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Do we apply a personalised lung cancer therapy? Use of molecular tests in scheduling a multilineage treatment in a patient with lung adenocarcinoma

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Oncology in Clinical Practice
2017, Vol. 13, No. 1, 24–29
DOI: 10.5603/OCP.2017.0004
Translation: dr n. med. Aleksandra Hołowiecka

ISSN 2450–1654

ABSTRACT

Molecularly targeted therapies, which can be used in genetically selected patients, play an increasing role in the multidisciplinary approach to the treatment of lung cancer. Treatment personalisation extends the scope of therapy, prolongs survival of patients and decreases the risk of life-threatening side effects. In this report, we present the diagnostic and therapeutic history of a 57-year-old male with lung adenocarcinoma and activating *EGFR* gene mutation. The whole therapeutic approach involved a diagnostic segmentectomy, cytoreductive surgery of the primary tumour, and a palliative hemipelvectomy of metastases in the right hip joint followed by adjuvant radiotherapy as well as six lines of systemic treatment based on standard cytostatics and novel personalised agents. Regardless of a patient's good performance status and relatively good tolerance of the treatment, futile continuation of the therapy despite the lack of a longer stabilisation of the disease remains questionable.

Key words: lung adenocarcinoma, chemotherapy, molecularly targeted therapy, immunotherapy

Oncol Clin Pract 2017; 13, 1: 24–29

Introduction

Lung cancer is the most common malignant neoplasm of the respiratory system and one of the main causes of malignant neoplasm-related death worldwide, with a mortality rate approaching 86%. The clinical stage of the disease, histologic type, and molecular and immunological status of the neoplasm, are the main factors influencing the choice of appropriate therapeutic strategy [1, 2]. Chemotherapy and radiotherapy are, next to surgery, the most important methods involved in a multidisciplinary approach in patients with lung cancer. Personalised therapies based on tyrosine kinase inhibitors (TKI) — of the epidermal growth factor receptor (EGFR; erlotinib, gefitinib, afatinib, ozimertinib) and of the anaplastic lymphoma kinase (ALK; crizotinib, ceritinib, alectinib) — result in the prolongation of progression-free survival (PFS) and overall survival (OS), compared to standard chemotherapy [3, 4]. Immunotherapeutic drugs targeted at the immune control checkpoints show high efficacy in a certain group of patients with non-small cell lung cancer (NSCLC) [5].

Case report

In March 2014 a 57-year-old man, former cigarette smoker (15 pack-years), received anti-inflammatory and analgesic treatment due to pain of the right lower limb and of the right hip-joint. Due to the increasing pain, in August 2014 the radiograms were repeated and revealed the presence of a 10-cm tumour in the right hip-joint. The computed tomography (CT) showed numerous measurable and unmeasurable nodules in both lungs (clinical stage cT4N2M1). In October 2014,

a diagnostic segmentectomy within the margins of healthy tissues of the right lung was performed. The histopathological examination confirmed the presence of a adenocarcinoma of differentiation grade G3. In the molecular testing a rare activating mutation (G719X) in exon 18 of the *EGFR* gene was detected, which could be responsible for the sensitivity to TKI EGFR. In October 2014 a hemipelvectomy of the tumour of the right hip-joint was done with adjuvant radiotherapy involving the surgery area. From December 2014 to August 2015 the patient received nine cycles of the molecularly targeted therapy with erlotinib in standard dose. The partial remission was achieved. A cytoreductive surgery involving the segmentectomy of the left lung (following the actual ESMO recommendations [6]) was feasible at the progression of the disease. The repeated genetic testing of the new postoperative tissue revealed, despite the primary G719X mutation, a coexisting, rare substitution E709X in exon 18 of the *EGFR* gene, the predictive value of which for the TKI EGFR therapy had not been previously well described (no possibility to use osimertinib). The substitution T790M in exon 20 of the *EGFR* gene was not detected, so there was no marker of the potential sensitivity to the third-generation TKI EGFR (osimertinib, rociletinib).

