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«Южно-Российский онкологический журнал»: профессиональное медицинское издание. В нем публикуются новости медицинского и фармацевтического сообществ, научно-практические статьи для целевой аудитории – врачей-онкологов. Редакция журнала ставит своей задачей популяризацию научно-исследовательских работ и достижений онкологов Южного федерального округа, анализ процесса глубокой реорганизации здравоохранения в России. Редакция приглашает в качестве авторов всех, кто ищет и находит интересные решения многогранных задач, стоящих перед современной медициной, и хочет поделиться своими мыслями и наблюдениями с коллегами.

Цель: способствовать развитию онкологической медицины Юга России и внедрению её достижений в практику.

Задачи: освещать современные достижения онкологической службы Юга России; содействовать обмену опытом и передовыми знаниями между специалистами; информировать читателей об итогах крупных медицинских форумов.

В журнале размещаются публикации различных рубрик: обзоры литературы, мета-анализы, клинические исследования, наблюдения клинических случаев, обсуждения, анонсы и описания новых методов лечения.

Журнал принимает к публикации: оригинальные статьи, организации здравоохранения, лучевой диагностики, обмен опытом, обзоры, клинические наблюдения.

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"South-Russian Oncological Journal": professional medical publication. It publishes news from the medical and pharmaceutical communities, scientific and practical articles for the target audience-oncologists. The editorial board of the journal aims to popularize the research works and achievements of oncologists of the Southern Federal District, to analyze the process of deep reorganization of healthcare in Russia. The editorial board invites as authors all those who are looking for and find interesting solutions to the multifaceted problems facing modern medicine and want to share their thoughts and observations with colleagues.

Purpose: to promote the development of cancer medicine in the South of Russia and the introduction of its achievements into practice.
Tasks: to highlight the current achievements of the oncology service in the South of Russia; to promote the exchange of experience and advanced knowledge between specialists; to inform readers about the results of major medical forums.
The journal contains publications of various categories: literature reviews, meta-analyses, clinical studies, observations of clinical cases, discussions, announcements and descriptions of new treatment methods.
The journal accepts for publication: original articles, health organizations, radiation diagnostics, exchange of experience, reviews, clinical case reviews.

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СОДЕРЖАНИЕ

CONTENTS

South Russian Journal of Cancer
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ORIGINAL ARTICLE

THE RESULTS OF ANTERIOR RECTAL RESECTION WITH THE FORMATION OF A HARDWARE ANASTOMOSIS IN CANCER PATIENTS

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ABSTRACT

Purpose of the study. A retrospective analysis of the immediate results of performing anterior rectal resections in cancer.
Materials and methods. In the Department of Abdominal Oncology No. 1 with a group of X-ray vascular methods of diagnosis and treatment of the clinic of the National Medical Research Centre for Oncology of the Ministry of Health of Russia treatment for rectal cancer operations of anterior rectal resection were performed in 334 patients, while in 143 (42.8 %) cases they were low. As a standard, total mesenteric excision and lymphoid dissection in volume D2 were performed. Combined surgical interventions were performed in 68 (20.4 %) patients for locally spread tumors. As a rule, they were resection in nature and were performed with tumor infiltration of adjacent organs (bladder with ureters, ovaries, uterus, vagina, small intestine, abdominal wall). Colorectal anastomosis using crosslinking devices was formed in all cases, in 316 (94.6 %) cases it was a "side – to-end" junction, in 18 patients – "end-to-end". A preventive proximal intestinal stoma was formed in 73 (21.9 %) cases, where 67 cases it was an ileostomy, and 6 – a transversostomy. The preventive proximal intestinal stoma was not formed among 261 patients.
Results. After performing anterior resections for rectal cancer operations, the complications developed in 75 (22.5 %) patients. The most threatening and dangerous complication was the failure of the colorectal anastomosis, which was noted in 12 (3.5 %) cases.
This complication occurred in 8.2 % (6 patients out of 73) of preventatively stoma-treated patients, in 2.3 % of patients without a stoma (6 patients out of 261).
Conclusion. The use of a preventive proximal intestinal stoma allows you to form a colorectal anastomosis even in the presence of complicated forms of rectal cancer. The number of complications directly referred to the formation of a preventive proximal intestinal stoma is relatively small, but when planning surgery for uncomplicated rectal cancer, the probability of their possible occurrence should be taken into account.

Keywords:
rectal cancer, anastomosis, stoma, transversostoma, failure of colorectal anastomosis sutures

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ОРИГИНАЛЬНАЯ СТАТЬЯ

РЕЗУЛЬТАТЫ ПЕРЕДНЕЙ РЕЗЕКЦИИ ПРЯМОЙ КИШКИ С ФОРМИРОВАНИЕМ АППАРАТНОГО АНАСТОМОЗА У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

Е. Н. Колесников[1], А. В. Снежко[2], В. С. Трифанов[1], М. А. Кожушко[1], Ю. А. Фоменко[1], Т. Б. Кациева[1], Р. Е. Мягков[1], С. В. Санамянц[1], М. А. Аверкин[1], Г. Ю. Егоров[1]✉

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РЕЗЮМЕ

Цель исследования. Ретроспективный анализ непосредственных результатов выполнения передних резекций прямой кишки при раке.

Материалы и методы. В отделении абдоминальной онкологии № 1 с группой рентгенэндоваскулярных методов диагностики и лечения (РЭМДЛ) клиники ФГБУ «НМИЦ онкологии» Минздрава России по поводу рака прямой кишки (РПК) операции передней резекции прямой кишки выполнены 334 больным, при этом в 143 (42,8 %) случаях они были низкими.

В качестве стандарта выполнялась тотальная мезоректумэктомия и лимфодиссекция в объёме D2. Комбинированные хирургические вмешательства выполнены у 68 (20,4 %) пациентов по поводу местно-распространённых опухолей. Колоректальный анастомоз с использованием сшивающих аппаратов формировали во всех наблюдениях, в 316 (94,6 %) случаях это было соустье «бок в конец», у 18 пациентов – «конец в конец». Превентивную проксимальную кишечную стому формировали в 73 (21,9 %) наблюдениях, из них в 67 случаях это была илеостома, в 6 – трансверзостома. У 261 пациента превентивную проксимальную кишечную стому не формировали.

Результаты. После выполнения передних резекций по поводу РПК осложнения развились у 75 (22,5 %) больных. Самым грозным и опасным осложнением была несостоятельность колоректального анастомоза, которая отмечалась в 12 (3,5 %) наблюдениях. У превентивно стомированных пациентов это осложнение возникло у 8,2 % (6 больных из 73), у больных без стомы у 2,3 % (6 пациентов из 261).

Заключение. Использование превентивной проксимальной кишечной стомы позволяет сформировать колоректальный анастомоз даже при наличии осложнённых форм рака прямой кишки. Количество осложнений, непосредственно связанных с формированием превентивной проксимальной кишечной стомы относительно небольшое, однако, при планировании хирургического вмешательства по поводу неосложнённого рака прямой кишки, необходимо учитывать вероятность их возможного возникновения.

Ключевые слова:
рак прямой кишки, анастомоз, стома, трансверзостома, несостоятельность швов колоректального анастомоза

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RELEVANCE

The basis for the treatment of rectal cancer (RC) is the performance of radical surgery. Currently, priority in the surgical treatment of RC belongs to sphincter-preserving surgical interventions, among which the most common is anterior rectal resection. Among these operations, there is a low anterior resection, used when the tumor is located 6–8 cm above the anus. Studies on the peculiarities of the spread of rectal tumors have significantly expanded the indications for low rectal resections. It has been proved that the minimum distance from the tumor to the lower border of rectal resection in cancer from the mucosa can be only 1 cm or less [1–3]. The widespread use of crosslinking devices that allow the formation of colorectal anastomoses almost at the level of the sphincter complex, as well as the use of various coloplasty techniques to replace the reservoir function of the rectum, has led to an improvement in the functional results of anterior resection operations in RPC.

However, the problem of postoperative complications is still relevant, the most formidable of which is the failure of the colorectal anastomosis sutures (FCAS). Literature data on the frequency of this complication range from 3 to 30 %. Modern studies do not include in the list of complications asymptomatically current and detectable only with a control X-ray examination of contrast agent congestion [4; 5]. Among the proposed methods of protection of the FCAS, the most common is the formation of a proximal intestinal stoma. The imposition of preventive intestinal stomas is considered as an intervention that allows avoiding not so much the occurrence of FCAS, as the severe consequences of its occurrence. The main indications for the formation of preventive intestinal stomas most often include the formation of a supraanal colorectal anastomosis and the presence of a positive air test for the tightness of the anastomosis, as well as manifestations of intestinal obstruction [1; 6–8].

At the same time, the use of preventive intestinal stomas in itself may be associated with the risk of additional complications directly related to both its formation and elimination [7; 9–11].

The purpose of the study: retrospective analysis of the immediate results of performing anterior rectal resections in cancer.

MATERIALS AND METHODS

Studies concerning the choice of surgery methods, optimal methods for the formation of colorectal anastomoses using crosslinking devices, an approach to the formation of preventive proximal intestinal stomas, drainage of the lumen of the rectum and abdominal cavity, tactics for the treatment of postoperative complications in the surgical treatment of colorectal cancer were conducted at the Rostov Research Institute in the period from 2007 to 2012 [1]. In the Department of abdominal Oncology No. 1 with a group of X-ray vascular methods of diagnosis and treatment clinic, National Medical Research Centre for Oncology of the Ministry of Health of Russia for RC anterior rectal resection surgery was performed in 334 patients, while in 143 (42.8 %) cases they were low. Of the operated patients, 178 were women and 156 were men (ratio 1:1.1). The average age of patients was 61.3 ± 3.4 years, 23 % were over 70 years old. The majority of patients (208 or 62.3 %) were operated in stage III of the disease, 87 (26.0 %) patients had stages I and II. In 39 (11.7 %) cases, distant metastases occurred, and patients were assigned to stage IV. Histological examination revealed adenocarcinoma in 98 % of patients, neuroendocrine cancer in 5 (1.5 %) patients, squamous cell carcinoma in 2 (0.6 %) patients. The degree of differentiation of adenocarcinoma G1 was noted in 38 (11.6 %) patients, G2, including with a mucus-forming component, in 243 (74.3 %), in 46 (14.1 %) adenocarcinoma G3 was detected.

Mainly in the lower third of the rectal ampoule, the tumor was localized in 110 (32.9 %) patients, in the middle third – in 94 (28.1 %), in the upper third with a spread to the rectosigmoid section – in 130 (38.9 %) patients.

More than half of the patients had concomitant diseases, mainly it was pathology of the cardiovascular system.

The preoperative preparation of patients included orthograde and retrograde colon cleansing, drug decontamination, prevention of thromboembolic complications, and, if necessary, correction of corresponding disorders on the part of organs and systems.

As a standard, total mesorectumectomy and lymphodissection in volume D2 were performed. Combined surgical interventions were performed in 68 (20.4 %) patients for locally spread tumors. As a rule, they were resection in nature and were performed with tumor infiltration of adjacent organs

(bladder with ureters, ovaries, uterus, vagina, small intestine, abdominal wall). Colorectal anastomosis using crosslinking devices was formed in all cases, in 316 (94.6 %) cases it was a side-to-end junction, in 18 patients it was an end-to-end junction. Preventive proximal intestinal stoma was formed in 73 (21.9 %) cases, of which in 67 cases it was ileostomy, in 6 – transversostomy. The main indication for the formation of a proximal intestinal stoma was the presence of manifestations of intestinal obstruction, due to which it was impossible to fully prepare the colon for anastomosis. Another common cause of the formation of a preventive intestinal stoma, especially with locally common tumors, was pronounced inflammatory infiltration in the pelvic cavity and pararectal adipose tissue, resulting from the occurrence of pararectal ulcers, urinary and vaginal fistulas. No preventive proximal intestinal stoma was formed in 261 patients.

RESEARCH RESULTS AND DISCUSSION

After performing anterior resections for RC, complications developed in 75 (22.5 %) patients (table 1).

