ANNOTATION

of dissertation work of Tumenbayeva Zhanar Saparkhanovna
on the topic of «Evaluation of the effectiveness of targeted lung cancer therapy» submitted for the degree of Philosophy doctor (PhD) in the specialty 8D10141 – «Medicine»

Relevance of the dissertation topic. Despite the achievements of social climax and medicine, lung cancer is growing every year, and currently the number of deaths is not decreasing.Targeted therapy has shown its promise in the treatment of patients with non-small cell lung cancer, the epidermal growth factor receptor (EGFR) was selected as a target, and the identification of clinically significant molecular targets in the treatment of lung cancer is crucial for the selection of appropriate targeted therapy [Gallant J.N., Lovly C.M., et al., 2018].

Treatment in patients with lung cancer is one of the urgent problems of modern medicine and the detection of a mutation of the epidermal growth factor receptor (EGFR) gene is an important step in the treatment of widespread non-small cell lung cancer, since this approach consists in the fact that the use of specially developed targeted therapy drugs is clinically effective and allows you to identify a special group of patients [Yang J.C., Sequist L.V., et al., 2015]. In the era of molecular and personalized therapy, the discovery of an EGFR mutation in 15-20% of lung adenocarcinomas and the associated response to tyrosine kinase inhibitors targeting EGFR provided a successful direction of attack on advanced stage adenocarcinomas [Siegelin M.D., Borczuk A.C., et al., 2014].In patients with disseminated non-small cell lung cancer and the presence of EGFR mutation leads to a significant increase in the frequency of objective effects, time to progression and improved overall survival, compared with the results of chemotherapy in patients with non-small cell lung cancer [Greenhalgh J., Boland A., et al., 2021].

I would also like to note that immunotherapy in the treatment of lung cancer prolongs overall survival in patients with PD-L1 expression and an integrated approach in the treatment of cancer patients has shown the importance of optimizing diagnosis and reducing the risk of adverse outcomes in patients with lung cancer at any stage of development, and the determination of molecular genetic research allowed the patient to choose the right treatment [Herbst R.S., Baas P., et al., 2016].

Thus, the issue of improving the provision of targeted therapy in patients with lung cancer remains relevant and requires scientific research in this direction.

The purpose of the study: Evaluation of the effectiveness of targeted therapy among patients with lung cancer using the example in the Turkestan region of the Republic of Kazakhstan.

The object of the study: Outpatient charts and medical histories of patients diagnosed with lung cancer who received targeted therapy and chemotherapy for 2019-2022 on the basis of the oncological center of the Turkestan region.

The subject (subject) of the study: methods of early diagnosis of lung cancer in patients who have received targeted therapy.

Research objectives:

1. To analyze the epidemiological characteristics of lung cancer in the Turkestan region of the Republic of Kazakhstan.

2. To study the molecular and genetic characteristics (EGFR, ALK, PD-L1) of lung cancer in the Turkestan region of the Republic of Kazakhstan.

3. To determine the features of histological forms in patients with lung cancer.

4. To evaluate the effectiveness of targeted therapy in patients with lung cancer.

Research methods:

1. Information and analytical:collection of information and analysis of literature data with similar topics.

2. Clinical:assessment of the state of the pulmonary-respiratory system (clinical examination with the study of family and medical history in patients with lung cancer, objective status, questionnaire - sociological survey (EORTCQLQ-C30, LC-13).

3. Instrumental: computed tomography of the chest, magnetic resonance imaging of the brain, computed tomography of the abdominal cavity, computer tomography of the thoracic and lumbar spine.

4. Laboratory: histological examination, immunohistochemical examination, molecular genetic examination.

5. Statistical: All statistical calculations were performed using the SPSS program (version 25.0, IBM Inc., Chicago, USA) and STATISTICA 12, the value of $p < 0.05$ was considered statistically significant. All data were summarized using descriptive statistics methods. All parameters were visually verified and also tested using the Shapiro-Wilk criterion, $\chi 2$ Pearson's, according to the RECIST 1.1 classification criteria and the logistic regression method. In order to study the effect of targeted therapy on the survival of patients with EGFR mutation without progression, a retrospective statistical study of treatment results using the Kaplan-Mayer survival analysis was conducted.

