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Innovations in lung cancer treatment

Anna Sieńko, Karolina Rożenek*, Piotr Nalewaj, Aleksandra Bożyk, Paweł Krawczyk

Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Poland

E-mail address: kroz93@o2.pl

ABSTRACT

Lung cancer is associated with one of the highest mortality rates among malignant tumors. It is the main death cause of men and women in Poland where over 15 000 men and 7 000 women die with this diagnosis annually. 1.7 million people die every year due to lung cancer in the world. Two main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The history of lung cancer treatment begins with surgical approach followed by addition of chemotherapy and radiotherapy, which were used either separately or in combination depending on the stage of the lung cancer. Many somatic mutations were identified and molecularly targeted therapies could have been established. One of the oldest and the best known group of molecularly targeted drugs used in lung cancer treatment are tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR). First EGFR-TKI was gefitinib, which has been examined in clinical trials before erlotinib, afatinib, dacomitinib and osimertinib. EGFR-TKIs increased overall survival (OS) with significantly less side effects when compared to standard chemotherapy. Another group of molecularly targeted drugs are anaplastic lymphoma (ALK) kinase inhibitors such as crizotinib, alectinib and ceritinib. Another innovation which was introduced in NSCLC treatment was immunotherapy. Its effect is based on modification of immune system leading to activation of cytotoxic T lymphocytes (CTL). Currently nivolumab and pembrolizumab (anti-PD1 antibodies) as well as atezoliumab (anti-PD-L1 antibody) are being used in NSCLC patients. The discovery of innovative therapies for NSCLC patients resulted in significant extension of patients' life expectancy while minimizing the side effects of such therapy. Moreover, the quality of patients' life was significantly improved. However, important problems still remain to be solved: overcoming the resistance in the course of molecularly targeted therapies and the lack of predictive factors that determine the effectiveness of immunotherapy.

Keywords: Lung cancer, Lung cancer treatment, Immunotherapy, targeted therapy

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1. INTRODUCTION

Lung cancer is the most prevalent malignant tumour worldwide. Out of over 12.7 million malignant tumour diagnoses, each year approximately 1.8 million are lung tumours. Moreover lung cancer is also the most common tumour-related cause of death with 1.7 million deaths annually [1].

Among 20 countries with the highest incidence of lung cancer, Poland is classified in the ninth position with age-standardised rate 38.0 per 100,000, in seventh position among men (60.5 per 100,000) and in seventeenth position among women (21.8 per 100.00). Lung cancer is the most common malignant tumour among Polish men and second most common in Polish women (after breast cancer) [2]. The risk of lung cancer is almost three times greater among men than women. What is more, the number of lung cancer diagnoses constantly increases in female population. In contrary, slight decrease of lung cancer incidence is observed in male population [3].

Clear correlation between incidence of lung cancer and exposition to cigarette smoke exists. Both active and passive smoking is associated with 90% of all lung cancer cases. Other risk factors include physical and chemical factors such as radon, nickel, chrome, arsenic, asbestos and carbohydrates as well as genetic factors (mostly polymorphisms of genes related to metabolism of carcinogenic substances in cigarette smoke) [4].

Thanks to rapid development of new therapeutic methods for lung cancer in the last decades, percentage of Polish patients with over-5-year survival increased from 10.8% to 11.9% in males and from 15.7% to 16.9% in females. Nonetheless, mortality rate still remains high, surpassing breast cancer mortality rate [5].

These facts clearly show that lung cancer is a major medical issue to be dealt with. Therefore, constant research concerning new treatment options is being done.

2. MATERIALS AND METHODS

Following paper is a review of the latest original papers concerning NSCLS treatment in Poland and all over the world. Original papers were searched on PubMed and additionally in references of found articles. The main focus was on molecularly targeted therapies and immunotherapy in lung cancer treatment. Original articles published in English, meta-analyses and reviews were analysed. Obtained data and information were used in the review.

