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ABSTRACT

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TARGETED THERAPY OF ANAPLASTIC THYROID CANCER

Introduction. Anaplastic thyroid cancer is an aggressive disease with meager patient survival. The tumors are often unresectable and insensitive to standard treatment methods (chemotherapy and radioiodine therapy). In recent years, much attention has been paid to new therapeutic strategies, mainly targeted therapy.

The purpose of our study was to summarize the data on targeted drugs used to treat anaplastic thyroid cancer and establish the main side effects associated with their use.

Materials and methods. A scientific search was conducted in Pubmed, Scopus, and Web of Science databases. The following search terms were used: "anaplastic thyroid cancer," "targeted therapy," and "clinical trials."

Results. A literature search was conducted regarding targeted drugs to treat anaplastic thyroid cancer. The results of clinical trials using BRAF/MEK, RET, NTRK, mTOR, and TKI inhibitors were analyzed. Several clinical trials have demonstrated that dabrafenib, combined with trametinib, has a sufficiently high therapeutic effect and can effectively treat anaplastic thyroid cancer. Other targeted drugs show limited clinical response, such as NTRK inhibitors, TKIs, and other BRAF/MEK inhibitors. Some drugs (e.g., lenvatinib) may only be effective with other anticancer agents. RETi and mTORi are believed to have some therapeutic potential, but more than several clinical trials are needed to evaluate their effectiveness.

Discussion. The main reason for the relapse of the disease and the ineffectiveness of targeted drugs is the appearance of new mutations. The RAS mutation is responsible for resistance to the combination of dabrafenib and trametinib; the S100A4 protein is responsible for the ineffectiveness of vemurafenib. Developing new drugs capable of overcoming resistance mechanisms is necessary to solve this problem.

Conclusions. Targeted therapy is a promising direction in the treatment of anaplastic thyroid cancer. Side effects are common but mostly manageable.

Keywords: anaplastic thyroid cancer, BRAF/MEK inhibitors, NTRK, RET, mTOR, TKI, targeted therapy.

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ТАРГЕТНА ТЕРАПІЯ АНАПЛАСТИЧНОГО РАКУ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Вступ. Анапластичний рак щитовидної залози – це агресивне захворювання з вкрай низькою виживаністю пацієнтів. Пухлина часто буває нерезектабельною та нечутлива до стандартних методів лікування (хіміотерапії та радіоїодтерапії). Останніми роками велика увага приділяється новим терапевтичним стратегіям, зокрема таргетній терапії.

Метою нашого дослідження було узагальнити дані про препарати таргетної дії, які використовують для лікування анапластичного раку щитоподібної залози та встановити основні побічні явища, пов'язані з їх прийомом.

Матеріали та методи. Науковий пошук проводився в базі даних Pubmed, Scopus, Web of Science. Були використані такі пошукові терміни: «анапластичний рак щитоподібної залози», «таргетна терапія», «клінічні дослідження».

Результати. Був проведений пошук наукової літератури щодо використання таргетних препаратів для лікування анапластичного раку щитоподібної залози. Проаналізовано результати клінічних досліджень з використанням інгібіторів BRAF/MEK, RET, NTRK, mTOR, TKI. У декількох клінічних випробуваннях продемонстровано, що дабрафеніб в комбінації з траметинібом має достатньо високий терапевтичний ефект та може використовуватися для ефективного лікування анапластичного раку щитоподібної залози. Інші таргетні препарати, такі як інгібітори NTRK, TKI, інші інгібітори BRAF/MEK, демонструють обмежену клінічну відповідь. Деякі препарати (наприклад, ленватиніб) можуть бути ефективними лише у комбінації з іншими протипухлинними агентами. Вважається, що RETi, mTORi мають певний терапевтичний потенціал, але кількість клінічних досліджень недостатня, щоб оцінити їх ефективність.

Обговорення. Основною причиною настання рецидиву захворювання та неефективності таргетних препаратів є поява нових мутацій. Мутація RAS відповідальна за стійкість до комбінації дабрафенібу з траметинібом, білок S100A4 – за неефективність вемурафенібу. Для вирішення цієї проблеми необхідна розробка нових лікарських засобів, здатних подолати механізми резистентності.

Висновки. Таргетна терапія є перспективним напрямком лікування анапластичного раку щитоподібної залози. Побічні явища зустрічаються часто, але здебільшого їх можна контролювати.

Ключові слова: анапластичний рак щитоподібної залози, інгібітори BRAF/MEK, NTRK, RET, mTOR, TKI, таргетна терапія.