The most formidable and dangerous complication was the failure of the colorectal anastomosis. It was understood as the excretion of intestinal contents through drains, through the vagina or with urine, or the excretion of urine through the rectum. Colorectal anastomosis failure was noted in 12 (3.5 %) cases. In 6 cases, a preventive proximal intestinal stoma was not superimposed, in 6 it was formed. Conservative therapy was performed in 11 patients, relaparotomy, resection of the anastomosis area and removal of a single-stem colostomy were required in 1 patient. In 4 cases, fistulas eventually formed between the rectum, the vagina (in 3 cases) and the bladder in 1 patient. All patients were operated on within 3 to 6 months, 2 of them underwent abdominal-perineal

Table 1. Complications after RC surgical treatment

Complication type	Absolute quantity (% of completed operations)
Complications after anterior rectal resections (*n* = 334)	
Failure of the colorectal anastomosis	12 (3.6 %)
Bleeding from the anastomosis area	3 (0.9 %)
Adhesive intestinal obstruction	5 (1.5 %)
Abdominal cavity abscesses	4 (1.2 %)
Perforation of the bladder, injury of the ureter	2 (0.6 %)
Rectal-vaginal and rectal-urinary fistulas	4 (1.2 %)
Suppuration of a laparotomic wound	12 (3.6 %)
Dysuric disorders (neurogenic bladder)	10 (3.0 %)
Anastomosis stricture	4 (1.2 %)
Thromboembolic complications	5 (1.5 %)
Pneumonia	8 (2.4 %)
Acute heart failure	6 (1.8 %)
Total	75 (22.5 %)
Complications after operations to eliminate preventive intestinal stomas (*n* = 68)	
Bleeding from the anastomosis area	1 (1.5 %)
Adhesive intestinal obstruction	2 (2.9 %)
Suppurations of a wound	3 (4.4 %)
Total	6 (8.8 %)

extirpation of the rectal stump in combination with vaginal resection, 1 had bladder resection, 1 managed to limit himself to fistula plastic surgery.

In our opinion, the data on the incidence of clinically pronounced insolvency in the group of patients without preventive proximal intestinal stoma and in those to whom it was formed are of interest. This severe complication occurred in 8.2 % (6 out of 73 patients) of preventatively stoma-treated patients, and 2.3 % (6 out of 261 patients) of patients without a stoma. It should be emphasized that almost all patients who received preventive intestinal stoma had complicated forms of colorectal cancer, the most frequent of which were signs of intestinal patency disorders. Thus, a preventive proximal intestinal stoma cannot completely remove the increased likelihood of developing colorectal anastomosis in the presence of complications, and, probably, in some cases, an extremely high risk of developing colorectal anastomosis, it is advisable to abandon its formation in favor of performing obstructive resections.

Bleeding from the anastomosis zone was noted in 3 patients, while in 2 cases it was stopped transanally, in 1 case a relaparotomy and additional stitching of the anastomosis zone were required.

Adhesive intestinal obstruction was diagnosed in 5 (1.5 %) patients, all of them were operated on. In 4 out of 5 patients, extensive combined operations were initially performed.

Abdominal abscesses were detected in 4 patients, in 2 of them they were an additional complication of the colorectal anastomosis failure, in 2 they were the result of anterior resection surgery on the background of a locally advanced perforating tumor. In 1 observation, spontaneous drainage of the abscess occurred through anastomosis into the intestinal lumen, in 3 cases, drainage of the purulent cavity was performed under ultrasound control.

Traumatic perforation of the bladder in 1 patient and the ureter in another, manifested in the early stages after surgery by urine excretion through drainage tubes and caused relaparotomy in both patients. In 1 case, the bladder was sutured, in the second – ureteral resection with the formation of ureterocystoanastomosis.

Patients with neurogenic bladder included patients who did not restore normal urination 7 to 10 days after surgery. Dysuric disorders were usually clinically manifested by acute urinary retention. In 7 patients, this required an increase in the time of catheterization of the bladder to 14–18 days, 3 patients were discharged with a urinary catheter, and normal urination was restored in 4 to 6 weeks and they needed an additional course of conservative therapy under the supervision of a neurologist.

The cause of strictures of colorectal anastomosis during the period from 6 to 14 weeks after surgery, in our opinion, was a "hidden" failure of the anastomosis, especially considering that 3 out of 4 patients had preventive proximal intestinal stomas. In 2 cases, effective stricture augmentation was performed, followed by closure of the ileostomy, in 2 patients, resection of the anastomosis zone was performed.

Thromboembolic complications were noted in 5 patients. 1 patient had acute arterial thrombosis of the right lower limb, and he underwent thrombintimectomy. 2 patients developed superficial phlebothrombosis of the lower limb, 1 patient underwent a crossectomy, the other underwent conservative therapy. 2 patients developed pulmonary embolism, both patients died.

Complications from the cardiovascular system in 6 patients were manifested by increased manifestations of angina pectoris, arrhythmogenic disorders and hemodynamic disorders, which were treated conservatively.

After resection operations for rectal cancer, 2 patients died, both from pulmonary embolism. Postoperative mortality was 0.6 %.

Reconstruction of the gastrointestinal tract after the formation of intestinal stomas was performed in 68 patients, from which 62 patients had ileostomy and 6 had transversostomy. These surgical interventions were performed either 5 to 6 weeks after the first operation, or, in most patients, after the completion of multi-course adjuvant chemotherapy, usually after 6 to 7 months. Refusal to perform intestinal reconstruction was associated with tumor progression in 4 patients and refusal of surgery in 1 patient. Preoperative examination necessarily included performing irrigoscopy to identify possible stricture of colorectal anastomosis. Reconstructive surgery in almost all patients was carried out from restricted access, the stoma was circularly excised, the bowel loop with the stoma was removed into the wound and later resected. In all patients, anastomosis was formed "side to side" with a nodular suture. Complications after

reconstructive operations were noted in 6 (8.8 %) patients who did not die (see table). Repeated operations were required in 3 patients, all laparotomies were performed. A patient with bleeding from the anastomosis underwent resection of the small intestine together with the anastomosis, patients with acute adhesive intestinal obstruction underwent viscerolysis.

The material given earlier presents the results of treatment of RC patients in a specialized surgical department. The presented results of practical work, consistently low indicators of the number of postoperative complications and mortality fully confirmed the correctness of the developed approaches to the surgical treatment of rectal cancer.

CONCLUSION

Surgical treatment of patients with rectal cancer in specialized departments within large medical centers allows to obtain good immediate outcomes of surgical procedures, relatively low rates of the number of postoperative complications and mortality. The use of a preventive proximal intestinal stoma makes it possible to form a colorectal anastomosis even in the presence of complicated forms of rectal cancer. The number of complications directly related to the formation of a preventive proximal intestinal stoma is relatively small, however, when planning surgery for uncomplicated rectal cancer, the probability of their possible occurrence must be taken into account.

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CLINICAL CASE REPORTS

A CLINICAL CASE OF PULMONARY FORM OF MUCORMYCOSIS IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Mucormycosis of the lungs is a severe infectious complication in patients with acute lymphoblastic leukemia, which develops at the stage of high-dose cytostatic therapy. It is characterized by an extremely aggressive, rapidly progressive course and, without specific treatment, is fatal in a short time. Reliable verification of mucor is necessary due to its resistance to the most commonly used antifungal drugs, particularly to voriconazole.

The article presents a clinical case of pulmonary mucormycosis in a 12-year-old child at the stage of diagnosis of acute lymphoblastic leukemia. The first symptoms of the disease (headaches, malaise and weakness, pallor), changes in the general blood count (hyperleukocytosis up to 200 thousand cells/μl, single platelets). Based on the results of the examination, the main diagnosis was verified for acute lymphoblastic leukemia L2, IFT T-II, CD1a$^-$. At the stage of diagnosis of acute lymphoblastic leukemia, the underlying disease was complicated by the development of right-sided pneumonia according to X-ray examination. To verify the etiology of infiltration of lung tissue, broncho-alveolar lavage was directed to microbiological diagnostics, which included studies: enzyme immunoassay, microscopic and cultural. On the aggregate of all the results obtained, invasive mucormycosis was diagnosed and antifungal therapy was started immediately.

Keywords:
acute lymphoblastic leukemia, invasive mycosis, oncohematology, mucormycosis, diagnosis of mucormycosis, treatment of invasive mycosis

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

КЛИНИЧЕСКИЙ СЛУЧАЙ ЛЕГОЧНОЙ ФОРМЫ МУКОРМИКОЗА У РЕБЕНКА С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ

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РЕЗЮМЕ

Мукормикоз легких – тяжелое инфекционное осложнение у больных острым лимфобластным лейкозом, которое развивается на этапе высокодозной цитостатической терапии. Оно характеризуется чрезвычайно агрессивным, быстро прогрессирующим течением и без специфического лечения заканчивается летальным исходом в короткое время. Достоверная верификация мукора необходима в связи с устойчивостью к наиболее часто используемым противогрибковым лекарственным средствам, в частности, к вориконазолу.

В статье представлен клинический случай легочной формы мукормикоза у ребенка 12 лет на этапе диагностики острого лимфобластного лейкоза. Первые симптомы заболевания (головные боли, недомогание и слабость, бледность), изменения в общем анализе крови (ОАК) (гиперлейкоцитоз до 200 тыс. кл/мкл, тромбоциты единичные). По результатам обследования верифицирован основной диагноз острый лимфобластный лейкоз L2, ИФТ T-II, CD1a$^-$. На этапе диагностики острого лимфобластного лейкоза, основное заболевание было осложнено развитием правосторонней пневмонией согласно рентгенологическому исследованию. Для верификации этиологии инфильтрации легочной ткани на микробиологическую диагностику был направлен бронхо-альвеолярный лаваж (БАЛ). Исследование включало методы: иммуноферментный, микроскопический и культуральный. На совокупности всех полученных результатов был диагностирован инвазивный мукормикоз и начата незамедлительно противогрибковая терапия.

Ключевые слова:
острый лимфобластный лейкоз, инвазивный микоз, онкогематология, мукормикоз, диагностика мукормикоза, лечение инвазивного микоза

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RELEVANCE

The continuing increase in the number of infections caused by fungi (micromycetes) remains one of the urgent problems of both global and domestic healthcare. Diseases caused by microscopic fungi (mycoses) have become an urgent clinical problem. Mycoses are a serious danger for people with an immunosuppressive condition. Especially in acute leukemia, taking into account the initial hyperleukocytosis and the development of life-threatening complications against this background, the increasing severity of the patient's condition, requiring immediate initiation of specific treatment. The optimization of high-tech medicine, the active use of cytostatic and immunosuppressive drugs, the use of broad-spectrum antibiotics in the prevention and treatment have led to an increase in the number of immunocompromised patients with a high risk of developing not only superficial, but also invasive mycotic infectious complications with severe clinical manifestations and very high attributive mortality [1–4].

Invasive mycoses (IM) are a common complication in oncological and hematological patients. The most common pathogen of IM in oncohematological patients is *Aspergillus spp.* Early diagnosis, prevention and treatment with voriconazole significantly reduced the incidence of invasive aspergillosis. At the same time, the frequency of IM caused by mucormycetes (*Rhizopus spp., Rhizomucor spp., Mucor spp., Lichtheimia corymbifera*) and other rare pathogens such as *Fusarium spp*. increased. These and other mucormycetes are resistant to the most commonly used antifungal drugs, in particular, voriconazole. Due to the difficulty of diagnosis (there is no clear picture during X-ray examinations, an invasive procedure is required to obtain a biopsy or bronchoalveolar lavage (BAL), the absence of specific tests to detect antigen or specific antibodies), the number of publications on rare pathogens caused by IM in cancer patients is limited [5–7].

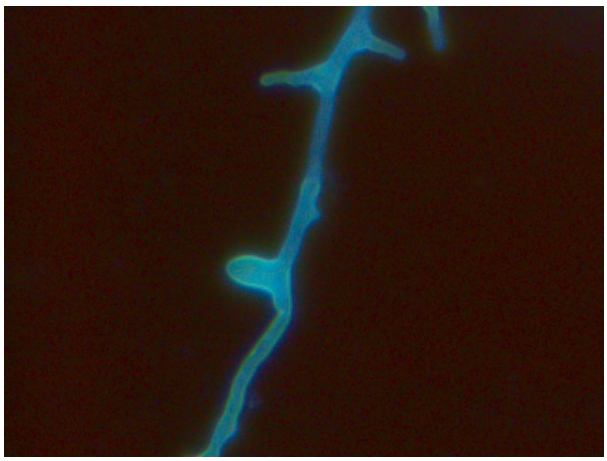

Fig. 1. Broncho-alveolar lavage microscopy; calcoflour white stain, × 600.