3. RESULTS

3. 1. Surgical treatment, chemotherapy and radiotherapy

The beginning of lung cancer effective therapies dates back to 1970s when first successful surgical procedures where implemented. Surgical treatment results in increased overall survivals and curability. Unfortunately, thoracic surgeries are often associated with dire consequences such as significantly lower quality of life or incomplete resection of tumour or metastatic lymph nodes resulting in ineffective treatment and rapid disease recurrence. Addition of chemo- (CTH) and radiotherapy (RTH) to surgical treatment has promising effects. *International Adjuvant Lung Cancer Trial* (IALT) and others clinical trials dedicated to NSCLC

patients showed the increase by 5-10% of 5-year survival among patients treated with surgical resection combined with chemotherapy compared to patients solely surgically treated [6]. Radiotherapy used in patients with incomplete surgery and in patients with mediastinal lymph nodes metastases also results in a slight increase in the percentage of cures and prolongs the time to the disease recurrence. However combination of these three methods (surgeries, CTH and RTH) doesn't always result in full recovery. Surgical resection can be used only in patients with early stages of non-small cell lung cancer (approximately 15% of NSCLC patients). In locally advanced lung cancer patients, the combination of chemo- and radiotherapy can be used, and in advanced lung cancer patients chemotherapy alone is one of treatment options. However, lung cancer cells show moderate sensitivity to the action of radiotherapy and chemotherapy because of their ability to repopulation and proliferation. Limited knowledge about molecular mechanisms of neoplastic transformations and tissue invasion as well as metastases formation underlie insufficient effectiveness of radiotherapy and chemotherapy in lung cancer treatment. Moreover, these therapeutic approaches were always associated with high toxicity and decreased quality of life.

3. 2. Molecularly targeted therapies

Gradually broadening knowledge and better understanding of molecular mechanisms of neoplastic formation led to a development of novel targeted approach to malignant tumours' treatment. Molecularly targeted therapies affect selectively proteins in cell's signalling pathways. These therapies usually inhibit cells' surface receptors responsible for activation of cells' proliferation, which leads to their apoptosis [7]. Due to their different mechanisms of action, targeted therapies can be used as addition to chemotherapy or as alternative method for standard treatment. The greatest advantages of molecularly targeted therapies are: existence of predictor factors to qualify patients for this type of treatment and relatively small side effects of targeted therapies [8]. These therapies could be effective in selected non-small cell lung cancers patients.

3. 3. Tyrosine kinase inhibitors

One of the oldest and best known groups of molecularly targeted drugs are tyrosine kinase inhibitors (TKIs). They inhibit phosphorylation of specific proteins by blocking tyrosine kinase enzyme. Therefore, the function of phosphorylated proteins is disturbed and signal for apoptosis is induced. Tyrosine kinases are present in almost every receptor on human cells and are vital for their proper working. They are an integral part of multiple receptors for growth factors such as platelet-derived growth factor (PDGFR), vascular endothelial growth factor (VEGFR) and epidermal growth factor (EGFR) [9].

3. 3. 1. EGFR tyrosine kinase inhibitors

In NSCLC patients, EGFR-TKIs (erlotinib, gefitinib, afatinib, dacomitinib, osimertinib) are being used. The first clinical trials involving EGFR-TKIs did not yield as satisfactory results as it was expected. In four large clinical trials: *Iressa NSCLC Trial Assessing Combination Treatment 1 and 2* (INTACT-1, INTACT-2) for gefitinib as well as *Tarceva Lung Cancer Investigation* (TALENT) and *Tarceva in Responses for Conjugtion with Palcitaxel and Carboplatin* (TRIBUTE) for erlotinib, EGFR-TKIs where combined with cytostatics in molecularly unselected NSCLC patients. EGFR-TKIs have been shown to be ineffective in

these clinical trials [10]. Consequently, next clinical trials focused on erlotinib and gefitinib use in advanced NSCLC patients, after progression on first or second line of chemotherapy. In such patients, erlotinib was proved to increase median overall survival (OS) and median progression free survival (PFS) when compared to placebo (2 months and 1.2 weeks, respectively) [11].

Some groups of patients tend to respond better to EGFR-TKI treatment, for example adenocarcinoma patients, women, Asians and non-smokers. This suggested that there exist some factors predicting good response to the treatment [12]. These factors were intensively sought during the development of molecularly targeted therapies. It turns out that majority of NSCLC patients with good response to EGFR-TKIs had activating mutation of *EGFR* gene [13]. However, only 10% of NSCLC patients acquired *EGFR* mutations in tumour cells. It was hypothesised that *EGFR* gene amplification detected by fluorescent *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) could correlate with better response to EGFR-TKIs. However, some clinical trials such as TRUST or *Iressa Survival Evaluation in Lung* (ISEL) did not fully confirm this hypothesis. Therefore *EGFR* gene mutations are considered to be important predicting factors for NSCLC patients qualification to EGFR TKIs [14].

