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MODERN VECTOR IN TREATMENT OF PATIENTS WITH LUNG CANCER: TYROSINE KINASE INHIBITORS IN EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS (literature review)

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Abstract. Modern vector in treatment of patients with lung cancer: tyrosine kinase inhibitors in epidermal growth factor receptor mutations (literature review). Smorodska O.M., Moskalenko Yu.V., Vynnychenko I.O., Vynnychenko O.I., Kostuchenko V.V. *Tumor molecular profiling in patients with non-small cell lung cancer (NSCLC) is used to identify driver mutations, which lead to premature carcinogenesis in more than 80% of adenocarcinoma cases, including epidermal growth factor receptor (EGFR) mutations. Identification of specific somatic aberrations allows to personalize treatment. Personalization of treatment resulted in improvement of NSCLC outcomes. The aim of our study was to consider scientific data on modern concepts of treatment of patients with non-small cell lung cancer with previously detected oncogenic mutations, especially EGFR mutation. In our study we analyzed scientific papers and data of international scientific literature on the problem of lung cancer treatment. Methods used: scientific research, analytical and generalizing. Different drugs are used in treatment of lung cancer. Choice of treatment scheme depends on type and presence of mutations. Patients with advanced non-small-cell lung cancer and detected mutation in the EGFR can be treated with tyrosine kinase inhibitors (TKIs). Nowadays three first generation drugs are recommended by FDA: afatinib, erlotinib, gefitinib. They showed good clinical benefit. Most patients with metastatic NSCLC typically show disease progression after approximately 9 to 13 months of erlotinib, gefitinib, or afatinib therapy. The first and only commercially available third-generation EGFR TKI is osimertinib - an oral drug, which selectively inhibits both EGFR-TKI and EGFR T790M resistance mutations. Nowadays scientists are in active investigation of mechanisms of acquired resistance to TKIs, but little is known yet. Clinical success can be observed in patients who were treated with TKIs. EGFR T790M is a mutation that leads to acquired resistance to EGFR TKI therapy. Its incidence is approximately 60% after disease progression on TKI drugs (erlotinib, gefitinib, or aphatinib). Third-generation EGFR TKIs demonstrate high efficacy, but acquired resistance development cannot be avoided. Mechanisms of acquired resistance to these agents are still investigated.*

Реферат. Сучасний вектор у лікуванні пацієнтів, хворих на рак легенів: інгібітори тирозин кінази при EGFR мутаціях (огляд літератури). Смородська О.М., Москаленко Ю.В., Винниченко І.О., Винниченко О.І., Костюченко В.В. *Молекулярне дослідження пухлин у пацієнтів з недрібноклітинним раком легень (НДРЛ) використовується для визначення драйверних мутацій, що призводять до раннього канцерогенезу в більше ніж 80% випадках аденокарциноми, включаючи мутацію рецептора епідермального фактора росту (EGFR). Визначення специфічних соматичних мутацій дозволяє лікувати хворих персоналізовано, що приводить до значного покращення результатів лікування НДРЛ. Метою роботи було вивчення проблеми таргетної терапії НДРЛ шляхом аналізу відповідної наукової літератури. В якості досліджуваного матеріалу було використано дані закордонних джерел, які досліджують проблематику лікування раку легень. Науковий пошук, аналіз та узагальнення були обрані в якості методів. Інгібітори тирозин кінази (TKIs) використовують в якості стандартної терапії першої лінії для лікування пацієнтів з недрібноклітинним раком легень, у яких наявна мутація EGFR. До першого покоління інгібіторів тирозин кінази відносять гефітиніб,*

ерлотиніб, афатиніб. Їх використання показало високі терапевтичні результати. У більшості пацієнтів із мутаціями EGFR та метастатичним недрібноклітинним раком легенів приблизно через 9-13 місяців терапії ерлотинібом, гефітинібом або афатинібом спостерігається прогресія захворювання. Першим і єдиним комерційно доступним інгібітором рецепторів EGFR третього покоління є осимертиніб. Осимертиніб – оральний, незворотний EGFR-інгібітор третього покоління, який вибірково інгібує як EGFR, так і мутації стійкості до EGFR – T790M. Наразі вчені активно досліджують механізми набутої резистентності до інгібіторів тирозин кінази, проте багато питань досі залишаються невирішеними. Перше покоління інгібіторів EGFR показало клінічний успіх серед пацієнтів, у яких наявна EGFR мутація. Наявність мутації EGFR T790M пов'язують з набутою резистентністю до терапії інгібіторами тирозин кінази. Було показано, що в 60% випадків виявлення вказаних мутацій було зафіксовано після прогресії захворювання за умови початкової відповіді на терапію ерлотинібом, гефітинібом чи афатинібом. Інгібітори тирозин кіназ третього покоління демонструють високу ефективність та не сприяють розвитку набутої резистентності. Мало відомо про механізми розвитку резистентності, тому дослідження в цьому напрямку тривають.