The possibilities of high-tech methods of diagnosis, prevention and treatment are increasing, but at the same time, invasive mycosis remains the dominant cause of infectious mortality in patients with cancer [8–10].

CLINICAL CASE DESCRIPTION

The article presents a clinical case of the pulmonary form of mucormycosis in a child at the stage of diagnosing of acute lymphoblastic leukemia. There is an informed consent of the patient for research.

A 12-year-old patient has been ill since January 2020, when the first symptoms of the disease appeared (headaches, malaise and weakness, pallor) during the examination, changes in the clinical blood count (CBC) were revealed (hyperleukocytosis up to 200 thousand cells / μl, single platelets). To clarify the diagnosis, the child was sent to the SBI of the RO "ODKB" in Rostov-on-Don. According to the results of the examination in the Department of Pediatric Oncology and Hematology with chemotherapy, the main diagnosis of acute lymphoblastic leukemia L2, IFT T-II, $CD1a^-$ was verified in the child. At the stage of diagnosis of acute lymphoblastic leukemia, the underlying disease was complicated by the development of right-sided pneumonia. According to the CT scan of the chest organs, infiltration of lung tissue was detected in S8, S9 on the right, located subpleurally with bronchial lumens and a cavity with fuzzy, uneven hyperintensive edges measuring 11 × 4 mm and a hypointensive center of an inhomogeneous structure; areas of centrilabular emphysema in S 1/2 on the right in the basal zone measuring 10 × 7 mm were determined. To verify the etiology of lung tissue infiltration, it was decided to conduct an invasive procedure in order to obtain a BAL. The BAL and blood serum were sent for research to the Laboratory of Clinical Microbiology of the National Medical Research Centre for Oncology of the Ministry of Health of Russia.

Microbiological diagnostics included studies: enzyme immunoassay, microscopic and cultural.

The presence of galactomannan (GM) in blood serum and BAL was determined by enzyme immunoassay using diagnostic test systems (XEMA GaLMAg EIA kit, Russia). The GM level was regarded as positive at values ≥ 0.59 OD (optical density). Microscopic examination of BAL was carried out using light and fluorescence microscopy with white calcofluor in order to identify fungal hyphae. The cultural study was carried out by a generally accepted microbiological method. On the first day, the following results were obtained: the level of galactomannan in the blood optical density index (IOP) – 0.12 (negative), in the IOP score – 0.17 (negative). The study using light microscopy did not reveal the pathogen, and with the help of fluorescence microscopy with white calcofluor, an unsepted mycelium branching at right angles was found in the material (Fig. 1).

It's worth pointing out that during the cultural mycological examination, the result was negative – the absence of growth for 2–5 days.

Thus, based on the totality of all the results obtained, invasive mucormycosis was diagnosed and antifungal therapy (amphotericin At 50 mg/day) was started immediately. Taking into account the positive dynamics on CT two weeks after the start of treatment, they decided to continue antifungal therapy with the rotation of the drug to posaconazole at a dose of 200 mg 4 times a day.) lasting up to 2 months. When assessing the child's condition in dynamics, a month after the start of treatment with MI, a positive effect was noted on CT of the chest organs in the form of a decrease in the focus of inflammation.

CONCLUSION

Mucormycosis is characterized by an extremely aggressive, progressive course with a very rapid destruction of all tissue barriers and, without specific treatment, ends in death in a short time from the moment of the appearance of clinical signs. The causative agents of mucormycosis are resistant to azoles and echinocandides used in clinical practice. It was not typical that the child developed mucoromycosis of the lungs in the initial stage of the disease (at the stage of diagnosis) before the use of high-dose cytostatic therapy. The development of pneumonia in immunocompromised patients requires caution in diagnosis in order not to miss mycosis. The results of the current review should help the doctor to establish a connection between the various manifestations of mucormycosis, the corresponding predisposing factors and pathogens.

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CLINICAL CASE REPORTS

THE USE OF TRANSDERMAL THERAPEUTIC SYSTEMS FOR CHEMICAL PLEURODESIS IN A PATIENT WITH PROLONGED AIR LEAKAGE AFTER LUNG RESECTION FOR CANCER

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ABSTRACT

This clinical observation demonstrates a method of a motivated use of a transdermal therapeutic system (TTS) based on fentanyl for chemical pleurodesis in a patient with prolonged air leakage after lung resection for cancer. The most common complication after elective lung resections is an alveolar-pleural fistula or prolonged air leakage. This clinical phenomenon occurs as a result of communication between the alveoli of the lung parenchyma distal to the segmental bronchus and the pleural cavity. In most cases, air leakage through the drains is eliminated spontaneously, but the frequency of prolonged pneumostasis absence in the postoperative period can reach 25 %, which has a negative effect on the outcomes of surgical interventions due to the development of pneumonia and empyema. Long-term drainage of the pleural cavity does not always end with aerostasis and requires repeated invasive interventions. One of the ways to achieve the tightness of the lung tissue involves various methods of chemical pleurodesis, which is a surgical manipulation – the introduction of a sclerosing chemical substance into the pleural cavity by spraying medical talc through a trocar or a injecting tetracycline solution into the pleural drains. The chemical causes aseptic inflammation and adhesions between the visceral and parietal pleura, followed by obliteration of the pleural cavity. The sclerosant introduction is accompanied by severe pain that can provoke respiratory and/or hemodynamic deficits, up to apnea and life-threatening heart rhythm disturbances. Pain relief during chemical pleurodesis is obviously an important factor in the prevention of a number of complications in patients undergoing surgery for lung cancer. Bolus intravenous injections of narcotic analgesics lead to an analgesic effect, but a short-term one due to the absence of a depot in the body and a sharp drop in the drug concentration in the blood serum. Unfortunately, this method of introducing narcotic drugs can cause various complications in weakened and elderly cancer patients, such as respiratory depression and cardiac arrest. The TTS action is characterized with continuous dosing and the creation of a constant concentration of the narcotic drug over a certain period of time. This method provides a multilevel and systematic approach to pain relief, reduces toxicity and minimizes the inhibition of the central mechanisms of external respiration regulation without causing respiratory and cardiac disorders in patients who underwent lung resection.

Keywords:
lung cancer, lung resection, bronchopleural complications, chemical pleurodesis, anesthesia, transdermal therapeutic systems

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

ПРИМЕНЕНИЕ ТРАНСДЕРМАЛЬНЫХ ТЕРАПЕВТИЧЕСКИХ СИСТЕМ ПРИ ПРОВЕДЕНИИ ХИМИЧЕСКОГО ПЛЕВРОДЕЗА У ПАЦИЕНТА С ДЛИТЕЛЬНОЙ УТЕЧКОЙ ВОЗДУХА ПОСЛЕ РЕЗЕКЦИИ ЛЁГКОГО ПО ПОВОДУ РАКА

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РЕЗЮМЕ

Данное клиническое наблюдение демонстрирует способ мотивированного применения трансдермальной терапевтической системы (ТТС) на основе фентанила при проведении химического плевродеза у пациента с длительной утечкой воздуха после резекции лёгкого по поводу рака. Наиболее распространенным осложнением после плановых резекций лёгкого является формирование альвеолярно-плеврального свища или длительная утечка воздуха. Это клиническое проявление возникает в результате сообщения между альвеолами паренхимы лёгкого дистальнее сегментарного бронха с плевральной полостью. В большинстве случаев утечка воздуха по дренажам устраняется спонтанно, однако частота длительного отсутствия пневмостаза в послеоперационном периоде может достигать 25 % случаев, что оказывает отрицательное влияние на исходы оперативных вмешательств из-за развития пневмонии и эмпиемы. Длительное дренирование плевральной полости не всегда заканчивается аэростазом и требует повторных инвазивных вмешательств. Одним из способов достижения герметичности ткани лёгкого является применение различных методик химического плевродеза, который представляет собой хирургическую манипуляцию – введение склерозирующего химического вещества в плевральную полость путем распыления медицинского талька через троакар или раствора тетрациклина, вводимого в плевральные дренажи. Химическое вещество приводит к асептическому воспалению и образованию сращений между висцеральным и париетальным листками плевры с последующей облитерацией плевральной полости. Введение склерозанта сопровождается сильными болями, способными спровоцировать респираторный и/или гемодинамический дефицит, вплоть до апноэ и жизнеугожающего нарушения сердечного ритма. Очевидно, что купирование боли при проведении химического плевродеза является важным фактором профилактики ряда осложнений у пациентов перенесших хирургическое вмешательство по поводу рака лёгкого (РЛ). Использование болюсного внутривенного введения наркотических анальгетиков приводит к обезболивающему эффекту, но кратковременного характера, что обусловлено отсутствием депо в организме и резким спадом концентрации препарата в сыворотке крови. К сожалению, у ослабленных и пожилых онкологических больных данный способ введения наркотических препаратов может вызвать различные осложнения такие, как угнетение дыхания и сердечной деятельности. Особенностью действия ТТС является обеспечение непрерывного дозирования и создания постоянной концентрации наркотического препарата на протяжении определенного промежутка времени. Данный способ обеспечивает многоуровневый и системный подход к устранению боли, способствует снижению токсичности и минимизирует угнетение центральных механизмов регуляции внешнего дыхания, не вызывая респираторные и кардиальные нарушения у больных, перенесших резекции легкого.

Ключевые слова:
рак лёгкого, резекции лёгкого, бронхоплевральные осложнения, химический плевродез, обезболивание, трансдермальные терапевтические системы

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RELEVANCE

Statistics from the International Agency for Research on Cancer determine the leading place of lung cancer (LC) among other malignant tumors. In the structure of oncological morbidity of the Russian Federation among the male population, tumors of the trachea, bronchi and lung account for 16.9 % [1].

Advances in cancer biology and significant progress in the identification of biomarkers with predictive value for various types of drug therapy allow us to hope for an increase in the effectiveness of RL treatment [2]. Of course, the modern capabilities of the multimodal approach are important, but the surgical method remains the main one in the treatment of patients with LC [3].

The improvement of the technique of radical surgical interventions in patients with RL and the latest technologies of intraoperative prevention of complications still do not completely solve the problems of the complicated course of the postoperative period, and bronchopleural surgical complications often develop after lung resection. The most common complication after planned lung resections is the formation of an alveolar-pleural fistula or prolonged air leakage [4]. This clinical manifestation occurs as a result of communication between the alveoli of the lung parenchyma distal to the segmental bronchus with the pleural cavity [5]. The Society of Thoracic Surgeons of the USA defines prolonged air discharge as an air leak that persists for more than 5 days after surgery. Air discharge after lung resection is observed in 25–50 % on the 1st day after surgery and above 20 % on the 2nd-4th day of the postoperative period [6]. Despite the fact that in most cases air leakage through drains is eliminated spontaneously, the frequency of prolonged absence of pneumostasis after lung resection for cancer according to the literature in the last decade is from 10 to 25 % [7]. In addition, in some patients, air leakage occurs delayed, i.e. 5 or more days after surgery against the background of a seemingly uncomplicated course of the postoperative period.

Prolonged air discharge negatively affects the outcomes of surgical interventions due to the development of complications such as pneumonia and empyema. The frequency of empyema with prolonged air leakage lasting more than 7 days is 10.4 % compared to 1 % with air discharge lasting less than 7 days (p = 0.01) [8]. Prolonged air discharge requires prolonged drainage of the pleural cavity, increasing postoperative pain; violation of lung expansion leads to an increased risk of pneumonia and thromboembolic complications due to reduced mobility of patients [4]. As a result, prolonged air discharge is associated with an increase in hospital mortality [9]. Patients with air leakage have a 3.4 times greater risk of dying than patients without this complication. Patients with prolonged air leakage stay in the hospital much longer, increasing the amount of costs by 30 %. In addition, prolonged air leakage causes a twofold increase in repeated hospitalizations of patients who have undergone lobectomy [10].

Prolonged drainage of the pleural cavity does not always end with aerostasis, which requires repeated interventions of varying degrees of invasiveness to eliminate air leakage [11]. The most effective ways to achieve tightness of lung tissue include various methods of chemical pleurodesis, endobronchial valves, repeated surgical interventions [11; 12]. Repeated surgery with the use of general anesthesia with separate bronchial intubation is accompanied by a significant functional load on the body, increasing the risk of surgical intervention in the group of older patients, as well as in patients with severe concomitant pathology [13].