More recent clinical trials focused on the use of EGFR-TKIs in first-line treatment in NSCLC patients with *EGFR* gene mutations. Three randomised, phase 3 studies comparing erlotinib and gefitinib with chemotherapy in first-line treatment clearly showed that patients with *EGFR* gene mutations could benefit from EGFR-TKIs monotherapy [15]. The PFS in patients treated with erlotinib was 13.1 and 9.7 months, in patients treated with gefitinib – 9.2 months and in patients treated with chemotherapy – 4.6, 5.2 and 6.3 months, respectively [16-18]. In next clinical trials, it was proved that two new EGFR-TKIs: afatinib [19] and dacomitinib [20] were also effective in first-line treatment in NSCLC patients with *EGFR* gene mutations. Therefore, EGFR-TKIs should be considered in first-line treatment in such patients.

Resistance in course of treatment with first- and second-generation of EGFR-TKIs is most often developed by selection of a cancer cells clone with Thr790Met mutation in the *EGFR* gene. Consequently, third-generation of EGFR-TKIs was designed. Osimertinib was tested and registered in patients with Thr790Met mutation who progressed after treatment with I or II generation of EGFR TKIs [21].

Apart from strong evidence of efficacy of EGFR-TKIs in certain groups of NSCLC patients, there are additional advantages of this kind of treatment. Firstly, all drugs from this group are in the form of tablets which makes them easily manageable for patients, reduces the number of necessary hospitalizations and invasive procedures associated with drug administration [22]. What is more, EGFR-TKIs have significantly less, in number as well as in severity, side effects. The most common side effects of EGFR-TKIs are rash and diarrhoea, mostly in grade 1 or 2. Other side effects of EGFR-TKIs therapy include: nausea and vomiting, oral cavity inflammation, paronychia and increased ALT level. In that field, EGFR-TKIs seem much more preferable when compared to classical chemotherapy [23].

3. 3. 2. ALK inhibitors

ALK (anaplastic lymphoma kinase) is a transmembrane tyrosine kinase receptor important in proliferation, survival and cell migration. Discovery of inversion on short arm of chromosome 2 resulting in creation of an *EML4-ALK* fusion gene triggered development of another branch of tyrosine kinase inhibitors – ALK inhibitors [24]. Lung cancer patients with *ALK* rearrangement (about 4% of all NSCLC patients) do not respond to EGFR-TKIs therapy.

Similarly to patients with *EGFR* gene mutations, *ALK* rearrangement occurs more often in no-smokers and in young patients with adenocarcinoma [25].

Crizotinib is an ALK inhibitor with proved antitumor activity in ALK-rearranged patients. Clinical trials of crizotinib on approximately 1500 advanced NSCLC patients with *ALK* rearrangement showed overall response rate (RR) of 57% with the PFS of at least 6 months in 72% of patients [26]. Moreover the drug was associated only with mild gastrointestinal side effects.

Therefore *Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology* recommend *ALK* molecular testing in adenocarcinoma and mixed lung cancer with an adenocarcinoma component in order to select patients eligible for crizotinib therapy [27]. These tests should be carried out in two stages. First is immunohistochemical test (IHC) with anti-ALK antibodies which indicate defective ALK protein expression on tumour cells. Positive result of IHC test must be confirmed with FISH method. Presence of *ALK* rearrangement (in IHC and FISH) allows to qualify NSCLC patients to first- or second-line treatment with ALK inhibitors [28].

Crizotinib is approved in treatment of advanced stage of *ALK*-positive NSCLC patients [29]. However majority of patients treated with crizotinib progressed after 10-12 months of therapy. The most common reasons for the acquired resistance to crizotinib therapy are: mutations in *ALK* gene, amplifications of *ALK* gene and up-regulation of bypass signalling pathways. [30]. Therefore, second-generation of ALK inhibitors was developed [31]. Ceritinib and alectinib show anti-tumour activity in crizotinib resistant patients. Nonetheless, ceretinib and alectinib resistance mutations were also observed and identified in some patients [32]. For that reason, new strategies in overcoming acquired resistance to ALK and EGFR TKIs are being explored. When created, they will offer the possibility of treatment that extends OS and PSF with significantly less severe side effects [33].

3. 4. Immunotherapy

During the last decade, major advancement in knowledge about human immune system occurred. Better understanding of anti-cancer activity of immune system allowed to develop completely new group of immunotherapeutics. Genetic engineering methods resulted in creation of monoclonal antibodies.