Introduction: Non-small cell lung cancer (NSCLC) occupies the leading positions among deaths from cancer [5, 9, 11, 27, 35, 42, 48]. Molecular tumor profiling in patients with NSCLC is used to detect genetic mutations. Among adenocarcinomas, epidermal growth factor receptor (EGFR) pathology is the most common [7]. Over 10 years ago, this laid the basis for scientifically sound treatment of abandoned forms of NSCLC. During last years the clinical management of this disease has transformed because scientists found out a lot of milestones. This discovery allowed to make treatment personalized which resulted in improvement of treatment outcomes in such patients [50].

The aim of the study is to determine the depth of the problem of targeted treatment of NSCLC by analyzing the relevant scientific data in the literature on the problem of lung cancer treatment. Methods used: scientific research, analytical and generalizing.

One of the keys to the success of NSCLC treatment was in testing for EGFR mutations. It was found that EGFR mutations frequency differs in subgroups. Thus in the subgroup of Asia-Pacific region the frequency of EGFR mutation was the highest – 47%, while the lowest level of frequency of EGFR mutation was found in Oceania – 12%. Frequency of EGFR mutation is higher in women than in men and differs in regions. In Europe mutation occures in 22% of women and 9% of men. In Africa – about 48% of women and 8% of men have this mutation. In North America – we can see 28% vs 19%. A history of smoking also affects the incidence of EGFR mutations. More often genetic mutation has been diagnosed in patients who had never smoked compared to those who have had this habit during lifetime [29].

The epidermal growth factor receptor (EGFR) is critical in proliferation and survival. Activating of these mutations are often seen in NSCLC [3, 14, 23, 27, 48]. EGFR mutation testing is recommended in patients with glandular or adenosquamous tumor variant, for squamous cell carcinomas it is uncommon [12, 22].

EGFR is one of the representatives in the tyrosine kinase receptor family. It is activated by binding dimerization ligand and receptor. This interaction leads to activation of several cellular signaling pathways: phosphoinositide 3 – kinase (PI3K) – AKT pathway, STAT pathway, and MAPK pathway. Activation of these pathways caused increased cell migration, proliferation, angiogenesis, survival and decreased apoptosis [13, 39]. In 2004 activating mutations of EGFR were identified [39]. A lot of activating mutations were described, but only two of them can be found in most cases. These main mutations are called classical activating mutations. The first one is exon 19 deletion. It was found in 85%. The second one is exon 21 L858R substitution (found in 90%). Presence of any of these two mutations is associated with a good clinical response to EGFR-targeted inhibitor therapies [11, 26, 36, 40, 49]. Clinical trials have shown that about 80% of patients had good results after treatment with tyrosine kinase inhibitors (TKI). Median of progression-free survival (PFS) was about 13 months [41]. It was found that treatment with TKIs improved overall survival compared with chemotherapy among patients with exon 19 deletion, while such improvement was not observed in patients with linked with disease L858R substition [18, 22, 38, 45, 49].

After 9-13 months of tyrosine kinase inhibitor therapy, 60% of patients develop a specific T790M mutation, linked with acquired resistance to aphatinib, erlotinib or gefitinib [6, 11, 24, 28, 47]. Resistance to treatment with targeted drugs may be primary. Most often, such patients have KRAS mutations or insertions of exon 20, as well as rearrangements of ALK or ROS1 genes [8, 9, 24, 47].

In 1948 Dr. Karnofsky reported that advanced lung cancer responds to cytotoxic chemotherapy. He also noticed that cytotoxic chemotherapy has lower outcomes in the treatment of advanced or metastatic lung cancer [30]. This idea leads to an absolutely new treatment concept of patients with advanced non-small-cell lung cancer with a mutant epidermal

growth factor receptor (EGFR). Thus, EGFR tyrosine kinase inhibitors (TKIs) were chosen as standard first-line therapy [44]. Afatinib gefitinib and erlotinib have shown clinical benefit.

The third phase of clinical studies (IDEAL-1/-2) with gefitinib has shown possibility to use it as second-/ third- line treatment for pretreated patients with advanced non-small-cell lung. Once-daily 250 or 500 mg dose showed high antitumor activity with midlle degree of toxicity (overall response rate – 9% to 19%; overall survival – 6 to 8 months) [37].

INTACT-1 and -2 study analyzes benefit of gefatinib vs platinum-doublet chemotherapy for treatment of patients with unresectable stage III/IV NSCLC. In this clinical trial chemotherapy-naïve patients were randomly divided into two groups: first group was treated with gefitinib, while second received placebo in combination with platinum-doublet chemotherapy. There were no additional benefits observed in the main indicators of survival and prognosis compared with standard chemotherapy. In 2003 based on the results of INTACT gefitinib was approved by the US FDA as monotherapy for patient with locally advanced or metastatic NSCLC after completion of the classic scheme of cytotoxic chemotherapy [35, 44].