Chemical pleurodesis is the introduction of a sclerosing chemical into the pleural cavity by spraying medical talc (magnesium hydrosilicate) through a trocar or tetracycline solution injected into drains. The chemical substance leads to aseptic inflammation and the formation of adhesions between the visceral and parietal pleural leaves, followed by obliteration of the pleural cavity [14]. Intrapleural administration of sclerosing drugs is accompanied by a painful reaction up to the development of pleuropulmonary shock with the possibility of its relief only with opioid analgesics [15]. Bolus intravenous administration of narcotic analgesics leads to an analgesic effect, but of a short-term nature, due to the absence of depots in the body and a sharp decrease in the concentration of the drug in the blood serum. Unfortunately, in weakened and elderly cancer patients, this method of administering narcotic drugs can cause life-threatening conditions, such as respiratory depression and cardiac activity with loss of consciousness. At the same time, the lack of adequate anesthesia can provoke apnea, bronchospasm, and collapse of lung areas with acute cardiovascular events [15]. It is obvious that pain relief during pleurodesis is an important

factor in the prevention of a number of complications in patients who have undergone surgery for RL.

To reduce pain symptoms during chemical pleurodesis, we selected a method of anesthesia using a transdermal therapeutic system (TTS) based on fentanyl. The motivation was the peculiarities of using an alternative and non-invasive route of administration of drugs, including opioid analgesics. The peculiarity of the action of TTS is to ensure continuous dosing and the creation of a constant concentration of analgesic drug for a certain period of time.

The purpose of the study: was to demonstrate a case of motivated use of a fentanyl-based transdermal therapeutic system when performing chemical pleurodesis after lung resection for cancer.

CLINICAL CASE

Patient K., 59 years old, was hospitalized at FSBI "Rostov Research Oncological Institute" of the Ministry of Health of the Russian Federation (since 2020 National Medical Research Centre for Oncology of the Ministry of Health of Russia) for specialized antitumor treatment. The main complaints at admission: dull chest pain of a permanent nature, periodic temperature rises. The diagnosis was made at the place of residence: Peripheral cancer of the left lung. Upon further examination, according to the SCT of the chest organs, a peripheral tumor of the upper lobe of the left lung was diagnosed 4.5 × 5.0 cm with germination into the mediastinal pleura, with an increase in the thoracic, bronchopulmonary and lymph nodes of the aortic window up to 1.0 cm. Fibrobronchoscopy: pathology of the tracheobronchial tree was not revealed, there are no signs of tumor centralization. Ultrasound of abdominal organs: hepatomegaly, fatty hepatosis, diffuse changes of the pancreas. The function of external respiration: the vital capacity of the lungs is 45 %, the forced vital capacity of the lungs is 34 %, the volume of forced air when exhaling in 1 second is 37 %, i.e. there is a pronounced decrease in all indicators. Electrocardiography: heart rate 88 beats/min, left anterior hemiblock – distal form, reduction of myocardial repair processes in the anterior-septum region of the left ventricle. Therapist's consultation: hypertension art. 2, arterial hypertension 3, risk 2, chronic heart failure 2 art., chronic obstructive pulmonary disease stage 1, grade 3 respiratory failure 2 art., obesity 2 art. Consultation of a vascular surgeon: varicothrombophlebitis of the right lower limb, chronic venous insufficiency 2 art., functional class 4. Morphological verification obtained as a result of transthoracic puncture: fragments of squamous cell carcinoma.

Based on the examination data, a clinical diagnosis was established: (C34.1) Cancer of the upper lobe of the left lung peripheral form sT2bNxM0 stage II, clinical group 2, Chronic obstructive pulmonary disease stage 1, grade 3 respiratory failure stage 2, hypertension stage 2, arterial hypertension 3, risk 2, chronic heart failure stage 2, Varicothrombophlebitis of the right lower limb, chronic venous insufficiency stage 2, functional class 4. Obesity 2st. Taking into account the clinical stage of RL, the consultation of doctors of the cancer center recommended performing surgical intervention in the volume of an extended upper lobectomy on the left. After preliminary drug preparation, the patient underwent surgery: An extended upper lobectomy on the left, combined with resection of the diaphragmatic nerve and mediastinal pleura. Postoperative therapy was aimed at antibiotic prophylaxis and prevention of thrombogenic complications with relief of postoperative pain by reduced double intramuscular administration of narcotic analgesics against the background of epidural analgesia. The postoperative period up to the ninth day proceeded without complications, when symptoms of pneumothorax appeared after a cough attack. Within three days, clinical and radiological symptoms of pneumothorax increased, and therefore surgeons decided to perform chemical pleurodesis using doxycycline, a semi-synthetic tetracycline – a broad-spectrum antibiotic with bacteriostatic action. As is known, doxycycline has a low resorptive ability and a pronounced adhesive effect [15].

Chemical pleurodesis was performed in the intensive care unit, which is justified by the unpredictable response of the patient's body to the introduction of an aggressive component of therapy. In some cases, during this manipulation, patients had a painful reaction with a collaptoid component in the form of loss of consciousness, respiratory and hemodynamic deficiency, up to apnea and life-threatening cardiac arrhythmia. As a rule, to prevent a painful reaction to the introduction of doxycycline solution into the pleural cavity, 2 ml of 2 % promedol solution was intramuscularly prescribed to the patient 30 minutes before the manipulation, and 1 % morphine solution – 1 ml was injected intravenously immediately before the procedure. Nevertheless, with such a scheme of

anesthesia, acute pain of varying degrees of intensity with the introduction of doxycycline was recorded in each patient, which required additional intravenous administration of narcotic drugs to relieve pain, often without the expected effect. At the same time, the patient's condition was aggravated by the development of poorly predictable manifestations of the toxic effects of opioids, namely, impaired consciousness, breathing, nausea and vomiting. As an alternative analgesia during chemical pleurodesis with doxycycline in patients with prolonged air leakage after lung resections for cancer, NMRC Oncology has proposed and patented a "Method of analgesia using a transdermal therapeutic system" (RF Patent No. 2712918). In clinical practice, the main indication for the use of fentanyl-based TTS is chronic pain syndrome in oncological diseases. When prescribing TTS to patients, the concentration of fentanyl in the applied method of pain relief should be taken into account. So, in the composition of the drug Fendivia®, the content of fentanyl varies in the range from 12.5 mcg/h to 100 mcg/h (1.38–11 mg).

Informed consent of the patient was obtained for anesthesia and processing of personal data. A day before the pleurodesis, a fentanyl-based patch was applied to the patient's shoulder at a dose of 75 mcg/hour. During the day, the patient's subjective well-being, objective respiratory and hemodynamic parameters were recorded, which, when using TTS, remained stable and corresponded to age-related physiological norms. An hour before the chemical pleurodesis, the blood gas composition was evaluated taking into account the following indicators: saturation ($SatO_2$) 93 %; partial voltage of carbon dioxide of arterial blood (pCO_2) 46 mmHg; partial voltage of oxygen of arterial blood (pO_2) 89 mmHg; pH 7.38; deficiency or excess of bases (BE) 2.8; bicarbonate (HCO_{3-}) 22.6 mmol/L. To determine the intensity of pain, a visual analog scale (VAS) was used; before manipulation, the subjective pain score was 0 points. 24 hours after the application of TTS, chemical pleurodesis was performed with doxycycline at a dosage of 500 mg dissolved in 20 ml of saline solution. The chemical pleurodesis was carried out by introducing the drug into the pleural drainage in compliance with the standards of asepsis and antiseptics in the patient's sitting position on the dressing table. During the manipulation, cardiomonitoring recorded the correct sinus rhythm; respiratory function without obvious signs of deficiency (respiratory rate 18 per minute, with pulse oximetry indicators $SatO_2$–94 %, without oxygen insufflation); pain symptoms were absent, subjective assessment of pain intensity by VAS – 1 point. Drowsiness, dizziness, nausea and vomiting characteristic of intramuscular or intravenous administration of narcotic drugs were absent. An hour after pleurodesis, the patient was active, with adequate breathing and stable hemodynamics, he did not complain of pain. Indicators of blood gas composition: $SatO_2$–94 %; partial voltage of arterial carbon dioxide (pCO_2) – 47 mmHg; partial voltage of arterial blood oxygen (pCO_2) – 99 mmHg; pH – 7.36; deficiency or excess of bases (VE) – 3.2; bicarbonate (HCO_{3-}) – 23.8 mmol/dL. The evaluation of laboratory parameters in dynamics demonstrates the stability of the gas composition of the patient's blood.

DISCUSSION

Most alveolar-pleural fistulas in the presence of drainage in the pleural cavity are eliminated spontaneously, and only in some cases prolonged air leakage requires special treatment. Despite the difference in approaches to the management of pleural drains, many surgeons prefer active aspiration of air from a Bobrov jar with a water level of about 20 cm until the morning of the 1st day of the postoperative period with the transition to a water gate, with which a small air leak is effectively controlled. However, with the appearance of subcutaneous emphysema or an increase in pneumothorax, especially a few days after surgery, you should return to active aspiration.

With the advent of portable pleural drainage systems, outpatient treatment of prolonged air discharge has become possible and widespread, provided adequate apposition of the visceral and parietal pleura is achieved. However, such tactics should be carefully weighed, taking into account the latest data on the need for re-hospitalization of 25 % of patients discharged with drainage systems after lung resection, who developed pleural empyema in almost 17 % of cases, which required lung decortication in 12 % of cases [16].

There is an obvious need to use more active methods of treating long-term air discharge, such as chemical pleurodesis with tetracycline, talc, iodine or silver nitrate, the introduction of a blood patch and endobronchial placement of a 1-way valve, which have shown high efficiency. Thus, with chemical pleurodesis, the frequency of resolution of prolonged

air leakage exceeds 95 %, with the installation of an endobronchial valve reaches 93 %, with the use of autoblood patches is 92 % [17].

Chemical pleurodesis by spraying talc is performed under general anesthesia, intrapleural administration of tetracycline or silver nitrate is accompanied by severe pain that can increase respiratory failure and cause cardiac arrhythmia [11]. In other words, chemical pleurodesis, despite its low invasiveness, is a very aggressive surgical manipulation against the patient, requiring adequate anesthetic measures to prevent the development of life-threatening pleuropulmonary shock.

When considering the pathological processes occurring in the body of patients after lung resection for cancer, it is necessary to take into account several factors: significant functional changes in gas exchange due to respiratory insufficiency and hypoxia and an imbalance of tissue and cellular oxidation with a violation of the effective biochemical maintenance of the body [18].

The subjective opinion of the patient in assessing the severity of pain (indicators of the visual-analog scale) and the analysis of laboratory parameters of the blood gas composition during chemical pleurodesis did not have negative dynamics, which may indicate adequate anesthesia and the absence of a stress reaction to aggressive surgical manipulation. On the contrary, in the absence of adequate anesthesia, the patient tries to neutralize pain by reducing the frequency of breathing, the depth of inspiration, suppressing coughing and, as a result, alveolar ventilation decreases with the phenomena of hypoxia and hypercapnia [12; 17]. The absence of changes in the parameters of the blood gas composition clearly demonstrates the stability of the functional state of the respiratory system, which is due to the effectiveness of the therapeutic measure.

The demonstration of clinical observation showed a number of advantages of the method of preventing the development of acute pain during chemical pleurodesis to eliminate prolonged air discharge after lung resection using fentanyl-based TTS. This method provides a multi-level and systematic approach to pain management, helps to reduce toxicity and minimizes the suppression of the central mechanisms of regulation of external respiration, without causing respiratory and cardiac disorders in patients who have undergone lung resection. A gradual increase in the concentration of fentanyl reaches its maximum value 24 hours after the application of TTS with the preservation of the analgesic effect for three days (Instructions for medical use of the drug Fendivia®). The absence of the need for additional anesthesia during and after chemical pleurodesis creates a positive psycho-emotional mood, contributing to a successful recovery. In addition, the advantage of the method is ease of use and cost-effectiveness – a single application of TTS provides sufficient analgesic effect.

The tactics of adequate anesthesia and leveling of the pain symptoms that have arisen, when providing high-tech medical care, must meet modern requirements for acute pain relief with minimal toxic effect, maximum safety of use, contributing to the normalization of the functional state of the patient's body in the early postoperative period. At FSBI National Medical Research Center of Oncology, a method for preventing acute pain during chemical pleurodesis in the early postoperative period due to prolonged leakage and/or persistent hydrothorax after lung resections for LC using a transdermal therapeutic system based on fentanyl has been introduced into everyday clinical practice.