Effectiveness of bevacizumab and ramucirumab as well ascetuximab and necitumumab were examined in several clinical trials in NSCLC patients [34]. Activity of bevacizumab and ramucirumab is based on reduction and normalization of pathological vessels in tumours. They decrease blood flow through neoplastic lesions and hence slow down tumour growth and metastases formation [35]. Cetuximab and necitumumab inhibit extracellular domain of EGFR. Both groups of drugs are proved to extend PFS and OS when combined with first-line chemotherapy [36].

Bevacizumab was a first immunomodulating drug which, when combined with CTH, increased OS to over one-year-long period (12.3 months) in non-squamous cell lung cancer patients [37]. However, bevacizumab therapy may be associated with severe side effects, which include intracranial bleeding, bleeding to respiratory system, hypertension and increase risk of febrile neutropenia. Hemoptysis and diagnosis of squamous-cell lung cancer are contraindications for bevacizumab therapy [38].

Newly discovered monoclonal antibodies approved for treatment of NSCLC patients are nivolumab and pembrolizumab (both approved in 2015) against receptor of programmed death 1 (PD-1) as well as atezolizumab (approved in 2016) against ligand for PD-1 (PD-L1).

PD-1 is a modulating particle present on lymphocytes surface. It is activated by PD-L1 or PD-L2 that can be found on numerous immune system cells as well as inflamed tissue, but also on tumour cells [39]. Physiologically, interaction of PD-1 with PD-L1 or PD-L2 is responsible for lymphocyte inhibition, which is necessary in immunological tolerance development. However, PD-1 stimulation by malignant cells results in anergy of lymphocytes in tumour's environment which allows further neoplastic activity.

Thanks to PD-1 or PD-L1 inhibition by nivolumab, pembrolizumab or atezolizumab, strong antitumor activity of lymphocytes can be observed. PD-L1 expression on tumour cells is one of predictive factors for therapy with anti-PD1 or anti-PD-L1 monoclonal antibodies [40]. Phase 3 studies, comparing nivolumab and docetaxel in patients with previously treated squamous and non-squamous NSCLC patients, proved that immunotherapy significantly improved overall survival (9.2 vs. 6.0 months in squamous-cell lung cancer patients and 12.2 vs. 9.4 months in non-squamous-cell lung cancer patients) [41,42]. Similar results were obtained when effectiveness of pembrolizumab and atezolizumab were compared with docetxel in previously treated NSCLC patients [43]. Moreover, pembrolizumab in comparison to chemotherapy showed efficacy in first-line treatment of NSCLC patients with high expression of PD-L1 on cancer cells [44]. Therapy with use of these monoclonal antibodies can cause immune-related side effects up to the 3 or 4 grade. However, these can be easily managed with standard procedures (including administration of steroids) without discontinuation of the treatment [38].

3. 5. Main focus of current research

Earlier clinical trials concentrated on such end-points as response to treatment, OS, PFS and toxicity of tested drugs. But more recent research also pays attention to patient-reported outcomes (such as alleviation of pain, caught and dyspnoea) translating directly to increased quality of life. These seem especially important when generally short OS of lung cancer patients is taken into consideration. Obviously, prolongation of OS and PFS still remains the main aim of new therapies. But hopefully, in future, patients' treatment experience will be evaluated in clinical trials alongside standard end-points and will be acknowledged in therapy planning process.

4. CONCLUSIONS

Even though constant development of new therapies takes place, advanced lung cancer still remains a fatal disease. However it is more and more often referred as a chronic disease. Molecularly targeted therapies in lung cancer treatment have generally better results in strictly selected groups of patients. But these patients are a very small percentage of the entire lung cancer population. It seems that individualized care that focuses not only on causative treatment, but also on early introduction of best supporting care (BSC), results in increased quality of life and extended overall survival. Apart from conventional surgeries, CTH and RTH, increasing number of patients has the opportunity to undergo molecular profiling tests detecting individual sensibility to targeted therapies (*ALK* gene rearrangement, *EGFR* gene mutations,

and PD-L1 expression on tumour cells). Obtained molecular profile allows to individually adjust treatment plan. Moreover, addition of molecularly targeted drugs or immunotherapeutics to treatment scheme and reduction of cytostatics use are associated with lower toxicity. Expected outcomes tend to concentrate equally on statistically significant end-points and patient's comfort and quality of life during and after the treatment. These tendencies not only appear to be well thought but also humanitarian. Further search of molecularly targeted medicines will enable the individualization of therapies and thus better outcomes of planned treatment, which is a future of lung cancer treatment.

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