with the participation of platinum compounds and other alkylating cytostatics. Yang et al. [4] analysed data from The Cancer Genome Atlas (TCGA) obtained from 316 women with low-differential serous ovarian cancer subjected to chemotherapy. In 35 women the *BRCA1* mutation was found, and in 27 women the *BRCA2* mutation was found, while in 219 none of the two mutations was noted. The patients underwent

chemotherapy with platinum compounds. The occurrence of *BRCA2* mutation was associated with high sensitivity to chemotherapy. Response to treatment was reported in 100% of patients with *BRCA2* mutation, 82% of patients with *BRCA1* mutation, and 80% of patients with mutations in these genes. Median progression-free survival was 18 months in carriers of the *BRCA2* mutation, 11.7 months in patients with *BRCA1* mutation, and 12.5 months in patients without *BRCA* gene mutations (statistically significant differences) [4].

The above observations can be justified by the increased efficacy of cell chemotherapy with higher DNA instability and impaired remedial function. Most cytostatics work by inhibiting the effect of mitosis (cell division) mainly through DNA damage and structures responsible for cell division. DNA damage ultimately drives cells to the path of apoptosis. In the present case, the presence of the *BRCA2* gene mutation, in addition to the obvious effect on tumour development, appears to have a simultaneous effect on the efficacy of cytostatic drugs through a synergistic effect on cell cycle disorder and DNA repair leading to cancer cell damage.

All authors have read and approved the final one working version to be submitted. Małgorzata Flis was the main co-creator in writing the manuscript. Małgorzata Flis, Izabella Drogoń and Katarzyna Kurek participated in collecting and interpreting data. Paweł Krawczyk, Robert Kieszko and Janusz Milanowski contributed to data analysis and interpretation.

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