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THE GENETIC BASIS OF RESISTANCE TO TARGETED THERAPY IN ONCOLOGY AND STRATEGIES FOR OVERCOMING IT

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Abstract
The urgency of the problem is determined by the fact that targeted therapy has become one of the central directions of modern drug oncology, but its clinical effectiveness is limited by primary and acquired tumor resistance.
The genetic nature of this phenomenon is particularly significant for Russian practice, where the expansion of molecular testing is already influencing the choice of treatment for non-small cell lung cancer, melanoma, colorectal cancer, thyroid cancer, renal cell carcinoma and hepatocellular carcinoma. In case of resistance to tyrosine kinase inhibitors, anti-EGFR drugs, BRAF/MEK inhibitors, multikinase inhibitors, and drugs acting on the PI3K-AKT-mTOR cascade, secondary mutations of the therapeutic target, amplification of alternative receptors, reactivation of downstream signaling pathways, loss of suppressor genes, clonal selection, and spatial heterogeneity play a crucial role. tumors.
The practical significance of the topic is related to the fact that later identification of the molecular mechanism of progression leads to an empirical change in therapy lines, while repeated testing of tumor tissue and circulating tumor DNA allows choosing a more targeted strategy.
The article systematizes the genetic mechanisms of drug resistance and discusses strategies for overcoming it in Russian real-world clinical practice: preliminary stratification of patients, repeated molecular testing in case of progression, next-generation therapy, reintroduction of the anti-EGFR approach in molecularly selected patients, combined blockade of signaling cascades and redirection of radioiodresistant tumors.

KEYWORDS: targeted therapy, drug resistance, oncology, EGFR, BRAF, RAS, molecular diagnostics, circulating tumor DNA, personalized medicine.

INTRODUCTION

Targeted therapy has changed the logic of treating malignant neoplasms: the decision to prescribe a drug is increasingly based not only on the organ affiliation of the tumor, but also on the identified molecular target. In Russian clinical practice, this is especially noticeable in the examples of BRAF-mutated melanoma, RAS/BRAF-stratified colorectal cancer, EGFR-dependent lung cancer, renal cell carcinoma, and radioiodresistant thyroid cancer [7]. However, the initial response is not equal to a cure, since the tumor population consists of clones with different sensitivity to drug pressure [12].
The genetic basis of resistance includes several interrelated levels. The first level is associated with a change in the drug target itself, when a secondary mutation reduces the binding of the drug or changes the conformation of the protein. The second level occurs when bypassing the activation of a parallel receptor or intracellular cascade, which makes the blockade of the original target incomplete. The third level is determined by the loss of suppressor genes, changes in DNA repair, amplification of oncogenes, and the formation of drug-tolerant cellular states [11].
To substantiate the topic, it is important to take into account Russian studies of real practice, since they do not show the idealized effectiveness of the drug in the protocol, but the result obtained with different testing availability, heterogeneity of previous treatment, and differences in patient routing. For example, in metastatic

colorectal cancer, a comparison of regorafenib and the repeated use of the anti-EGFR approach demonstrates that the molecular context of wild-type RAS/BRAF retains clinical significance even after several treatment lines [3]. In BRAF V600E-mutated colorectal cancer, the problem of resistance is manifested by the aggressive course of the disease and the need for combined blockade, since isolated exposure to one point of the MAPK pathway is often accompanied by compensatory reactivation of signaling transmission [6]. A similar logic underlies the redefinition of radioiodresistant thyroid cancer, where BRAF-/MEK-blockade can restore the ability of a tumor cell to accumulate radioactive iodine and thereby restore sensitivity to a previously ineffective method [10].

The purpose of the study was to scientifically substantiate the genetic mechanisms of resistance to targeted therapy and to identify practical strategies for overcoming it in Russian oncology. The object of the study was malignant neoplasms, for which molecular-directed medicinal approaches are used in the Russian Federation.