Scientific novelty:

1. For the first time in the Turkestan region of the Republic of Kazakhstan, an analysis of the incidence in patients with lung cancer was conducted. A comprehensive analysis of clinical and morphological characteristics and the profile of molecular genetic results in patients with lung cancer with the «EGFR mutation» was carried out.

2. For the first time, the most common exons were identified in patients with non-small cell lung cancer with the «EGFR mutation» in the Turkestan region of the Republic of Kazakhstan.

3. The analysis of the features of histological forms in patients with lung cancer was carried out

4. The effectiveness of targeted therapy in patients with lung cancer in the Turkestan region of the Republic of Kazakhstan was evaluated (Author's certificate № 41404 «Evaluation of the effectiveness of targeted therapy in patients with non-small cell lung cancer»).

The main provisions of the dissertation submitted for defense:

1. Based on a comprehensive assessment of the lung cancer examination and statistical processing of the data obtained, among patients receiving targeted therapy, we determined for the first time the analysis of exons by the frequency of occurrence of «EGFR mutation» in patients with lung cancer ($x2_{calc}=38.6$, $p=0.000<0.05$).

2. The study of the features of histological forms in patients with non-small cell lung cancer with the «EGFR mutation» provided a choice of tactics for treatment and, based on the analysis of the results of treatment with targeted therapy, allowed us to determine the improvement in survival in patients with non-small cell lung cancer with the "EGFR mutation" in stage III-IV of the disease ($x2_{calc}=42,2$ $p=0.000<0.05$).

3. The effectiveness of targeted therapy of lung cancer with an «EGFR mutation» was evaluated, it was noted that the type of therapy (targeted or chemotherapy) used in patients with an «EGFR mutation» affects the life expectancy of patients after the start of treatment, that is, the stabilization of the process lasted more than 12 months, improving their quality of life ($x2_{calc}=27.37$, $p=0.000<0.05$).

4. A comprehensive assessment of the results of the clinical and instrumental study obtained by us in integration with the data of a sociological survey in patients with lung cancer, it was noted that the improvement in the detection of morphological verification of lung cancer, which led to a change in patient treatment tactics.

Integration.

In the educational process:

- The Department of Surgery, Oncology and Traumatology of JSC «South Kazakhstan medical academy» (Shymkent, Republic of Kazakhstan).

In the practice of medical institutions:

- The oncological center of the Turkestan region (Shymkent, Republic of Kazakhstan),

- The oncological center of the city of Shymkent (Shymkent, Republic of Kazakhstan).

Scientific and practical significance of the dissertation research:

1. The results of a comprehensive examination of those who received targeted therapy for early detection of lung cancer and complications of the disease, based on clinical and instrumental research methods and a sociological survey, allow us to recommend that doctors of the oncology service be guided by the developed algorithm «Algorithm of tactics for managing patients with lung cancer».

2. The prepared methodological recommendations on "Evaluating the effectiveness of targeted therapy in patients with non-small cell lung cancer" dictate the need to strengthen theoretical knowledge and practical skills in early diagnosis of lung cancer, to ensure preventive measures and health promotion through the organization of training webinars.

3. The identified mutations EGFR, ALK, PD-L1 for evaluation in patients with lung cancer received targeted and immunotherapy, is able to provide early diagnosis

and treatment of lung cancer, which allows it to be recommended in educational programs for training doctors in oncology, surgery and rehabilitation.

4. Our results of an integrated approach in the study of patients with lung cancer with the «EGFR mutation» with complications of the disease allowed us to develop tactics to improve the treatment of targeted and immunotherapy therapy, for subsequent use in outpatient and chemotherapeutic departments and monitoring of existing patients in order to improve the provision of medical care in the healthcare of the Turkestan region of the Republic of Kazakhstan.

The personal contribution of the doctoral student.

The author formulated the purpose and relevant objectives of the study, as well as created all accounting and statistical documents, fully collected and followed by a thorough analysis of the materials obtained and the results of the study.

Approbation of the results of the dissertation.