CONCLUSION

Thus, the use of a transdermal therapeutic system for the purpose of relieving acute pain during chemical pleurodesis provides an adequate analgesic effect and prevents the development of cardiorespiratory and toxic complications. This method undoubtedly takes place in the treatment of pain syndrome in LC patients after radical surgical treatment.

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REVIEW

METHODS FOR MODELING TUMOR GROWTH IN MICE IN EXPERIMENTAL STUDIES OF HUMAN GASTRIC CANCER

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ABSTRACT

Gastric cancer (GC) is a group of malignant tumors originating from the gastric mucosa cells. The highest incidence of GC is recorded in Japan, China and Russia, and the lowest one in the USA and New Zealand. Extensive molecular genetic research of GC has revealed its heterogeneity associated with the genomic instability of the tumor and the complexity of its phenotype due to simultaneous changes in several oncogenes and suppressors. This was the basis for the creation of the GC classification by molecular subtypes. The creation of a realistic preclinical model is essential for translational GC studies. Cancer cell lines and xenografts derived from them are among the most common preclinical models. They are easy to generate, but they also have limitations, since these models cannot sufficiently reproduce the unique characteristics of each cancer patient. Patient-derived xenografts (PDX) are currently the best model for testing targets and predictors of response to therapy. PDX models are created by transplanting surgically resected human tumors into immunodeficient mice. These models maintain morphological similarity and replicate the molecular characteristics of parental tumors providing an indispensable tool for assessing anticancer drug response. Statistical data from preclinical studies with PDX models can significantly save the time and resources required for clinical trials. Transgenic and knockout mouse models are also widely used in scientific laboratories in order to study specific genetic pathways of oncogenesis and develop experimental therapy for GC. This review discusses the molecular classifications of GC and experimental murine models that reproduce cancer in situ and are a universal platform for preclinical research in experimental oncology.

Keywords:
gastric cancer, molecular subtypes, PDX model, orthotopic xenograft, genetically modified models, targeted therapy

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ОБЗОР

ПУТИ МОДЕЛИРОВАНИЯ ОПУХОЛЕВОГО РОСТА У МЫШЕЙ В ЭКСПЕРИМЕНТАЛЬНЫХ ИССЛЕДОВАНИЯХ РАКА ЖЕЛУДКА ЧЕЛОВЕКА

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РЕЗЮМЕ

Рак желудка (РЖ) – группа злокачественных опухолей, происходящих из клеток слизистой оболочки желудка. Самый высокий уровень заболеваемости РЖ регистрируется в Японии, Китае и России, низкий – в США и Новой Зеландии. Обширные молекулярно-генетические исследования рака желудка выявили его гетерогенность, что связано с геномной нестабильностью опухоли и сложностью её фенотипа за счет одновременных изменений в нескольких онкогенах и супрессорах. Это явилось основанием для создания классификации по молекулярным подтипам. Создание реалистичной доклинической модели имеет важное значение для трансляционных исследований рака желудка. Раковые клеточные линии и полученные из них ксенотрансплантаты – одни из самых распространенных доклинических моделей. Но, несмотря на легкость генерации, они имеют и ограничения, поскольку эти модели не могут в достаточной степени воспроизводить уникальные особенности каждого больного раком. Ксенотрансплантаты, полученные от пациентов (Patient-derived xenograft; PDX), в настоящее время являются лучшей моделью для проверки мишеней и предикторов ответа на терапию. PDX-модели создаются путем трансплантации хирургически резецированных опухолей человека иммунодефицитным мышам. Эти модели поддерживают морфологическое сходство и повторяют молекулярные характеристики исходных опухолей, таким образом, являясь незаменимым инструментом для оценки противоопухолевого лекарственного ответа. Статистические данные, полученные в ходе доклинических исследований с использованием PDX-моделей, помогают значительно сэкономить время и ресурсы, необходимые для клинических испытаний. Также с целью изучения специфических генетических путей онкогенеза и разработки экспериментальной терапии рака желудка в научных лабораториях широко применяют трансгенные и нокаутные мышиные модели. В данном обзоре обсуждаются молекулярные классификации РЖ и экспериментальные модели мышей, которые воспроизводят рак *in situ* и являются универсальной платформой для доклинических исследований в экспериментальной онкологии.

Ключевые слова:
рак желудка, молекулярные подтипы, PDX-модель, ортотопический ксенотрансплантат, генно-модифицированные модели, таргетная терапия

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Gastric cancer (GC) is the third most common cause of cancer death worldwide. Unfortunately, approximately 90 % of cases of the disease are diagnosed at late stages, which leads to unsatisfactory treatment results. The development of GC, along with hereditary factors, is influenced by environmental factors and the presence of H. pylori [1]. Nitroso compounds, smoking, and improper nutrition significantly increase the risk of GC. The pathological processes leading to GC include: atrophic gastritis, intestinal metaplasia and dysplasia. Resection in gastric ulcer disease increases the risk of adenocarcinoma by 2 times [2]. To date, there is a need to improve our understanding of the pathogenesis of GC and to create more effective and less toxic therapeutic drugs, which can only be achieved by using adequate preclinical models in the experiment. The search for literary sources was carried out using the databases Web of Science, Scopus, Pubmed and CyberLeninka by keywords: gastric cancer, mouse models, PDX, target therapy, transgenic and gene knockout mice, stomach cancer, mouse models, targeted therapy, transgenic and knockout mice.

Morphological classification of GC

According to the International Histological Classification (WHO 2010), GC can be divided into the following histological types: adenocarcinomas (papillary, tubular highly/moderately differentiated, low-differentiated, mucinous, ring-shaped cell), glandular cell carcinoma, squamous cell carcinoma, carcinosarcoma; choriocarcinomas; undifferentiated cancer [3].

The International TNM Classification of Stomach Cancer was revised in 2017 (8th edition) The American Joint Committee on Cancer (AJCC). This classification is applicable only for a confirmed diagnosis of gastric carcinoma. According to the TNM system, carcinoma is classified according to the following criteria: T – primary tumor (the degree of invasion of the tumor into the stomach wall and neighboring structures is estimated); N – regional lymph nodes (the number of regional lymph nodes affected by metastases is estimated); M – distant metastases (distant metastases and tumor cells in ascitic fluid are evaluated). There is a classification of gastric cancer according to Lauren (1965), according to which tumors can be represented by intestinal, diffuse and mixed types [4]. Stomach cancer is also divided into types according to the degree of differentiation and localization of the tumor. The proximal (cardiac) and distal varieties of GC differ markedly in epidemiology, etiology and pathogenesis, while the cardiac form of stomach cancer is similar in many ways to esophageal tumors [5].

Molecular genetic classifications of GC

The prognosis for the diagnosis of gastric cancer depends on the following indicators: the degree of invasion, the presence of metastases in the lymph nodes, the histological type of tumor and the stage of the process. But even for "twin" tumors with a similar size, stage and histotype, the prognosis can vary greatly. This may be due to the fact that standard morpho-histological criteria cannot fully predict the course of the disease. The Cancer Genome Atlas (TCGA) project performed a full-scale study of 295 tumor tissue samples from patients with stomach cancer using sequencing and bioinformatics methods. As a result, four molecular subtypes of gastric cancer were described: microsatellite instability (MSI), Epstein-Barr virus (EBV), chromosomal instability (CIN) and tumors with genomic stability (GS) [6]. The Asian Cancer Research Group (ACRG) has established another classification based on the transcriptomic tumor profile. The mRNA expression level of 300 patients' tumors was analyzed, on the basis of which 4 subtypes were identified: microsatellite instability (MSI), microsatellite stability with signs of transition from epithelium to mesenchyma (MSS/EMT), microsatellite stability with activity of tumor suppressor p53 (MSS/TP53) and microsatellite stability with loss of activity of suppressor p53 (MSS/TP53-). The Singapore-Duke research team analyzed gene expression in 248 gastric tumors and identified 3 subtypes (proliferative, metabolic and mesenchymal) [7].

The listed molecular classifications of gastric cancer describe the main pathways of the pathogenesis of this disease and facilitate the search for biomarkers and targets for targeted therapy in each tumor. Table 1 shows the main characteristics of all molecular subtypes of gastric cancer according to four classifications. Each subtype is characterized by specific gene mutations and changes in signaling pathways, as well as prognosis and response to chemotherapy.

One of the primary tasks is to study the molecular mechanisms underlying the pathogenesis of gastric cancer in order to develop new treatments that can improve patient survival. A number of chemically and genetically modified mouse models of stomach cancer have provided a significant insight into the contribution of genetic and environmental factors to the onset and progression of the disease.

Induced mouse models of stomach cancer

N-nitroso compounds (N-nitro-N-nitrosoguanidine (MNNG) and N-nitroso, N-methyl-N-nitrosourea (MNU)) – chemical carcinogens, the addition of which to drinking water induces gastric adenocarcinoma in rodents. The use of MNNG leads to adenomatous tumors only in the glandular epithelium of the stomach. At the same time, MNNG and MNNG cause adenocarcinomas in the mucosa of the antrum and rarely in the normal mucosa of the fundus [8; 9]. Butylated hydroxyanisole (BHA), an antioxidant used in food preservatives, when introduced into the diet of rodents for 2 years caused an increase in hyperplasia and papillomas in the cardiac part of the stomach [10]. ethylenedibromide (EDB), a soil, grain fumigant, was also used as a carcinogen, which, when administered to rats and mice, promoted oncogenesis in the cardiac part of the stomach [11].

After the World Health Organization (WHO) declared H. pylori one of the class I carcinogens, it became urgent to develop a correct animal model in vivo in order to study the pathogenesis mechanisms of this pathogen H. felis, a close relative of H. pylori isolated from the stomach of a cat, colonizes the gastric mucosa of a mouse and forms gastric lymphomas with somewhat similar patterns of human disease. Although these models provided the initial, very important experimental data, they did not completely simulate the process of human infection with H. pylori. Several strains of H. pylori adapted to mice with different genotypic combinations (SS1 and AM1) have been reported in the literature [12]. Most of the research is currently focused on the preventive effect of H. pylori eradication. It has been shown that eradication of helicobacter in mice can be useful for the prevention of stomach cancer, even if it is carried out relatively late in the natural history of the disease [13].

In 6–16 % of cases, stomach cancer worldwide is associated with Epstein-Barr virus (EBV) and is characterized by unique morpho-phenotypic features. In order to study the mechanisms of EBV-induced gastric cancer (EBV-GC), researchers have developed models of EBV engraftment using infected epithelial cell lines. The obtained xenographs showed moderately differentiated carcinomas without the formation of glands and areas of necrosis [14].

Genetically modified mouse models with GC

The appearance of genetically modified mouse models is due to gene transfer technologies and allows us to investigate the significance of various specific genetic pathways in oncogenesis: abnormal expression of growth factors and cytokines, mutations in oncogenes loci and tumor suppressor genes. A transgenic mouse is an animal whose genome contains an artificially introduced foreign gene (transgen), it is used most often to study the consequences of overexpression of genes. In a knockout mouse, certain genes are removed from the body or rendered inoperable. Transgenic and knockout mice infected with Helicobacter and treated with carcinogens develop precancerous and cancerous lesions and are used in the study of gene function and the development of experimental therapy [15].

The INS-GAS transgenic mouse contains two exons of the human gastrin gene that encode a progastrin precursor under the control of an insulin promoter. This model was used to study the effect of gastrin on the development of stomach cancer. The INS-GAS mice showed an increase in the maximum secretion of gastric acid and an increase in the number of parietal cells. At the age of 20 months, metaplasia, dysplasia and stomach cancer were observed in INS-GAS mice [16]. Infection of INS-GAS mice with H. felis or H. pylori led to accelerated carcinogenesis (7 months after infection) [17].

Gastrin-knockout mice (Gastrin knockout mice, GAS-/-) lack gastric acid secretion and, as a result, the architecture of the stomach is changed and the number of parietal cells is reduced. At the age of 12 months, these mice develop spontaneous tumors of the antrum of the stomach associated with excessive bacterial growth and inflammation [18].