From August 2015 the patient received four cycles of chemotherapy based on the two-drug regimen containing cisplatin and pemetrexed. The therapy was well tolerated and resulted in a partial remission. In November 2015 in a control CT the increase of the previously observed nodules was shown in both lungs as well as the appearance of several new nodules in the upper lobe of the left lung. From January to May 2016 the patient was receiving again erlotinib. Due to the lack of the recommendations and of the appropriate drug programme, the patient covered the costs the three month long therapy by himself. The re-use of EGFR TKI maintained the stabilisation of the disease; however, there was significant exacerbation of the drug-related toxicity (intense eczema, paronychia, and intermittent diarrhoea). In May 2016 the patient was qualified to therapy with docetaxel and nintedanib (a multikinase inhibitor of VEGFR, PDGFR, and FGFR). The treatment was applied according to ESMO recommendations. However, there was no refund of the therapy by any of the drug programs and the patient again paid for the therapy. The treatment was continued for eight cycles (a maintenance therapy), and a partial remission of the disease was observed (Fig. 1).

The expression of PD-L1 on the neoplastic cells was tested in this patient at the moment of another progression of the disease (November, 2016). A strong positive immunohistochemical reaction was shown on 30% of the neoplastic cells. From December 2016 the patient received four courses of anti-PD-1 therapy with nivolum-

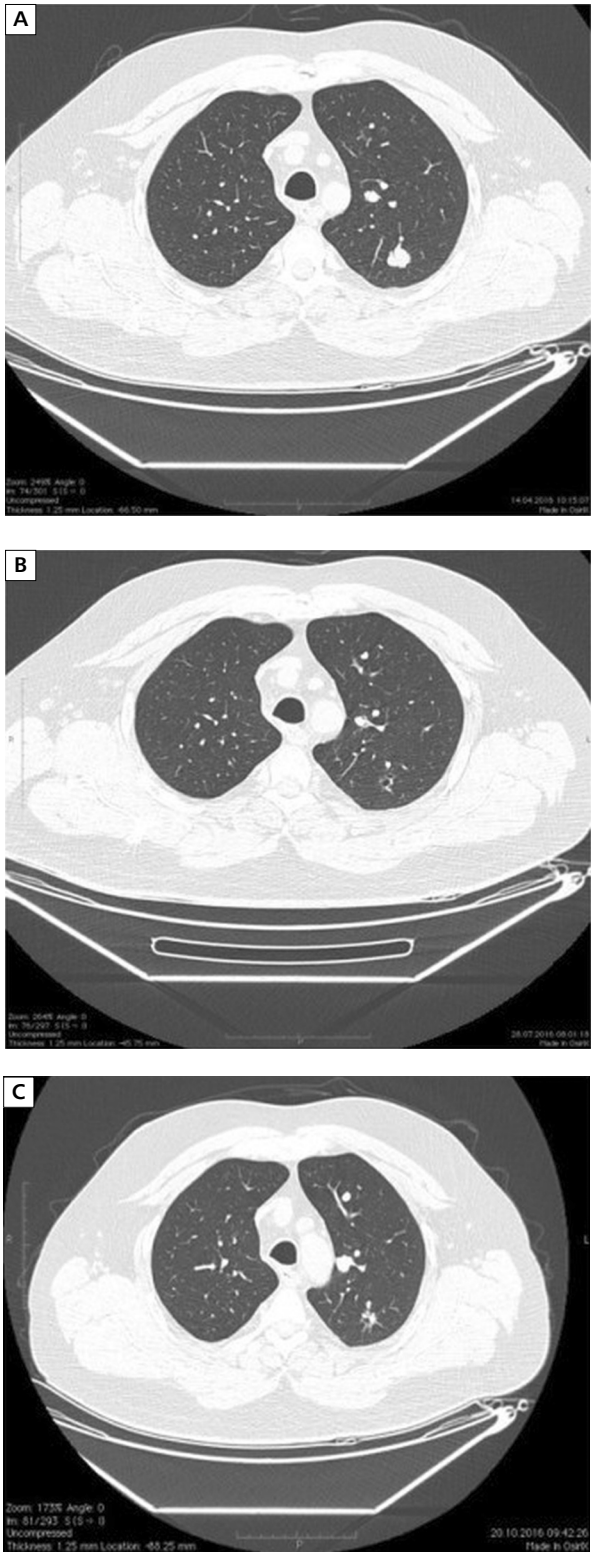

Figure 1. Monitoring of response to the treatment with docetaxel and nintedanib. **A**) CT scan performed at the moment of qualification of the patient to the therapy (April 2016); **B**) CT scan performed during the therapy showing a partial remission (July 2016); **C**) CT scan showing the progression of disease during therapy (November 2016)