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INTRODUCTION / ВСТУП

Anaplastic cancer is a rare histological variant of thyroid tumors. This malignant neoplasm occurs in only 1–2% of patients [1]. The cancer is very aggressive and has an unfavorable prognosis. The average survival of patients is five months [2]. Anaplastic thyroid cancer occurs mainly in women. Its primary clinical symptoms are a hard, painful tumor that overgrows and leads to shortness of breath and hoarseness. Unfortunately, most patients at the time of diagnosis have an advanced stage of cancer, so they are not amenable to surgical treatment. Anaplastic thyroid cancer is not sensitive to chemotherapy and radioiodine therapy, so it needs a modern treatment approach, mainly targeted therapy.

Mutations in the RET, EGFR, and KIT genes disrupt the transmission of the main signaling pathways (MAPK, PI3K/AKT/mTOR, and JAK-STAT). This leads to impaired growth, proliferation, cell apoptosis, and the appearance of anaplastic thyroid cancer. Targeted therapy is the only treatment that can block specific signaling pathways and stop the proliferation of atypical cells.

A large number of genetic mutations are associated with anaplastic thyroid cancer. BRAF and RAS oncogenes are essential to the RAS-ERK signaling pathway [3]. Next in importance is the TP53 mutation. In connection with the gradual accumulation of genetic abnormalities, there is a loss of differentiation of the cells of the thyroid gland. This phenomenon is not at all characteristic of differentiated tumors. The insensitivity of anaplastic cancer to chemotherapy and radioiodine therapy is associated with this phenomenon [4]. The discovery of the importance of signaling pathways has led to many studies devoted to the targeted therapy of anaplastic thyroid cancer. The American Thyroid Association (ATA) recommends genetic testing for all patients with suspected anaplastic carcinoma [2].

The purpose of our study was to summarize the data on targeted drugs used to treat anaplastic thyroid cancer and establish the main side effects associated with their use.

MATERIALS AND METHODS

A scientific search was conducted in Pubmed, Scopus, and Web of Science databases. The

following search terms were used: "anaplastic thyroid cancer," "targeted therapy," and "clinical studies."

RESULTS

1. BRAF/MEK inhibitors (BRAF/MEKi)

BRAF mutation occurs in 50% of patients with malignant melanoma. However, it is also the most common somatic mutation in individuals with anaplastic thyroid cancer. About 90% of patients may have BRAF V600E mutations [2].

1.1. Dabrafenib and trametinib are targeted drugs against BRAF and MEK1/2 mutations. These drugs inhibit the proliferation of tumor cells by blocking the RAF-MEK-ERK signaling pathway. A clinical trial in patients with anaplastic thyroid cancer demonstrated that combination therapy with dabrafenib and trametinib was effective in individuals with the BRAF V600E mutant gene. In differentiated forms of thyroid cancer, the overall response rate was significantly lower (33 vs. 80%, respectively) [5]. The Food and Drug Administration (FDA) approved the combination of dabrafenib and trametinib for treating patients with unresectable or metastatic mutant anaplastic thyroid cancer. A study by Subbiah et al. [6] reported that dabrafenib 150 mg twice daily and trametinib 2 mg once daily significantly prolonged patient survival. In addition, these drugs can be used for neoadjuvant therapy in patients with inoperable tumors [7].

The most common side effects after using dabrafenib and trametinib in patients with anaplastic thyroid cancer were anemia, nausea, fatigue, anorexia, and neutropenia. In general, the treatment is well tolerated.

1.2. Vemurafenib is a drug that selectively inhibits oncogenic BRAF kinases. Vemurafenib is widely used to treat unresectable or advanced metastatic melanoma with the BRAF V600E mutation. The FDA does not approve this drug for treating patients with anaplastic thyroid cancer. The research team of Hyman et al. [8] evaluated the effect of vemurafenib on survival in patients with BRAF V600E mutants. Only seven people participated in the study and showed good treatment results: 2 had a complete response, and 5 had a partial response.

The side effects include fatigue, rash, hematologic toxicity, alopecia, arthralgia, and

gastrointestinal disturbances. The severe consequences of taking can be squamous cell cancer of the skin, trachea, head, and neck, and stomach adenocarcinoma. It is worth noting that no clinical studies are dedicated to investigating vemurafenib's safety in patients with anaplastic thyroid cancer. Data on complications were collected based on a study of drug use in patients with malignant melanoma.