Since 2004 erlotinib has been used to treat patients with locally advanced or / and metastatic NSCLC. It was prescribed after at least one previous chemotherapy regimen [19, 33]. For patients with sensitizing EGFR mutations, the FDA has permitted the use of this drug as first-line therapy in the case of metastatic, recurrent, or progressive tumors [17, 19]. Treatment of patients with the most common activating EGFR mutations with the first generation EGFR TKIs lead to good clinical success [4, 33]. Reliable data were obtained in a randomized phase III study (IPASS). Patients with EGFR sensitizing mutations receiving gefitinib had significantly higher survival and better quality of life compared with the group of patients treated with paclitaxel and carboplatin (standard chemotherapy) [16]. A significant improvement in disease-free survival up to 11.8 months when using erlotinib as a first-line therapy is reported in Chinese studies on phase III OPTIMAL and phase II JO22903 [15].

The aim of the updated study (CALGB 30406) was to compare treatment with erlotinib and its combination with chemotherapy in patients (predominantly white) with longstanding lung cancer. Patients receiving erlotinib as monotherapy had fewer side effects compared with chemotherapy and erlotinib group. If EGFR sensitizing mutations are detected during chemotherapy, it was recommended to discontinue or finish planned chemotherapy and switch to target therapy. According to the NCCN guidelines based on the CALGB study, it is not recommended to combine erlotinib, gefitinib or aphatinib with chemotherapy. If the patient has a progression of the disease, but has no clinical symptoms, it is possible to continue target therapy [34].

A similar drug was afatinib. It has slightly more side effects than erlotinib or gefitinib, but has been approved by the FDA as a first-line therapy drug [2, 17, 25, 40].

It is a proven fact that the progression of the disease begins about a year after taking targeted drugs. EGFR T790M mutation occurs, which indicates the development of resistance to therapy with TKI [31, 35]. Occurrence of T790M mutation in exon 20 of the EGFR gene leads to loosing of efficacy of quinazoline-based first-generation EGFR TKI. Loosing of efficacy is observed due to absence of opportunity to bind to the ATP binding pocket at a receptor, which decreases efficacy of inhibition of signaling in future. Biology and epidemiology of the T790M resistance mutation has been studied well. For targeting at T790M mutation, third-generation EGFR TKIs were designed [1, 20]. Pyrimidines named WZ3146, WZ4002 and WZ8040 were investigated and WZ4002 was found to be the most powerful against EGFR T790M. However, the drug has not been approved by the FDA [20].

The only commercially available third-generation TKI is osimertinib. Osimertinib is a third-generation EGFR-TKI. One of its benefits is that the drug is used orally. It can selectively inhibit both sensitizing to EGFR-TKI mutations and EGFR T790M resistance mutations. But it has lower activity against wild-type. Positive results of the AURA clinical trial let osimertinib be approved worldwide for the treatment of patients with the T790M mutation, which arose during treatment with TKIs of previous generation [8, 38].

A randomized study of phase III EGFRA (among patients with EGFR T790M-positive metastatic NSCLC), evaluating platinum and pemetrexed chemotherapy against osimertinib was performed. The study showed that treatment with osimertinib increased PFS compared with standard chemotherapy (10.1 vs 4.4 months), especially among patients with CNS metastases. The disease controlled rate was higher in patients treated with osimertinib compared with standart chemotherapy (93% vs 74%) [10].

It was found, that osimertinib showed good clinical benefits for treatment of patients with metastatic EGFR T790M-positive NSCLC with disease progression after or during TKI EGFR therapy. Due to this the FDA approved it. Later osimertinib was also recommended by the NCCN [34, 38].

Even after disease progression, it is recommended to continue treatment with erlotinib, gefitinib or aphatinib as this is beneficial for the patient. It is known that discontinuation of therapy leads to faster progression of the disease (appearance of symptoms, increase in tumor size and deterioration of the response during PET scan) [32].

In 2017, the NCCN group made adjustments to the treatment protocols of patients with EGFR sensitizing mutations which progressed on erlotinib, gefitinib, or aphatinib. After review, osimertinib was recommended for the treatment of patients with symptomatic brain metastases. As an alternative treatment regimen, continuation of afatinib, erlotinib or gefitinib therapy was suggested for this group of patients. When continuing therapy, it was recommended to add or modify additional therapy (e. g. local or systemic therapy). First-line systemic therapy combinations were recommended for patients who have multiple symptomatic lesions and were not sensitive to T790M. If the patient was positive for T790M, it was recommended to include osimertinib in his therapy [34].

Other mechanisms of resistance are multivarious. They include HER2 and / or MET amplification, PIK3CA and / or BRAF mutation, and small cell lung cancer transformation. Their incidence is much lower than the T790M mutation. Extremely rare these mutations or amplifications occurred together with T790M mutation [43, 46].

CONCLUSIONS

1. Clinical success was observed in treatment with the first generation EGFR TKIs. Similar resuits were observed in patients with the most common EGFR activating mutations.
2. Presence of 790M mutation in EGFR leads to resistance to TKI therapy. Its incidence is approximately in 60% among patients with disease progression on TKI drugs (erlotinib, gefitinib, or aphatinib).
3. Third-generation TKIs of EGFR demonstrate high efficacy, but acquired resistance development cannot be avoided.
4. Reasons and ways of development of acquired resistance to these agents are still investigated.

Conflict of interests. The authors declare no conflict of interest.

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