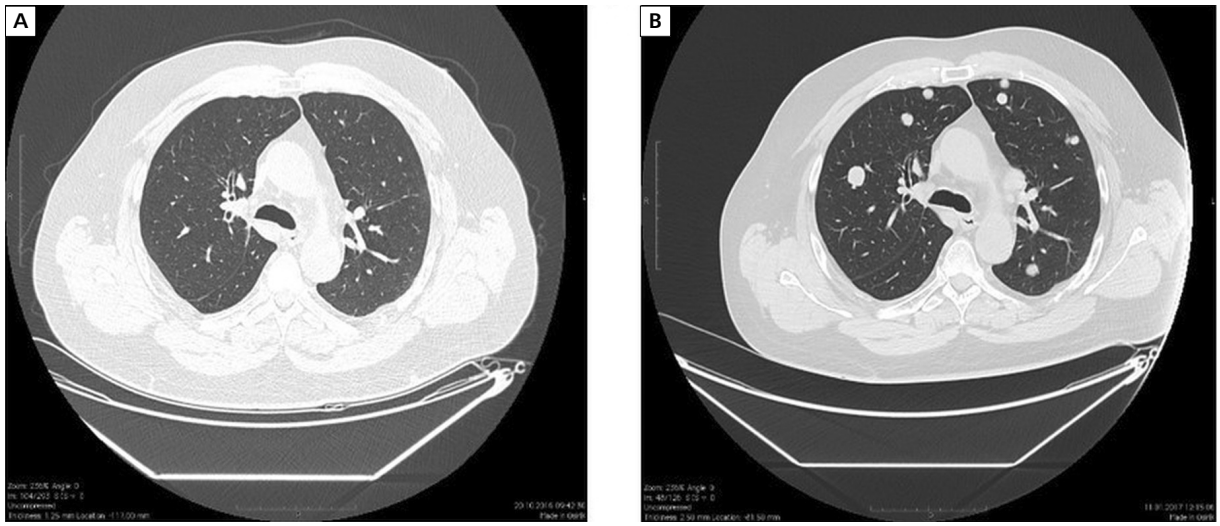

Figure 2. Monitoring of the response to immunotherapy (niwolumab). **A**) CT scan perfomed at the moment of patient qualification to the immunotherapy (November 2016); **B**) CT scan showing rapid progression of the disease with numerous disseminated tumors during immunotherapy (January 2017)

ab. Unfortunately, rapid local progression (Fig. 2) and a severe adverse event of the therapy (CTEA grade 3), manifested as chronic fatigue, was observed during the immunotherapy. Imaging exams detected metastases to the central nervous system — to the cerebellum, and to the frontal and parietal lobe, which were treated by radiotherapy in January 2017 (whole brain radiotherapy, WBRT).

Intensive molecular testing, aimed at discovering the cause of the progression, was started at that moment. The immunohistochemical exam of the postoperative material excised during the secondary segmentectomy (progression after therapy with erlotinib) revealed the presence of the expression of the abnormal ALK protein in 5% of the neoplastic cells. FISH testing showed the presence of the *ALK* gene rearrangement in 13% of the analysed cellular nuclei. This result disqualified the patient from the ALK TKI therapy. Furthermore, the T790M substitution in the *EGFR* gene was tested again in the circulating free DNA (cfDNA). A weak amplification of the fragment of the *EGFR* gene containing the T790M mutation was detected with use of good internal control (this patient was treated with erlotinib twice). In February 2017 the patient was qualified for osimertinib therapy (a third-generation EGF TKI selective to the T790M mutation of the *EGFR* gene), which at that time was accessible in Poland in the expanded access to therapy program. The patient tolerated the two cycles of therapy well (the main side effect were cracks in the skin on the fingertips). The control CT showed progression of the disease in the primary tumour and in the metastatic changes in both lungs. The patient continues the treatment, outside the treating medical centre. He covers the costs of the therapy himself and with the help of his family. Currently, he has decided to try a therapy with a combination of afatinib and cetuximab.

