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Algorithmf molecular genetic testing for lung cancer in the Republic of Kazakhstan

Relevance: *According to Globocan 2018, lung cancer ranks first in terms of mortality worldwide. In 2018, 2.1 million new cases of lung cancer were recorded (11.6% of all oncological diseases), with a mortality of 1.8 million cases. The tumor pathogenesis is based on a number of genetic changes that determine the course of the diseases, predict the response to therapy and prognosis of the disease.*

Molecular genetics testing (MGT) allows determining the presence of activation mutations, as well as mutations of primary and acquired resistance, which ensure personalized approaches to patients.

The purpose of the study *was to develop an optimal MGT algorithm for lung cancer in the Republic of Kazakhstan to ensure comprehensive and complete coverage of patients with target therapy.*

Results: *The proposed MGT algorithm in non-small cell lung cancer (NSCLC) was developed based on international recommendations. This algorithm streamlines the patient's route, shortens the decision-making time for the oncologist and reduces the time before treatment.*

Conclusion: *MGT in NSCLC is an integral step in diagnostics and the selection of adequate therapy for the personalization of treatment of cancer patients. The introduction of MGT for malignant neoplasms in the framework of the Comprehensive Plan will ensure the widespread use of molecular genetic testing methods in the Republic of Kazakhstan.*

Keywords: *lung cancer, non-small cell lung cancer (NSCLC), molecular genetic testing (MGT), personalized approach, targeted therapy.*

Introduction: According to Globocan 2018, lung cancer ranks first in terms of mortality worldwide. In 2018, 2.1 million new cases of lung cancer were recorded (11.6% of all oncological diseases), with a mortality of 1.8 million cases. The tumor pathogenesis is based on a number of genetic changes that determine the course of the diseases, predict the response to therapy and prognosis of the disease.

Molecular genetics testing (MGT) allows determining the presence of activation mutations and mutations of primary and acquired resistance to ensure a personalized approach to patients.

The development of modern oncology implicates the introduction of up-to-date technologies for the diagnostics and treatment of malignant neoplasms (MN) in the daily practice of an oncologist. A precision approach to oncology diseases involves the selection of adequate treatment based on a combination of biological factors of the tumor, taking into account the individual characteristics of the body and available therapeutic options.

Recently, MGT methods of study occupy an increasing place among diagnostic measures for MN. Determination of driver mutations leading to the development and proliferation of cancer cells of one kind or another is a necessary prerequisite for the selection of target therapy and chemotherapy, an important predictor, and often a criterion to control the disease and its treatment.

All modern recommendations, diagnostic and treatment protocols for MN, along with other diagnostic methods, strongly require to conduct MGT both at the initial diagnostics and in the case of disease progression [1]. The determination of tumor biomarkers and the genetic stability of an organism is of the greatest importance in light of the tactics of prescribing targeted drugs due to the on-going introduction of new molecules to treat MN and the wide use of the so-called tissue agnostic approach. In this approach, a certain group of medicines is prescribed based on the identification of clinically significant substitution and biomarkers more than on the tumor type and localization. Besides, bioinformatics analysis is required to interpret the combinations of detected driver mutations and biomarkers. This analysis takes into account the proportion of malignancy of the detected changes, the occurrence, and many other factors. All this entails a change in the paradigm of drug treatment of cancer [2].

Since 2018, the Republic of Kazakhstan (RK) is implementing the Comprehensive Cancer Control Plan for 2018-2022 adopted by Decree of the Government of the Republic of Kazakhstan No. 395 of June 29, 2018, "On Approval of the Comprehensive Cancer Control Plan in the Republic of Kazakhstan for 2018 - 2022." One of the important items of the Plan is the provision of MGT of tumors of various localizations, including lung cancer, colorectal cancer, and cutaneous melanoma. As a part of the funding allocated, MGT is free of charge for all patients diagnosed with MNs of the mentioned localizations. The range of mutations studied includes activating mutations of the EGFR gene (exons 18, 19, 20, 21), translocations of ALK/ROS1, the mutations of BRAF, KRAS, and the determination of PD-L1 status. The laboratories of the Kazakh Institute of Oncology and Radiology (Almaty), the Multidisciplinary Medical Center (Nur-Sultan) and the Regional Oncology Dispensary (Karaganda) were chosen as reference centers since they possess trained specialists and specialized laboratories conducting pathomorphological, immunohistochemical studies, and MGT. In the following years, the list of laboratories shall be expanded to simplify the logistics and accelerate the testing procedure.