To investigate the Wnt pathway in gastric carcinogenesis, K19-WNT1 transgenic mice were created that express Wnt1 in the gastric mucosa. K19 Mice-

Table 1. Classifications of molecular subtypes of human gastric cancer

GS molecular classification TCGA (The Cancer Genome Atlas)				
Molecular s/ type	Molecular characteristics	Localization	Sex/ age/ prognosis/ therapy	Type according to the classification of Lauren
MSI	• Hypermethylation of the MLH1 promoter • High mutation rate in PIK3CA, KRAS/ KRAS, JAK2, ERBB3, ERBB2, and EGFR genes • Changes in the two main genes of the class 1 histocompatibility complex (B2M and HLA-B)		Women/ elderly/ better prognosis/ lower frequency of metastasis into lymph nodes	Intestinal type
EBV	• DNA hypermethylation (CDKN2A promoter hypermethylation • Mutations in the PIK3CA, ARID1A genes and the B-cell lymphoma 6 corepressor gene • Amplification of PD-L1/2 and JAK2 • Activation of immune cell signaling pathways	The bottom and body of the stomach	Males/ the worst prognosis	
CIN	• Activation of receptor tyrosine kinase signaling pathways (RTK)/RAS • Amplification of MET, EGFR, HER2 and FGFR2high mutation rate of TP53 • Changes in tumor suppressor genes SMAD4 and APC	The area of the gastro-esophageal junction and the gastric cardia	The greatest benefit of adjuvant chemotherapy	Intestinal type
GS	• Mutations in CDH1 and RHO-family GTPase (RAS) genes • Activation of angiogenesis and cell adhesion (E-cadherin) • CLDN18/ARHGAP gene fusion		Young age/best prognosis/ least benefit from adjuvant chemotherapy	Diffuse type
GC molecular classification ACRG (Asian Cancer Research Group)				
Molecular s/ type	Molecular characteristics	Localization	Prognosis/recurrence rate/diagnosis	Type according to the classification of Lauren
MSI	• Mutations in the genes of the KRAS, ALK, ARID1A and PI3K pathways	Antral part of the stomach	The best prognosis/ lowest recurrence rate/ is diagnosed in the early stages (I-II)	Intestinal type
MSS/ EMT	• Loss of PDX1 expression • Reduction in the number of mutations compared to other subtypes		The worst prognosis/ highest recurrence rate/ is diagnosed in the late stages	Diffuse type
MSS/ TP53	• Associated with EBV infection • Mutations in APC, ARID1A, KRAS, PIK3CA and SMAD4 genes			
MSS/ TP53-	• High mutation rate of TP53 • Amplification of HER2, EGFR, cyclin E1 (CCNE1), CCND1, MDM2, Robo2, GATA6 and MYC			

Wnt1 were crossed with K19-C2ME transgenic mice to study the effect of Wnt and PGE2 on gastric carcinogenesis [19].

Cyclin-dependent kinase (CDK) inhibitor p27Kip1 plays an important role in the regulation of the cell cycle and is associated with many malignant neoplasms. p27Kip1 knockout mice develop mild gastric hyperplasia, occasional foci of moderate metaplasia and atypia or dysplasia of low degree. After infection with H. pylori, these mice have intestinal metaplasia, high-grade intraepithelial neoplasia of the stomach, polypoid adenomas and sometimes in situ carcinoma or intramucosal carcinoma. Thus, a mouse with p27Kip1 deficiency is a useful model for studying the pathogenesis of H. pylori in gastric carcinogenesis and for testing eradication and chemoprophylaxis strategies [20].

IL-1β-transgenic mice have in their genome an alien human interleukin-1ß gene, the increased production of which leads to the risk of H. pylori-induced hypochlorhydria and stomach cancer. Under conditions of H felis infection, these mice show accelerated development of gastric inflammation and carcinoma compared to control mice. There is also a decrease in the recruitment of macrophages and neutrophils in H. pylori infection and a decrease in the activation of NF-KB [21].

Transgenic COX-2 mice obtained on a C57BL/6 genetic background expressing full-sized human

Table 1. Classifications of molecular subtypes of human gastric cancer

Molecular classification of gastric cancer Singapore-Duke			
Molecular s/type	Molecular characteristics	Therapy sensitivity	Type according to the classification of Lauren
Proliferative	• Increased expression of cell cycle genes • Frequent mutations of the TP53 gene • DNA hypomethylation • Activation of E2F, MYC and RAS genes		Intestinal type
Metabolic	• Increased regulation of metabolism and digestion genes • Hyperactivation of antispasmodics-polypeptide-expressing pathway of metaplasia	Sensitive to 5-fluorouracil	
Mesenchymal	• Increased expression of cell adhesion-related genes with extracellular matrix-receptor interaction, focal adhesion and activation of EMT and cancer stem cell pathways • Changes in p53, TGFβ, VEGF, NF-κB, mTOR and Shh signaling pathways	Sensitive to PI3K/AKT/mTOR inhibitors	Diffuse type
Classification of internal subtypes of gastric cancer (Tan, et al.)			
Molecular s/type	Molecular characteristics	Prognosis/sensitivity to therapy	Type according to the classification of Lauren
G-INT	• High expression of carbohydrate and protein metabolism genes (FUT2) and cell adhesion (LGALS4, CDH17)	A successful forecast/Sensitive to 5-FU and oxaliplatin	Intestinal type
G-DIF	• High expression of cell proliferation (AURKB) and fatty acid metabolism (ELOVL5) genes	Poor prognosis/Sensitive to cisplatin	Diffuse type

COX-2 cDNA showed an increased incidence of MNU-induced gastric cancer [22].

Mutations of the K-ras gene are detected in diffuse (6 %) and intestinal (18 %) gastric cancers. K-ras transgenic mice with systemic activation of K-ras are characterized by changes in gastric cellular homeostasis, depletion of parietal cells, increased levels of inflammatory response factor (COX-2), stem cell marker (DCAMKL1, CD44), activated MAPK pathway, as well as hyperproliferation of the squamous epithelium in the gastric cardia and metaplasia in the glandular stomach, reminiscent of preneoplastic changes that occur during gastric carcinogenesis in a person. This suggests that mutant K-ras signaling modulates important molecular events in initiated gastric carcinogenesis [23].

Tff1-knockout mice –TFF1-/-) are mice in which the shamrock tumor suppressor gene factor 1 has been knocked out. TFF1 expression is often lost in gastric carcinomas and leads to activation of the β-catenin and AKT-GSK3ß signaling pathway. Homozygous mutant Tff1 (TFF1-/-) mice develop anthropiloric adenoma and even multifocal carcinomas, which is consistent with increased indicators of inflammation of Tff1+/- mice used for studies of gene heterozygosity and transcript regulation [24].

Xenogenic models of GC

The preclinical phase of gastric cancer research should include in vivo models that accurately simulate the clinical situation in the human body. To promote the concept of precision medicine, xenogenic models of gastric cancer have been developed, capable of reproducing the histological and genomic features of a patient's tumor and predicting the reaction to the antitumor drugs under study. In the creation of experimental models of stomach cancer, special thymus-free Bald/nude mice with a mutation in the Foxn1 gene are used [25]. Deficiency of T-lymphocytes significantly weakens the immunity of mice, which contributes to the engraftment, growth and metastasis of tumor cells in xenografts after implantation [26]. However, intact innate immunity and high NK cell activity may limit the rate of engraftment of most primary solid tumors. Also in experimental oncology, mice with severe combined immunodeficiency in T and B lymphocytes (SCID mice), mice with severe immunodeficiency and diabetes (NOD-SCID mice) and mice with the absence of mature T, B and NK cells, dysfunction of macrophages and dendritic cells and reduced activity of the complement system (NOG mice) are used [27].

Xenografts derived from cancer cell lines (cell-line-derived xenografts; CDX) are frequently used model systems in the field of studying the genetics of gastric cancer. However, such models have a number of limitations: the inability to reproduce intra-tumor heterogeneity and microenvironment, weak predictive ability to assess the effectiveness of drug treatment, highly aggressive cell lines and their susceptibility to genetic changes due to prolonged in vitro cultivation [28].

Xenografts obtained from a patient (patient-derived xenografts – PDX) are currently the best preclinical model of GC for testing targets and predictors of response to therapy. Modern procedures for creating PDX models include both heterotopic (subcutaneous) and orthotopic methods of transplantation. Heterotopic xenografts are obtained by implanting human tumor tissue or cells into a mouse area unrelated to the original tumor site, usually subcutaneously in the lateral or dorsal region or subrenally. The obtained models are morphologically and biochemically similar to the primary tumors of donors, but they have a number of limitations, such as abnormal microenvironment and pseudocapsule. In a large-scale study by Takeshi Kuwata et al. Out of 232 primary tumors of patients with diagnosed gastric adenocarcinoma, 35 PDX models and 32 CDX models were created. Most PDX tumors showed histologically consistent morphology with primary tumors, and more than half of CDX had histologically confirmed inconsistency with primary tumors. PDX, whose donors had lesions with lymph node metastases, had a higher rate of engraftment. In more than half of the cases, lymphoproliferative lesions obtained from B-lymphocytes were observed at the site of engraftment of the donor's tissue [29]. Also in this study, it was shown that none of the subcutaneous PDX and CDX models developed matastatic lesions in mice. In Hernandez MC, et al. the possibility of creating subcutaneous PDX models from biopsy samples of patients with unresectable or metastatic disease in clinical settings has been shown [30].

To study the mechanisms of tumor metastasis, orthotopic mouse models are used, which are created by transplanting fragments of patient material into the organs of tumor origin to

immunodeficient mice. The technique of creating an orthotopic xenograft has been improved from the "stitching" method to the "sticking" method. Illert B, et al. In 2003, a technique was described for creating an orthotopic xenograft of GC, in which the serous membrane of the anterior wall of the mouse stomach was removed with a scalpel and 2–3 fragments of the donor tumor were sewn with non-absorbable sutures. Primary tumor growth was observed in 90 % of mice and metastases spread to the liver (70 %), lungs (10 %) and lymph nodes (10 %) [31]. Jones-Bolin and his research group developed a technique for creating orthotopic xenografts by stitching two fragments of a 2 × 2 mm^3 donor tumor with the dorsal side of the mouse stomach in the middle part using 2–3 nodes. The tumor grew in more than 90 % of the animals, and metastases developed in the liver (40 %), lymph nodes (40 %) and the surface of the peritoneum (60 %) [32]. In 2009, a group of scientists from Germany proposed a method for creating a PDX model by fixing a fragment of a donor tumor in a tissue pocket of the stomach with one drop of tissue glue. The pocket was made either in the submucosa of the distal stomach or in the cardia. Orthotopic tumor growth was observed in 100 % of cases, metastases spread to the lungs, pancreas, liver, intestines and kidneys [33]. In the studies described above, animals were slaughtered if the tumor increased in diameter to 10 mm or the general condition worsened. Li, et al. a method for generating a PDX model by "gluing" a tumor fragment into a tissue pouch made in the middle of the large curvature of the recipient mouse's stomach was published. 100 % tumor engraftment was observed, metastases after necropsy were found in lymph nodes (79 %), liver (91.5 %), kidneys (62.5 %) [34]. In a study by Busuttil, et al. three gastric cancer cell lines (MKN45, AGS, MKN28) were taken, 50 microliters of cancer cell suspension and Matrigel were inoculated into the subserous layer of the antrum of the stomach. Successful engraftment was observed in 76 % of cases, metastases were found in the thoracic and abdominal regions. As a result of the analysis of the above-mentioned works, it can be concluded that the rate of engraftment of the donor tumor and the spread of metastases do not depend on the place of implantation of the sample into the stomach.

The use of PDX models of gastric cancer in the development of molecular targeted therapy

The lack of standard chemotherapy strategies and the low overall survival rate create a need for a treatment method with more specific anticancer efficacy and low non-selective toxicity and resistance. As a result of molecular genetic studies of gastric cancer, special attention was focused on understanding the mechanisms underlying targeted therapy of advanced cancer. Targeted inhibitors effectively regulate the work of signaling pathways involved in tumor growth processes, which ensures better specificity and selectivity of anticancer therapy. PDX models are an important tool for screening patients who may benefit from targeted therapy.