Discussion

In our patient, in the postoperative material (a diagnostic segmentectomy) a rare activating mutation of the *EGFR* gene (substitution G719X in exon 18) was detected. For this reason, erlotinib was used as a first-line therapy, which resulted in an eight-month response to treatment and further stabilisation of the disease. Until now, Yang at al. proved that the use of EGFR TKI in the group of genetically selected patients results in prolongation of the PFS and OS, regardless of the type of activating mutation detected in the *EGFR* gene [7]. However, only a few papers investigated the predictive value of rare mutations of the *EGFR* gene [8–10]. Yatabe at al. and Sharma at al. first postulated to extend the routine diagnostic profile and to include rare mutations of the *EGFR* gene [8, 9]. Two years later Beau-Faller et al. confirmed the efficacy of EGFR TKI in a group of 50 patients, carriers of rare mutations in exon 18 and 20 of the *EGFR* gene. However, they stressed the fact that the response to a personalised treatment in this kind of patient may be shorter and less predictable than in patients with common activating mutations. Beau-Faller et al. calculated the median of PFS for patients with rare *EGFR* mutations, which was three months. The shorter PFS in patients with rare mutations compared to patients with common mutations of the *EGFR* gene was caused by inclusion in the study of patients with

insertions in exon 20, who relatively rarely responded to treatment. The authors of a cited review confirmed the possibility of achieving response to EGFR TKI therapy in more than 50% of patients with G719X, in whom the median of PFS exceeds six months [10].

Surgery is a primary method of treatment in patients with NSCLC in I and II clinical stage and in some patients in clinical stage IIIA. Moreover, surgical treatment may also be offered to patients in clinical stage IV but only in cases when radical surgery of the primary tumour and of the metastatic changes is feasible [11]. Newly, a cytoreductive surgery is recommended in selected patients with NSCLC in clinical stage IIIB or IV in whom a spectacular effect of systemic therapy was observed [6]. In the presented case, a segmentectomy of the lung was done after effective therapy with erlotinib, which resulted in a significant decrease of the primary tumour size. However, when other measurable (according to RECIST 1.1 criteria) changes were present it was decided to administer a two-drug adjuvant chemotherapy shortly after the cytoreductive surgery. This approach was also concordant with the European recommendations concerning treatment of patients with advanced NSCLC, who progress after EGFR TKI therapy and in whom the T790M *EGFR* gene mutation was not detected (not sensitive to the third-generation EGFR TKI inhibitors). In this subset of patients, administration of two-drug chemotherapy containing a platinum derivatives and pemetrexed is recommended [6, 13].

According to the accepted recommendations and to the reimbursement status in Poland, patients with NSCLC resistant to platinum derivative-based chemotherapy may receive in further lines of treatment a monotherapy with docetaxel [14]. However, at the patient's explicit request erlotinib was used again in a third-line therapy, which permitted a four-month stabilisation of the disease. Some authors suggest that this approach is reasonable and that the cytoreductive strategy using surgery and platinum derivative-based adjuvant chemotherapy may re-sensibilise a patient to EGFR TKI. Hata et al. proved that patients with activating mutations of the *EGFR* gene, in whom EGFR TKI had been used and then chemotherapy administered to treat progression of the disease with a subsequent re-use of EGFR TKI therapy, had significantly longer median overall survival (22.6 months) compared to patients who did not receive EGFR TKI therapy again (10.4 months) [15]. The IMPRESS study revealed significantly longer overall survival of patients with activating mutations in the *EGFR* gene treated with gefitinib in first-line therapy, but only when in the moment of progression the therapy with the EGFR TKI was continued in combination with chemotherapy, as compared to stopping EGFR TKI therapy [16]. The ASPIRATION study suggests that continuation of the EGFR TKI therapy in patients with confirmed radiologic progression after first-line therapy with EGFR TKI may delay the moment of clinical progression, protect patients against disease flair, or even prolong their overall survival [16]. In the FASACT-2 study the intercalate combination of erlotinib and chemotherapy resulted in a significant improvement of the median PFS and OS compared to the chemotherapy alone [17].