2. RET inhibitors (RETi)

RET gene mutation occurs in patients with thyroid and non-small cell lung cancer. The RET gene can be expressed in transcriptionally silent cells. This eventually leads to the fusion of RET and activating the RAS, PI3K, and STAT signaling pathways. Cells begin to divide and overgrow [9].

2.1. Selpercatinib is an FDA-approved drug for treating RET-mutant medullary thyroid carcinoma. A phase I-II clinical trial (LIBRETTO-001) [10] investigated the efficacy and safety of selpercatinib in a cohort of 143 patients with anaplastic thyroid cancer. It was found that a partial response was observed in 79% of patients, and the one-year progression-free survival was 64%.

Patients who took this targeted drug complained of hypertension, xerostomia, nausea, constipation, or diarrhea. Among the laboratory indicators, the most common side effect was increased liver transaminases and hyponatremia. Separate studies have not been conducted on the safety of selpercatinib in patients with anaplastic thyroid cancer. Data on side effects were collected based on studies among patients with non-small cell lung cancer [11].

2.2. Pralsetinib is another representative of targeted therapy that inhibits the phosphorylation of RET and its molecules. The FDA has approved the drug for the treatment of adults and children with neglected RET-positive thyroid cancer. In the ARROW clinical study [12], the efficacy of pralsetinib was evaluated in patients with RET mutations. The overall response was 89%. However, the studied cohort did not include patients with anaplastic thyroid cancer. This direction may be promising and requires a separate study.

The scientific team of Griesinger et al. [13] reported the results of a study of the efficacy and safety of pralsetinib in patients with non-small cell lung cancer. It was noted that this drug has a higher frequency of hematological toxic effects (lymphopenia, anemia, neutropenia) compared to selpercatinib. However, severe side effects are much less common. The most common serious

complication was pneumonia, which was recommended to be treated with high doses of corticosteroids.

3. NTRK inhibitors (NTRKi)

The TRK (tropomyosin receptor kinase) receptor family is encoded by the NTRK1, NTRK2, and NTRK3 genes and is involved in intercellular interaction and communication.

3.1. Larotrectinib is a TRK (TRKA, TRKB, TRKC) receptor inhibitor approved by the FDA for treating children and adults with NTRK fusion tumors. The drug can be used for the therapy of various solid tumors. There have been only a few small-scale clinical trials of larotrectinib in people with anaplastic thyroid carcinoma. For example, a study by Waguespack et al. [14] found that overall response to treatment was achieved in 29% of patients. However, this rate is better than the cytotoxic chemotherapy response [2]. Isolated cases of larotrectinib use in children have been described [15]. Additional clinical studies are required to confirm the drug's effectiveness in patients with anaplastic thyroid cancer.

In 90% of patients taking larotrectinib, there were side effects: fatigue, myalgia, nausea, cough, constipation, and increased level of liver transaminases [14, 15]. There are no data on the safety of use in patients with anaplastic thyroid cancer.

3.2. Entrectinib is a broad-spectrum-targeted anticancer drug for treating adults and children with NTRK fusion solid tumors. It is believed that it can be used for thyroid cancer. Although 7% of patients with solid tumors had a complete response, and 50% had a partial response, the treatment outcome in individuals with anaplastic thyroid cancer remains unknown [16]. Some studies suggest that entrectinib can cross the blood-brain barrier and effectively treat patients with anaplastic thyroid cancer with brain metastases [17].

Entrectinib is quite toxic. Almost all patients experience taste disturbances, increased creatinine levels, dizziness, and fatigue. Gastrointestinal reactions often develop, but less often do pulmonary reactions (shortness of breath, pneumonia, thromboembolism of the pulmonary artery) [16].

4. mTOR inhibitors (mTORi)

Long-term activation of the mTOR (serine-threonine protein kinase) signaling pathway leads to intensive long-term growth, cell proliferation, and the appearance of malignant neoplasms [18]. mTOR inhibitors stimulate apoptosis and have anti-inflammatory, autophagic, and antiproliferative effects.

4.1. Everolimus is the primary representative of drugs in this group. It suppresses mTOR kinase activity and inhibits angiogenesis by influencing endothelial growth factor (VEGF) [19]. Lim et al. [20] investigated the effect of everolimus on patients with different histological thyroid cancer variants. The studied cohort included only six patients with anaplastic tumors. The median recurrence-free survival of these patients was ten weeks. Harris et al. [21] evaluated the survival of 5 patients with anaplastic thyroid cancer who received everolimus as palliative therapy. The average survival of patients was 7.4 months.