The subject of the study was genetic alterations and clonal processes that determine primary or acquired resistance to targeted drugs.

MATERIALS AND METHODS OF RESEARCH

The work was performed as a clinical and analytical study focused on the Russian practice of using targeted drugs in solid tumors. The unit of analysis was a molecular clinical scenario in which the initial therapeutic target, the mechanism of sensitivity loss, and a possible strategy for subsequent treatment are known. This approach makes it possible to compare different nosologies without mechanically confusing clinical outcomes, since resistance is assessed through the biological cause of progression.

The molecular profiling in the scenarios under consideration is based on real diagnostic methods used in oncological practice. Allele-specific polymerase chain reaction, Sanger sequencing, and targeted next-generation sequencing panels are used to identify EGFR, BRAF, KRAS, NRAS, and PIK3CA point mutations. Fluorescent in situ hybridization, chromogenic in situ hybridization, and NGS with copy number analysis are used to detect amplifications of MET, ERBB2, and other copy rearrangements. Immunohistochemical reactions with validated antibodies are used to evaluate the expression of protein targets, and digital PCR or NGS of circulating tumor DNA is considered to monitor the dynamics of resistant subclones.

The clinical interpretation of the results was based on the principle of comparing genetic alteration with drug vulnerability. If the detected alteration was a driver and had a registered or clinically proven method of pharmacological blockade, it was considered as a potential therapeutic target. If the alteration occurred after treatment and explained the progression, it referred to the mechanisms of acquired resistance. Variants without sufficient clinical significance were not used for direct therapeutic withdrawal.

The assessment of strategies for overcoming resistance included an analysis of the biological validity of drug change, increased cascade blockade, a combination of targeted and immune approaches, as well as the reappointment of previously effective anti-EGFR therapy after an interval without appropriate pressure. Particular attention was paid to scenarios where retesting can change treatment: progression after anti-EGFR therapy in colorectal cancer, radioiodresistance in BRAF-positive thyroid cancer, and therapy after primary line failure in tumors with activated signaling pathways.

RESULTS AND DISCUSSIONS

Analysis of Russian data shows that resistance to targeted therapy is not a single process. In some tumors, resistance is established before the start of treatment due to the initial molecular profile, for example, RAS or BRAF mutations in colorectal cancer, making anti-EGFR blockade biologically ineffective or requiring a different combination. In other situations, the sensitive clone is initially suppressed, but a subclone with an alternative signaling dependence expands under the influence of the drug [2].

In a 2026 Russian multicenter study in left-sided metastatic colorectal cancer with wild-type RAS and BRAF, repeated use of the third-line anti-EGFR approach was associated with a higher incidence of disease control compared with regorafenib. This observation is important not as a universal proof of the superiority of one scheme, but as confirmation of clonal dynamics: after a period without anti-EGFR pressure, the proportion of resistant subclones may decrease, and the tumor partially returns sensitivity to the previously used strategy [3].

In BRAF V600E-mutated colorectal cancer, Russian clinical observations emphasize that the aggressiveness of the molecular subtype requires early planning of combination therapy. BRAF blockade without EGFR-dependent feedback control is biologically vulnerable, therefore, it is more logical to combine a BRAF inhibitor with an anti-EGFR antibody, and in some modes, with effects on MEK [6].

In renal cell carcinoma, real-world practice data compared with immunotherapy and immune-targeting regimens reflect another aspect of resistance. Here, not only mutations in a narrow target are important, but also the functional state of the angiogenic cascade, the immune microenvironment, and the hypoxic adaptation of the tumor. Therefore, overcoming resistance is more often associated with a combination of mechanisms of action, rather than with a simple replacement of one inhibitor with another [5].

Before systematizing the results, it is advisable to identify those genetic events that most often determine the clinical loss of sensitivity to targeted drugs. Table 1 shows that the same progression phenotype may have different molecular causes, which means that the same clinical picture should not automatically lead to the same change in therapy.