In the fourth line of treatment our patient received docetaxel combined with nintedanib — an inhibitor of the following tyrosine kinase receptors: VEGF, PDGF, and FGF. The efficacy of this therapy was proven in the third-phase clinical study LUME-Lung 1, in which Reck et al. observed a significant improvement of the median of PFS (3.4 m *vs.* 2.7 m) and of OS in patients with NSCLC receiving a combined therapy, as compared to patients receiving docetaxel in monotherapy. The main difference between the efficacy of docetaxel combined with nintedanib compared to docetaxel in monotherapy was observed in patients with adenocarcinoma and quick progression of the disease after first-line chemotherapy [18, 19]. Based on the results of this study a combination therapy with docetaxel and nintedanib is recommended by ESMO in patients with lung adenocarcinoma progressing after first-line chemotherapy [6]. In our case report we suggest that therapy with docetaxel and nintedanib may also be effective in further lines of treatment in patients with lung adenocarcinoma and rare *EGFR* gene mutations, who had previously been successfully treated not only with chemotherapy but also with EGFR TKI (Fig. 1).

There are some promising reports concerning the efficacy of immunotherapy with use of antibodies targeted against immune checkpoints, in patients with different types of neoplasms. The efficacy of second-line therapy with anty-PD-1 (nivolumab, pembrolizumab) or with anti-PD-L1 (atezolizumab) antibodies in patients with advanced NSCLC, regardless of the histopathologic type of the neoplasm [20–22]. All clinical studies showed the association between the expression of PD-L1 on the neoplastic cell surface and the efficacy of the anti-PD-1 or anti-PD-L1 antibodies in patients with lung adenocarcinoma [23]. However, expression of PD-L1 does not seem to be a perfect, predictive marker for immunotherapy. The following may also become good predictive factors: the presence of CD8+cell infiltrates in the tumour tissues, high expression of genes responsible for the intensity of the immunologic response, and high tumour mutation burden. In the presented case, the immunohistochemical exam showed a strong expression of the PD-L1 receptor on the neoplastic cells. However, the use of nivolumab was unsuccessful. During the two first months of therapy new, numerous, and disseminated metastases were detected in both lungs (Fig. 2). The probable cause of the resistance to immunotherapy in this patient was the presence of 'driver mutation' only

in one gene (mutations in the *EGFR* gene rarely coexist with other mutations), which resulted in expression of only a few neoplasm-specific antigens and weak reactivity of the immune system. These observations were confirmed by clinical studies, which proved that carriers of *EGFR* gene mutations usually do not benefit from the immunotherapy [20–22].

The selection of the neoplastic cell clone carrying the T790M substitution in exon 20 of the *EGFR* gene is considered the main cause of the aquired resistance of the NSCLC cells to the first-generation of EGFR TKI. This mutation determines also the sensitivity to third-generation EGFR TKI (osimertinib, rociletinib). Therefore the detection of this mutation has an important predictive value [4, 5, 12]. Unfortunately, in the reported case the T790M mutation was primarily not detected in the material from the cytoreductive surgery. However, molecular testing detected in the tumour cells a clone with another, rare mutation — E709X substitution in exon 18 of the *EGFR* gene, the predictive value of which for EGFR TKI therapy has not yet been proven [8, 11]. During the progression on the nivolumab therapy T790M was tested again (in the meantime the patient again received erlotinib therapy) and it was detected in the circulating free DNA. The material from the cytoreductive segmentectomy was tested in parallel for *ALK* gene mutation, and the rearrangement was detected in 13% of the cellular nuclei. We may suppose that the multiple and complex lines of therapy in our patient generated an important heterogeneity of the tumour, which preselected as multiple neoplastic cell clones carrying three different *EGFR* gene mutations and a rearrangement of the *ALK* gene. Despite this hypothesis, the patient was started osimertinib. Unfortunately, this final therapy resulted in further progression of the disease in both lungs and the appearance of the excaudate in the pleural cavity [23, 24].

Summary

Monitoring of the genetic and molecular factors during therapy may enable patients with lung adenocarcinoma qualification to multiple lines of molecularly targeted therapies, and to immunotherapy. However, the molecular instability induced by the treatment may be the main cause of failure of personalised therapy. Regardless of good performance status and relatively good tolerance to the treatment, a futile continuation of the therapy despite the lack of longer stabilisation of the disease remains questionable. Futile medical care, which in this case was due to the activity of the patient's family, resulted in repeated admissions to the hospital, shorter time free from therapy, and significantly worse quality of patient's life.

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