The epidermal growth factor receptor (EGFR) should be considered as a target for targeted therapy of gastric cancer in the first place. It is a transmembrane glycoprotein with tyrosine kinase activity. Also, the family of epidermal growth factor receptors is represented by its other types: HER2, HER3 and HER4. These receptors are involved in the activation of signaling pathways that promote proliferation, differentiation, cell invasion and suppression of apoptosis. Therefore, it is expected that drugs targeting EGFR and HER2 will improve the therapeutic effectiveness of the treatment of stomach cancer. An example is the drug Cetuximab, which is a monoclonal antibody and specifically binds to the extracellular domain of EGFR. In a Chinese study by Wang X, et al. It was found that the number of copies of the EGFR gene is a prognostic biomarker of the effectiveness of cetuximab in the PDX model of gastric cancer [35]. A monoclonal antibody that inhibits the formation of ligand-dependent heterodimers of the HER2 receptor with other representatives of the family – pertuzumab in combination with trastuzumab, capecitabine and cisplatin – demonstrate pronounced antiproliferative and antitumor activity on xenographic models of gastric cancer with HER2 overexpression. Trastuzumab, in turn, is a humanized monoclonal antibody that binds to the HER2 receptor to eliminate or reduce the activity of the receptor [36]. Preclinical studies have shown that pertuzumab in combination with trastuzumab enhances the antitumor effect in the HER2-positive xenograft model of gastric cancer [37].

Studies have found that the dysregulation of the MET signaling pathway occurs in gastric cancer, which correlates with poor clinical outcomes and drug resistance. At the same time, the drug volitinib (EGFR inhibitor) demonstrates strong antitumor activity in PDX models with overexpression of MET and pMET by inhibiting the PI3K/mTOR pathway. In addition, the efficacy of two EGFR monoclonal antibodies (BK011 and cetuximab) was evaluated on five PDX models with different levels of EGFR expression or amplification. Both BK011 and cetuximab induced complete regression of the PDX model with EGFR amplification [38].

Recent studies have shown that monotherapy with afatinib, a selective irreversible inhibitor of protein kinase receptors of the ErbB family, led to regression of HER2-amplified GC by prolonging inhibition of HER3 and EGFR, which was superior to trastuzumab monotherapy. In Zuhua Chen et al. PDX models of GC with EGFR amplification, EGFR overexpression, or HER2 amplification have been shown to be treatable with afatinib. Afatinib is a pan-HER inhibitor; Therefore, further studies are needed to determine whether afatinib is effective in patients with changes in the EGRF family [39].

Lapatinib is a dual inhibitor of tyrosine kinase receptors type 1 and type 2 (ErbB1 and ErbB2). PDX models with high microvessel density are more sensitive to apatinib compared to other models with low CD31 expression [40].

Violation of the regulation of the cell cycle in GC occurs quite often, while amplification of the CCNE1, CCND1 and CDK4 genes is observed/6. In this case, cyclin-dependent kinase inhibitors can be used. CDK1/2/9 inhibitor AZD5438 was shown to have significant tumor inhibition in two PDX models with a high CCNE1 copy number [41].

Thus, PDX are universal models for evaluating potential targeted molecules and serve as a screening tool for patients for targeted therapy.

CONCLUSION

As precision medicine develops, molecular-oriented therapeutic strategies should be individualized for cancer patients. When creating preclinical models, it is important to evaluate the differentiation and classification of xenografts according to Loren, since changes in these characteristics can lead to a shift in the genetic and histopathological parameters of xenografts in relation to the primary tumor. The reason for such changes is the high heterogeneity of stomach cancer. Mouse models are an important experimental platform (tool) for studying the molecular mechanisms of the occurrence and development of gastric cancer, as well as for screening and testing the effectiveness of new targeted drugs that target tumor cells with virtually no damaging effect on normal tissues. Further study of the molecular features of the pathogenesis of GC and the use of xenogenic, "avatar", mouse models to predict the reaction to the studied drugs in patients' tumors should make a significant contribution to the development of translational medicine.

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REVIEW

MOLECULAR TARGETS OF NON-SMALL CELL LUNG CANCER OUTSIDE THE "TOP THREE"

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ABSTRACT

Lung cancer (LC) is the most frequent cancer and the leading cause of cancer death in men in Russia and other countries. The majority of new LC cases are diagnosed in patients over 65 years old, and the number is growing. LC is a heterogeneous group of malignant tumors with different genetic and biological characteristics. Although smoking is considered the leading cause of non-small cell lung cancer (NSCLC), genetic predisposition and environmental influences are responsible for 10–15 % of cases. The tactics of treating patients with NSCLC alone has long been developed and, as a rule, does not cause any difficulties. Surgery is the main treatment for the early NSCLC stages. However, as the disease progresses the risk of metastasis increases and the effectiveness of the surgical treatment decreases sharply. The development of new medical therapy regimens and the use of targeted drugs have improved the survival rate of LC patients with carcinogenic driver mutations. Personalized treatments are becoming more available as sequencing technology develops. Targeted therapy undoubtedly improves the outcomes of NSCLC patients with tumors carrying carcinogenic EGFR driver mutations, ALK fusion, and ROS1 rearrangement. However, in addition to the main molecular targets, other genetic alterations have been identified and studied, such as: KRAS, MET, RET, HER2 and NRG. Some of these mutations (BRAF and NTRK) are already available for targeted therapy. The list of genetic alterations is growing and the molecular profiling of patients with NSCLC is expanding, which is very important in the progression of the disease. Molecular genetic selection identifies specific groups of patients who benefit from targeted therapy and provides insight into the potential mechanisms of resistance. Despite the progress made, further studies are needed to clarify interactions with immune cells in the tumor microenvironment as factors affecting survival. In addition, it is becoming increasingly important to study targeted therapy in the context of multimodal treatment. This review is devoted to understanding genetic changes, searching for new genetic targets, problems and future directions of development of targeted therapy in the treatment of patients with lung tumors.

Keywords:
genetic alterations, KRAS, BRAF, HER2, NTRK, RET, MET, targeted therapy

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ОБЗОР

МОЛЕКУЛЯРНЫЕ МИШЕНИ НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЕГКОГО ВНЕ «ГЛАВНОЙ ТРОЙКИ»

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РЕЗЮМЕ

Рак легкого (РЛ) занимает первое место в структуре общей онкологической заболеваемости и смертности у мужчин как в России, так и в зарубежных странах. Большинство новых случаев РЛ диагностируется у пациентов старше 65 лет, и в последние годы наблюдается тенденция к увеличению данного показателя. РЛ представляет собой гетерогенную группу злокачественных опухолей с различными генетическими и биологическими характеристиками. Несмотря на то, что курение считается основной причиной немелкоклеточного рака легкого (НМРЛ), генетическая предрасположенность и воздействие окружающей являются причиной развития 10–15 % случаев заболевания. Тактика лечения пациентов с одним НМРЛ давно отработана и, как правило, не вызывает никаких трудностей. Хирургическое вмешательство является основным методом лечения ранних стадий НМРЛ. Однако, по мере прогрессирования заболевания возрастает риск метастазирования, и в этом случае эффективность хирургического метода лечения резко снижается. Разработка новых схем лекарственной терапии, использование таргетных препаратов улучшила выживаемость больных с РЛ, несущими онкогенные драйверные мутации. Персонифицированное лечение становится все более доступным по мере развития технологии секвенирования. Таргетная терапия несомненно улучшает исходы больных НМРЛ, опухоли которых несут онкогенные драйверные мутации EGFR, слияние ALK и реаранжировки ROS1. Однако, помимо основных молекулярных мишеней, выявлены и изучаются другие генетические альтерации, такие как: вирусный онкоген Kirsten RAS (KPAS), MET, RET, HER2 и NRG. Некоторые из таких мутаций (BRAF и NTRK) уже доступны для таргетной терапии. Перечень генетических альтераций растет и расширяется молекулярное профилирование больных НМРЛ, что имеет весьма важное значение при прогрессировании заболевания. Молекулярно-генетический отбор идентифицирует конкретные группы пациентов, которые получают пользу от таргетной терапии и дает представление о потенциальных механизмах резистентности. Несмотря на достигнутый прогресс, необходимы дальнейшие исследования для выяснения взаимодействий с иммунными клетками в микроокружении опухоли как факторов, влияющих на выживаемость. Кроме того, становится все более важным изучение таргетной терапии в контексте мультимодального лечения. Настоящий обзор посвящен пониманию генетических изменений, поиску новых генетических мишеней, проблемам и будущим направлениям развития таргетной терапии в лечении пациентов с опухолями легких.

Ключевые слова:
генетические альтерации, KRAS, BRAF, HER2, NTRK, RET, MET, таргетная терапия

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INTRODUCTION

Lung cancer is a heterogeneous genomic disease [1]. Despite the fact that smoking is considered the main cause of non-small-cell lung cancer (NSCLC), genetic predisposition and environmental exposure are responsible for the development of 10–15 % of cases of the disease. Targeted therapy improved the survival of patients with tumors carrying oncogenic driver mutations [2]. There is an obvious need to deepen knowledge about genetic changes in NSCLC in order to create new targeted drugs. This review examines molecular genetic targets that are outside of the epidermal growth factor receptor (UPAC) gene mutation, ADC fusion and ROS1 rearrangement, new drugs, problems and future directions of targeted therapy development.

Viral oncogene KRAS

The viral oncogene Kirsten RAS (KRAS) is the most frequently mutating isoform of the RAS family and is found in 22 % of solid tumors, being one of the most common oncogenic driver mutations in cancer [3]. KRAS mutations are present in approximately 20–30 % of NSCLC patients. Despite the early discovery of the mutation, KRAS-mutant NSCLC is very heterogeneous, and therapy aimed at the KRAS mutation is just beginning to develop [4]. Most KRAS mutations were found in exons 12 and 13: 012C – 39 %, G12V –18–21 % and G12D – 17–18 % [5]. The presence of the KRAS mutation in the tumor is associated with a worse prognosis of NSCLC [6].

KRAS is one of the 4 proteins encoded by the RAS gene, guanosine triphosphate binds to KRAS in the active state, and guanosine diphosphate binds to KRAS in the inactive state. Activating point KRAS mutations initiate oncogenesis by losing the activity of GTPases (GTPase – guanosine triphosphate hydrolase enzymes), which leads to an active state and constantly activates the downstream signaling pathways of PI3K and MARK, causing resistance of NSCLC to existing drug therapy methods [7].

Early attempts to use the KRAS mutation as a target for targeted therapy failed due to the lack of known allosteric binding sites, alternative pathways, and the high affinity of the protein to the active guanosine triphosphate-bound state [8]. Combination therapy with (MEK1/MEK2) MARK kinase inhibitors formed the basis of a phase 2 clinical trial in patients with advanced KRAS-mutant NSCLC. The combination of selumetinib with docetaxel resulted in an increase in the overall response to treatment (ORR- Overall Tumor Responses Rate) to 37 % and the duration of median survival to progression (RFS) by 3.2 months. compared to patients who received only docetaxel. In the combination therapy group, there was an increase in the number of adverse toxic events of the 3rd degree by 15 %, among which neutropenia, febrile neutropenia and asthenia prevailed [9]. As a result, the study demonstrated sufficient effectiveness, but at the expense of increased toxicity. Another phase 1 study showed that in patients with KRAS-mutant NSCLC treated with trametinib with docetaxel, ORR reached 24 %, while in patients treated with trametinib with pemetrexed, this indicator was 17 % [10].

The first phase 1 clinical trial of the small molecule AMG 510, which specifically and irreversibly inhibits the KRAS G12C mutation by blocking it in the bound state, presented immediate results of treatment of 22 patients with progressive solid tumors carrying the KRAS G12C mutation. Of the 6 patients with NSCLC, 2 had a partial response after 6 weeks of treatment and 2 more had stabilization of the disease. The average duration of therapy, which was well tolerated, was 9.7 weeks [11]. Adverse toxic phenomena of the 1st degree were noted in 68 % of observations; two toxic reactions of the 3rd degree, namely anemia and diarrhea, have been reported.

A study examining KRAS co-mutations found lower response rates of KRAS-mutant lung adenocarcinomas with inactivation of KEAR1 (Kelch-like ECH-associated protein 1) [12]. A subset of tumors resistant to anti-PD1 antibodies was characterized by low expression of PD-L1 and inactivation of the tumor suppressor gene STK11/LKB1 (Serine – Threonine Kinase 11/Liver kinase B1), which led to the accumulation of tumor-associated neutrophils with a suppressive effect on T cells [13]. Somatic mutations of LCV1 are noted in about 30 % of lung adenocarcinomas. Preliminary studies have shown that NSCLC with KRAS/LKB1 co-mutations clearly responds to targeted therapy. A study on mice with KRAS/LKB1 or KRAS/p53 mutations revealed a selective apoptotic response of KRAS/LKB1 – mutant NSCLC to the metabolic drug phenformin, an analog of metfurmin. Apoptosis is observed in NSCLC cell lines with the LKB1 mutation, but not with wild-type KRAS [14]. Thus, KRAS – mutant NSCLC is once again becoming a rapidly developing area of research for

the development of new treatment options for patients with unrealized liver needs.