Table 1 – Genetic mechanisms of resistance and clinical interpretation

Mechanism	Typical genes and pathways	Clinical manifestation	A potential strategy
Secondary mutation of the target	EGFR, BRAF, KIT, ALK	The primary response is followed by progression in the previous foci	A next-generation drug or a new combination
Activating a workaround	MET, ERBB2, PIK3CA, MAPK	Progression while maintaining the original target	Combined blockage of the parallel cascade
Clonal breeding	RAS, BRAF, TP53, oncogen amplification	The appearance of a stable subclone after several months of treatment	Repeated tissue profiling or ctDNA
Phenotypic plasticity	EMT programs, epigenetic states	Decreased response depth without a new apparent driver mutation	Combinations with effects on the microenvironment and stress adaptation

Analysis of table 1 shows that genetic resistance is rarely limited to a single mutation. In practice, it forms a network of causes where secondary mutation, receptor amplification, and clonal selection can simultaneously reinforce each other. Therefore, in Russian patient routing, it is fundamentally important not only to perform initial testing, but also to provide for repeated examination with progression [8].

Further, clinical scenarios were identified in which the genetic mechanism directly determines the therapeutic solution.

Table 2 compares tumor models, key alterations, and the practical possibility of overcoming resistance.

Table 2 – Russian clinical resistance scenarios and possible actions

Nosology	The genetic context	The problem of resistance	Practical conclusion
Metastatic colorectal cancer	RAS/BRAF wild type or BRAF V600E	Loss of response to anti-EGFR or aggression of the BRAF subtype	Reintroduction of anti-EGFR in selected patients or combined BRAF/EGFR blockade
Melanoma of the skin	BRAF V600E/K and MAPK-dependence	Adaptive reactivation of the MAPK pathway	Combination of BRAF and MEK inhibition, toxicity control and follow-up line planning
Radioiodresistant thyroid cancer	BRAF V600E, loss of iodine accumulation	Insensitivity to radioactive iodine	BRAF-/MEK- redefinition with re-evaluation of iodine accumulation
Renal cell carcinoma	Angiogenic and immune dependence	Incomplete blockade of one growth axis	Immune-targeting regimens and sequence personalization

Table 2 shows that a strategy for overcoming resistance should be based around a verifiable biological cause. In colorectal cancer, this is especially noticeable: in wild-type RAS/BRAF, it is possible to return to anti-EGFR blockade after the temporary disappearance of resistant clones, whereas in BRAF V600E, increased cascade blockade is required, taking into account the reverse activation of EGFR [2].

Melanoma deserves special attention, since Russian data on adjuvant targeted therapy of BRAF-positive patients in real clinical practice show the value of early appointment of a molecular-based treatment. However, even with an effective combination of BRAF and MEK inhibitors, there remains a risk of cell selection with reactivation of the MAPK signal, changes in cell cycle regulation, and microenvironment adaptation [7].

Hepatocellular carcinoma demonstrates a more complex variant of resistance, in which Lenvatinib acts on several tyrosine kinase targets, but the tumor is able to change angiogenic dependence and include alternative ways of survival. The Russian results of using Lenvatinib as the first line are important because they emphasize the need to assess liver function, tumor burden, and molecular signs of progression as a single clinical complex [1].

For hormone-positive HER2-negative breast cancer with alterations of the AKT signaling pathway, the problem of resistance is associated with endocrine resistance and the transition of the tumor cell to alternative proliferation mechanisms. Expert discussion in Russia emphasizes the role of detecting changes in the AKT pathway, since the presence of such an alteration turns general hormone resistance into a specific therapeutic task [9].