Patients who take everolimus have side effects mostly of 1–2 degrees of severity: skin rash, mucositis, increased liver enzymes, anemia, and cough. Side effects of the 3–4th degree are rare. It can be stomatitis, neutropenia, hypercholesterolemia, and fatigue [20, 21].

4.2. Rapamycin is an effective drug used to treat autoimmune diseases. In addition, it can suppress the proliferation and growth of atypical cells. The effectiveness of rapamycin was studied only on cell lines of anaplastic thyroid cancer [22]. Significant suppression of the growth of tumor cells was observed, so this direction can be auspicious.

5. TKI (tyrosine kinase) inhibitors

Anaplastic thyroid cancer tumor cells actively produce vascular endothelial growth factor (VEGF). In this regard, the tumor becomes well-vascularized, which increases its metastatic potential [23]. Inhibitors of tyrosine kinases can inhibit neoangiogenesis.

5.1. Sorafenib is an anticancer drug that targets endothelial and platelet-derived growth factor receptors (EGFR and PDGFR). The drug showed satisfactory results in an experiment on animals [24]. However, in a study of patients with anaplastic thyroid cancer, the median recurrence-free survival was only 2.8 months, and the median overall survival was five months [25]. Some scientists claim that sorafenib's effectiveness increases when combined with metformin [26].

Patients with anaplastic thyroid cancer experienced such side effects as weight loss, skin rash, fatigue, anemia, hypertension, and elevated liver enzymes [25, 26].

5.2. Lenvatinib is an angiogenesis inhibitor approved in Japan for treating neglected anaplastic thyroid cancer [95]. Huang et al. [27] investigated the effectiveness of lenvatinib in this category of

patients through a meta-analysis. It was established that a partial response was achieved in 15% of patients and stabilization of the disease in 42%. One of the studies was terminated due to unsatisfactory patient outcomes. Nevertheless, there is evidence that lenvatinib can enhance the effect of other anticancer drugs (adriamycin, vinorelbine, paclitaxel) [28, 29].

This drug's most frequent side effects were anorexia, arterial hypertension, proteinuria, and asthenia [27]. The effectiveness of other tyrosine kinase inhibitors affecting neoangiogenesis (imatinib, sunitinib, apatinib, vandetanib) is questionable [30, 31, 32, 33].

DISCUSSION

Anaplastic thyroid cancer is challenging to treat. Usually, patients have an unresectable tumor insensitive to chemotherapy and radioiodine therapy. If anaplastic thyroid cancer is suspected, the doctor must send a tumor tissue sample for molecular genetic testing. This will make it possible to correctly choose a drug with a targeted effect and prolong the patient's life.

According to the results of our study, the combination of dabrafenib and trametinib in patients with BRAF V600E mutation shows the best treatment results. Other targeted drugs show limited clinical response, such as NTRK inhibitors, TKIs, and other BRAF/MEK inhibitors. Some drugs (for example, lenvatinib) may be effective only in combination with other anticancer agents. RETi, and mTORi are believed to have some therapeutic potential, but more than several clinical trials are needed to evaluate their effectiveness.

Targeted therapy has many side effects: hematological toxicity, inhibition of kidney and liver function, skin rash, hypertension, gastrointestinal disorders, and fatigue. Such patients require careful monitoring and a long follow-up period.

The main reason for the relapse of the disease and the ineffectiveness of targeted drugs is the appearance of new mutations. The RAS mutation is responsible for resistance to the combination of dabrafenib and trametinib, and the S100A4 protein is responsible for the ineffectiveness of vemurafenib [34, 35]. Developing new drugs capable of overcoming resistance mechanisms is necessary to solve this problem. Combined drug use with a targeted effect is also a promising research direction [36].

CONCLUSIONS / ВИСНОВКИ

Targeted therapy is a promising direction in the treatment of anaplastic thyroid cancer. According to the results of many studies, the combination of dabrafenib with trametinib is the most effective since the proportion of patients with a BRAF mutation is high. One of the essential areas of clinical research can be the evaluation of the effectiveness and safety

of a combination of two or more targeted drugs. Studies have shown that combining cytotoxic and targeted anticancer drugs can overcome resistance mechanisms. Side effects are common but are mostly manageable. For a more informative assessment of the effectiveness and safety of drugs, it is necessary to conduct clinical studies with the participation of a large cohort of patients.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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