The purpose of the study was to develop an optimal MGT algorithm for lung cancer in the Republic of Kazakhstan to ensure comprehensive and complete coverage of patients with target therapy.

Materials and methods: The researchers used statistical data on lung cancer incidence in the Republic of Kazakhstan obtained by Kazakh Institute of Oncology and Radiology. In 2018, 3,741 patients were primarily diagnosed with lung cancer in the Republic of Kazakhstan. 85% of them had non-small cell lung cancer (NSCLC). Half (50%) of all NSCLC patients were diagnosed with stage III-IV and were subject to MGT.

Results: KazIOR proposed the following MGT algorithm for the stratification of patients with lung cancer based on international recommendations. All patients with an established lung cancer diagnosis (non-squamous LC, including dimorphic LC) and with the progression of the disease are subject to mandatory MGT [1, 3]. The number of patients was calculated based on the data from the Cancer Patient Electronic Registry information system (IS EROB) and the indicators of the cancer care service of the Republic of Kazakhstan, adjusted for the availability of biological material during diagnostic procedures or surgical intervention, as well as the impossibility of material collection taking into account the severity of the patient's condition [4, 5].

The material for MGT is paraffin blocks of all patients with NSCLC (mainly, in an advanced or metastatic form). After histological examination, the **first step** is the determination of **EGFR** gene mutations using real-time PCR.

The EGFR gene encodes the epidermal growth factor receptor (EGFR). EGFR is a transmembrane protein from the family of receptor tyrosine kinases, which affects proliferation, angiogenesis, and increased metastatic activity of cells [6, 7]. Identification of EGFR gene mutations in exons 19 and 21 is associated with the sensitivity to EGFR tyrosine kinase inhibitors (TKIs) and is the basis for the administration of targeted first-line therapy (gefitinib, erlotinib, afatinib, etc.). A deletion in exon 19 (del19) [8] requires the prescription of afatinib to increase overall survival compared to chemotherapy. Besides, the mutations associated with TKI resistance can also be detected in the EGFR gene, e.g., the T790M mutation in exon 20 [9, 10]. The detection of this mutation requires a change in therapy. KazIOR performs the detection of T790M mutation in the framework of a research project followed by an introduction into common practice in 2020.

EGFR-positive patients (about 30%) require no further testing. Patients with an identified EGFR mutation are prescribed an appropriate targeted TKI therapy.

The material of EGFR-negative patients (70%) is sent to determine the ALK, ROS1 translocation by fluorescence in situ hybridization (FISH), IHC test. The method is chosen based on the laboratory capacity to perform specific testing. Such translocation forms the chimeric gene EML4-ALK that stimulates tumor cells reproduction and growth. ALK-positive patients receive TKIs (crizotinib, ceritinib, alectinib) in first-line therapy, ROS1-positive receive crizotinib. These mutations are quite rare in NSCLC patients (ALK – 3.8%, ROS1 – 1.7%). However, high sensitivity to TKI makes testing for the above mutations mandatory with negative EGFR.

Together with testing for EGFR mutations and ALK, ROS-1translocations, all patients with advanced NSCLC are sent to determine the level of PD-L1 expression. PD-L1 is a ligand of the PD1 membrane protein that plays a role in cell differentiation. PD1 has an inhibitory effect on the immune system by double stimulating apoptosis of antigen-specific T-lymphocytes. PD1 and its PD-L1 and PD-L2 ligands are a part of the checkpoint system of the immune system. The expression of PD-L1 is determined by IHC testing. In NSCLC, the expression level is estimated using the Tumor Proportion Score (TPS) scale that takes into account the percentage of viable tumor cells expressing PD-L1 (with full or partial membrane staining of any intensity) among the total number of tumor cells. The PD-L1 expression level (the percentage of tumor cells expressing PD-L1) is an indication for immunotherapy with pembrolizumab [11].

Sometimes, the disease progression urges a repeated MGT to identify the resistance mutations or possible new clinically significant mutations and select adequate therapy.

Conclusions: MGT in NSCLC is an integral step in diagnostics and the selection of adequate therapy for the personalization of treatment of cancer patients. The proposed MGT algorithm in non-small cell lung cancer (NSCLC) was developed based on international recommendations. This algorithm streamlines the patient's route, shortens the decision-making time for the oncologist and reduces the time before treatment. The introduction of MGT for malignant neoplasms in the framework of the Comprehensive Plan will ensure the widespread use of MGT methods in the Republic of Kazakhstan.

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