The role of repeated testing is particularly important with long-term treatment. A biopsy of a progressive lesion allows us to study the actual clone, but it is not always technically possible and does not always reflect the entire

spatial heterogeneity of the tumor. A liquid biopsy, on the contrary, can record the total contribution of several foci, but it depends on the level of isolation of circulating tumor DNA. Therefore, the optimal Russian model should combine tissue examination, when it is safe and informative, and ctDNA analysis, when dynamic monitoring is required [4].

The practical rationale for choosing methods to overcome resistance is presented in Table 3. It shows that each strategy has not only biological strength, but also limitations related to the availability of testing, toxicity, and evidence base.

Table 3 – Strategies for overcoming resistance: advantages and limitations

Strategy	Biological basis	Expected effect	Limitation
Initial advanced profiling	Identification of the driver before starting treatment	Reducing the risk of biologically ineffective therapy	Price and test completion dates
Repeat biopsy or ctDNA	Identification of a new clone as it progresses	Targeted line change instead of empirical therapy	False negativity with low tumor DNA
Combined cascade blockade	Suppression of reverse signal reactivation	Deeper and longer-lasting disease control	Increased toxicity and the need for monitoring
Reintroduction of the targeted approach	Reduction in the proportion of resistant subclones after the interval	Return of sensitivity in selected patients	The need for molecular confirmation
Redeferentiation of the tumor	Restoration of lost function under the action of inhibitors	A return to the previously ineffective local method	So far, limited clinical series

Table 3 shows that the most rational strategy is not one universal strategy, but a sequence of actions. First, it is necessary to determine the initial target as accurately as possible, then monitor the biological evolution of the tumor, and then select a drug change, combination, or reintroduction based on the current molecular profile. This approach corresponds to the modern understanding of resistance as a dynamic continuum, rather than as a one-time event [12].

A comparison of Russian and international data allows us to formulate an important methodological position: the narrower the target of the drug, the higher the importance of accurate diagnosis of the mechanism of inefficiency. In broad multikinase regimens, resistance can be multifactorial and clinically vague, whereas in EGFR, BRAF, or AKT-dependent tumors, even a single mutation or amplification can change the entire therapeutic logic [9].

The introduction of molecular monitoring in the Russian Federation should take into account not only the technological aspect, but also the organizational one. The genetic result should be received by the doctor at a time when it is able to influence the appointment, and the conclusion should contain a clinical interpretation, not just a list of options. Otherwise, even high-quality sequencing becomes an archival document that does not change treatment outcomes.

The scientific significance of the results lies in combining the genetic model of resistance with data from Russian real clinical practice. The practical significance lies in the fact that oncological tactics in the course of progression should begin not with the choice of the next available scheme, but with the question of which clone has become the leading one and which target now determines the viability of the tumor [8].

CONCLUSION

The genetic basis of resistance to targeted therapy includes secondary mutations of the drug target, activation of bypass signaling pathways, amplification of oncogenes, loss of suppressor mechanisms, clonal selection, and phenotypic plasticity of tumor cells. These processes form a dynamic system in which the molecular profile before treatment and the profile during progression can differ significantly.

Russian data from real clinical practice confirm that the molecular selection of patients affects not only the first line of therapy, but also subsequent decisions. In colorectal cancer, the reintroduction of the anti-EGFR approach is possible in patients with wild-type RAS/BRAF, combined blockade is required in BRAF-mutated tumors, in radioresistant thyroid cancer, redirection is promising, and in renal cell carcinoma, combined immune-targeting regimens play a special role.

The most reasonable strategy for overcoming resistance is a consistent model: initial extended profiling, repeated testing with progression, interpretation of the result by a molecular consultation, and the choice of therapy aimed at the current mechanism of resistance. This model reduces the proportion of empirical prescriptions and makes targeted therapy truly personalized.

The prospects for further research in the Russian Federation are related to the development of registers of molecular outcomes, standardization of the analysis of circulating tumor DNA, assessment of the cost-effectiveness of repeated testing, and the creation of algorithms that make it possible to predict in advance the appearance of a stable clone.

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