The main materials of the dissertation research were presented at:

At the international scientific and practical conference «The best young scientists 2020» (Nur Sultan, September 28, 2020);

At the VII International Scientific and practical conference «Prospects for the development of biology, medicine and pharmacy» (Shymkent, December 10, 2020);

At the VIII Congress of Oncologists and Radiologists of Kazakhstan with International participation (Turkestan, October 14, 2021);

At the international scientific and practical conference «Call for Science and Education in the modern world» (Nur Sultan, April 22, 2021);

At the international scientific and practical conference «Modern approaches to drug therapy, radiology and surgery in oncology» (Nukus, May 20, 2022, Republic of Uzbekistan);

At the III International scientific and practical conference«From experience to project» (Almaty, April 14, 2023);

At the international scientific and practical conference of young scientists «Science and youth: conference on the quality of medical care and medical literacy» (Almaty, April 25, 2023);

At the international scientific and practical conference «Medicine of Tomorrow: The scientific legacy of Academician M.A.Aliyev» (Almaty, June 19, 2023).

Conclusions:

1. For the first time in the Turkestan region of the Republic of Kazakhstan, there was a decrease in the incidence of lung cancer. There was an improvement in the detection rates of morphological verification of lung cancer, which led to a change in patient treatment tactics. Due to the fact that adenocarcinoma was identified as the most common form of lung cancer, it was 85%. And in more than 50% of cases, when making an accurate morphological diagnosis, additional research methods (immunohistochemical and molecular genetic) will be required.

2. In the Turkestan region of the Republic of Kazakhstan, exons with a frequency of occurrence were identified in 48 patients with the "EGFR mutation":

Ex19 del – 36 (75%) patients, Ex 20ins – 3 (6%) patients, Ex 21ins L 858 R – 9 (19%) patients. That is, it was found that Ex19 del is more common in the EGFR gene χ2 Pearson ($x2_{calc}=38.6$, $p=0.000<0.05$).

3. As a result of studies of histological forms of lung cancer among patients receiving targeted therapy, the frequency of occurrence revealed: in 41 (85.4%) patients - adenocarcinoma, in 3 (6.3%) patients – undifferentiated cancer, in 4 (8.3%) patients – squamous cell carcinoma. Thus, adenocarcinoma is the most common histological form of non-small cell lung cancer χ2 Pearson ($x2_{calc}=58.62$, $p=0.000<0.05$).

4. The effectiveness of the treatment in patients with lung cancer who received targeted therapy (n=48) resulted in the following results: in 33 patients (68%) - stabilization of the process, in 9 patients (19%) - partial regression, in 6 patients (13%) - progression the process. The hypothesis of the equality of the frequencies of different treatment outcomes in patients with lung cancer who received targeted therapy was tested using the χ2 Pearson consent criterion ($x2_{calc}=27.37$, $p=0.000<0.05$).Thus: since the p-value is significantly less than the significance level α=0.05, the hypothesis of frequency equality is rejected. This means that the differences between the number of patients who experienced stabilization of the process, partial regression or progression of the process are statistically significant. In other words, stabilization of the process prevails among patients taking targeted therapy.

Publications

15 papers have been published on the topic of the dissertation, including 6 articles (3 articles in journals included in the List of publications recommended by the Science and Higher Education Quality Assurance Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan, where the author of this scientific work is the main author, and 1 article in a journal indexed in international databases Scopus: in the Journal of Physical Education and Sport (Romania) 2023; 1568-1575 pages.; quartile – Q2, percentile - 58, 2 articles of the scientific and practical conference), 9 abstracts and 1 methodological recommendation ISBN:978-601-08-4279-3;UDC:616-006:615; LBC:55.6; T79.

4 copyright certificates have been received:

1.Author's certificate №41404 «Evaluation of the effectiveness of targeted therapy in patients with non-small cell lung cancer». 2.Author's certificate № 41274 «Early diagnosis, routing and prevention in patients with lung cancer». 3.Author's certificate № 41275 «Algorithm of tactics for managing patients with lung cancer».

4.Author's certificate № 39670 «Memo for patients receiving targeted therapy».

The structure and scope of the dissertation work

The dissertation includes an introduction, 5 sections, conclusion, conclusions, practical recommendations, appendices and 125 sources of used literature. The text of the dissertation is presented on 111 pages and contains 34 figures and 6 tables.