BRAF proto-oncogene

The BRAF proto-oncogene encodes serine/threonine kinase, which is located below RAS and leads to the transmission of signals via RAS-RAF (rapidly accelerated fibrosrcoma) – MARK (mitogen-activated protein kinase) – MARK/ERK (extracellular-signal-regulated kinase) MARK/ERK signaling pathway, which is a key molecular cascade regulating cell growth [15]. After the discovery of BRAF mutations in melanoma, mutant BRAF was found to mediate lung adenocarcinoma carcinogenesis. BRAF mutations are detected in 2–3 % of lung adenocarcinomas and in 50–75 % are represented by the BRAF V600E mutation, more often observed in smokers or quit smoking patients [16; 17].

Vemurafenib has demonstrated its effectiveness in patients with generalized NSCLC carrying the BRAF V600E mutation [18; 19]. Dabrafenib was studied in a phase 2 clinical trial in patients with BRAF V600E mutant metastatic NSCLC [20]. ORR reached 33 %, and the median overall survival(s) was 12.7 months. The combination of dabrafenib and trametinib was studied in another phase 2 study in patients with BRAF V600E mutant NSCLC. Combination therapy led to an increase in ORR to 63.2 % and was approved by the European Medicines Agency and the US FDA (Food and Drug Administration) for the treatment of patients with stage IV BRAF V600E mutant NSCLC [7].

Neurotrophin tyrosine kinase receptor

The tropomyosin receptor kinase (TRK) gene encodes tyrosine kinase receptors for neurotrophins found in many tissues and associated with the nerve growth factor family. Three members of the family are proto-oncogenes encoded by NTRK1, NTRK2 and NTAK3, which respectively produce TrkA, TrkB and THC proteins, activation of which leads to the transmission of signals along the signaling pathways of MARK and ACT, leading to cell proliferation, differentiation and survival [21]. NTRK rearrangements occurring in all 3 genes have been identified in various malignancies, including lung cancer [22]. Less than 1 % of cases of NSCLC carry NTRK mergers and occur in men and women of different ages with different smoking history [23].

Numerous tyrosine kinase inhibitors (TRK) are being investigated in the treatment of malignant tumors with altered NTRK. The US FDA approved the appointment of larotrectinib and entrectinib for the treatment of solid tumors with NTRK mutations in adults and children [21]. The first report of a patient with a regression of the tumor carrier NTRK fusion, achieved as a result of the appointment of a selective tyrosine kinase inhibitor larotrectinib, dates back to 2015 [24]. Subsequently, the inhibition of tumor growth was confirmed experimentally. In a phase 1 clinical trial, larotrectinib was studied in adults and children with different tumors carrying NTRK mergers. In 55 patients with 13 types of tumors included in the study, the most common were NTRK3 mergers (n = 29), followed by NTRK1 (n = 25) and NTRK2 (n = 1). As a result, the study demonstrated an overall response rate of 75 % to therapy [25].

The results of the phase 1 study of entrectinib indicated the antitumor activity of the drug in a patient with NTRK 1 positive NSCLC [26].

Analysis of the results of 3 studies of entrectinib, which included 54 patients with NTRK or ROS1 positive tumors, demonstrated an ORR equal to 57 % with a median progression-free survival of 11.2 months and a median of 20.9 months [27]. Additional clinical trials of TRK inhibitors are currently underway.

Epidermal growth factor receptor 2

The human epidermal growth factor receptor 2 (NR2), a member of the ErbB receptor tyrosine kinase family, activates signaling via the RISC–ACT and MEK–EAK signaling pathways. NONR2 is activated by homo- and heterodimerization with other members of the ErbB family, but has no established ligand [28]. Overexpression of NR2 is observed in 13–20 % of cases of NSCLC and is more common in women who have never smoked with adenocarcinoma [29]. HER2 mutations are oncogenic and lead to constitutive HER2 phosphorylation and activation of EGFR stimulating signaling pathways. Amplification and mutations of NONR2 are rare, accounting for 9 % and 3 % of cases of NSCLC, respectively [30]. NONR2 mutations usually occur in exons 18–21, usually in exon 20 in codon 776 with a 12-pair duplication/insertion of the YVMA amino acid sequence. It remains unclear whether patients with NONR2 mutant NSCLC have a worse outcome compared to other patients.

A prospective study of the pan-HER tyrosine kinase inhibitor dacomitinib, irreversibly binding NONR2, NONR1(EGFR) and HER4, included 26 patients with NONR2-mutated and 4 with NONR2-amplified NS-

CLC [31]. The overall response rate to therapy was 12 % in patients with NONR2 – mutant NSCLC; in patients with NONR2-amplified NSCLC, no tumor response was registered in any observation. Median RES was 3 months for all patients. In the group of NONR2 mutant tumors, the median progression-free survival was also 3 months. with a one-year OV equal to 44 %. Pan-HER tyrosine kinase inhibitor afatinib, has shown limited action in NONR2-mutant NSCLC. The study of afatinib activity showed a median progression-free survival of 15.9 weeks, and a median of 56 weeks [32].

Other low-molecular-weight TCS are also being tested. Thus, with monotherapy with the irreversible pan-HER inhibitor neratinib, the median PFS was 2.9 months. Median PFS increased to 4 months. with the combined appointment of neratinirb and temsirolimus [33].

It was found that the response to neratinib varied depending on co-mutations and parallel activation of signaling pathways. Patients with NONR2-mutant NSCLC were characterized by a very low response rate and often had co-mutations in TP53 and NONR3. Activation of the RAS/RAF signaling pathway coinciding with aberrations of cell cycle control points was associated with worse results and generally with a lack of clinical efficacy [34].

Antibody-based drugs have shown efficacy against NONR2-mutant NSCLC. In a phase 2 study, 18 patients with NONR2 mutant lung adenocarcinomas were treated with T-DM1 with a 44 % partial response rate and a median PFS of 5 months [35].

A European retrospective study analyzed data from 101 patients with NONR2-mutant NSCLC who received chemotherapy and/or NONR2-targeted therapy. The median OV was 24 months for all patients, despite whether or not targeted therapy was performed. The overall response to treatment was highest in patients who received trastuzumab with or without chemotherapy, or in those who received T-DM1 with a median PFS of 4.8 months [36].

Mesenchymal-epithelial junction (MET) is a protooncogene encoding transmembrane METH. Binding of the hepatocyte growth factor ligand by it activates the signaling pathways PI3K/ACT, MARK, NF-KB, as well as a signal transductor and activator of transcription proteins that promote proliferation, increase cell mobility and invasion, block apoptosis. METH alterations are found in many cancers, including NSCLC. They induce tumor progression through gene amplification, mutations, rearrangements, overexpression and phosphorylation of proteins [37].

MET-positive NSCLC is most often manifested by overexpression of proteins, while MET amplification is relatively rare and is observed in about 2.2 % of newly diagnosed cases of adenocarcinoma and up to 7 % of cases of all NSCLC. The amplification of the MET gene is a negative prognostic factor in the surgical treatment of NSCLC with an OV equal to 25.5 months in patients with 5 or more copies per cell versus 47.5 months for patients with less than 5 copies per cell, respectively. KIF5B MergerMETH was registered in lung adenocarcinoma, other METH rearrangements are rare [38].

Alterations of the MET gene in exon 14, observed in 4 % of lung adenocarcinomas, are diverse and lead to carcinogenesis; changes are associated with age and a long history of smoking [39]. Substitutions of bases or deletions in MET that violate the 3' or 5' sites of the intron 14 junction lead to the omission of the 14 exon of MET. The omission of exon 14 causes a decrease in ubiquitination and degradation of METH, which leads to an increase in the level of METH and the downward transmission of a signal stimulating carcinogenesis. Alterations of the 14 exon of MET vary widely. 126 different variants were identified in 223 different aberrations of 14 exons [40].

Multi-purpose TKI and TKI with increased sensitivity to METH are used against METH alterations. In addition, monoclonal antibodies are being studied in patients with METH-driver tumors. The dual MET/ALK inhibitor crizotinib demonstrated objective responses of MET-amplified and MET-mutant NSCLC [40]. Additionally, the combination of crizotinib with cabozantinib causes an antitumor response in patients with lung adenocarcinoma carrying a MET mutation in exon 14. A phase 1 clinical study showed that in patients with NSCLC with a high level of METH amplification, crizotinib has antitumor activity with a median PFS of 6.7 months [41].

A phase 2 study considered a specific MET inhibitor for the MET mutant in exon 14 of NSCLC-tepotinib. In patients with MET mutation identification by liquid biopsy, preliminary results showed a 50 % level of objective response with a median PSF of 9.5 months; in patients with mutation detection in tumor tissue during biopsy, the level of objective response was 45.1 % with a median PSF of 10.8 months [42].

In another phase 2 study, a specific MET inhibitor capmatinib was studied in progressive NSCLC

carrying a MET mutation in exon 14. According to preliminary data, the level of objective response was 40.6 %, and the median PFS was 5.42 months. Previously untreated patients had an objective response rate of 67.9 % and a median PFS of 9.69 months [43]. Kapmatinib has demonstrated action against brain metastases and good tolerability.

A specific biomarker for the selection of patients remains unidentified, therefore, at present, the detection of mutation is a predictor of an effective response to NONR2-targeted therapy. Molecular aberrations in NONR2 mutant NSCLC are heterogeneous, which determines the different effectiveness of NONR2 kinase inhibitors. It is necessary to take into account important characteristics such as the type of mutation, the presence of NONR2 amplification, expression and parallel activation of signaling pathways.

Proto-oncogene (RET)

RET – receptor tyrosine kinase mediating the development of the neural crest, the activation of which causes cell proliferation, migration and differentiation of cells [44]. Alterations of RET genes are most common in thyroid and lung cancers [45]. With NSCLC, fusion with KIF5B is most common. RET mergers lead to ligand-independent dimerization and activation of the downstream signaling pathway.

RET mergers occur in approximately 1.4 % of cases of NSCLC and in 1.7 % of lung adenocarcinomas and are found mainly in non-smoking patients older than 60 years. An NGS study of more than 4,800 patients with various malignancies showed that the altered status of the RET gene occurs in 1.8 % of cases, most of which had concomitant genomic changes, suggesting that successful treatment should include individual combined approaches [46].

Various multikinase TKIs have been studied with NSCLC carrying RET rearrangements. A prospective phase II study to evaluate the efficacy of cabozantinib in 25 patients with RET-positive lung adenocarcinoma revealed a 28 % response rate to therapy with a median PFS of 5.5 months and median S = 9.9 months [47]. A similar clinical study of vandetanib in 19 patients with PFS-positive NSCLC showed a 53 % overall response rate with a median RET of 4.7 months [48]. The global multicenter registry contains data on the results of treatment of 165 patients with RET-positive NSCLC, of which 53 were prescribed at least one RET inhibitor therapy [49]. The use of cabozantinib, sunitinib and vandetanib gave an overall response rate of 37 %, 22 % and 18 %, respectively, in addition, lenvatinib and nantedanib also caused a tumor response. In all patients, the median PFS was 2.3 months, and the median S reached 6.8 months. Despite the fact that studies have confirmed the inhibitory activity of multikinase TKI in RET-positive NSCLC, the reaction to them was modest and short-lived.

RET-specific inhibitors are being developed in the hope of overcoming the limitations inherent in multikinase inhibitors. A report on patients with RET-positive malignancies showed that the powerful KW inhibitor LOXO-292 caused a general response to treatment in 65 % of 26 patients with NSCLC. BLU-667, another selective RET inhibitor, has demonstrated activity in preclinical studies and objective tumor responses in patients with RET-positive NSCLC [50]. A study of 48 patients showed a 58 % overall response rate for the entire group, in addition, BLU-667 is effective in patients with various KW mergers and metastases [51; 52].

Neuroregulin 1

The neuregulin 1 gene (NRG1) encodes the neuregulin protein. Unlike other mergers in NSCLC, NRG1 encodes the tyrosine kinase receptor ligand HERZ and HER4. In these mergers, NRG1 is a 3' partner, other genes such as CD74, RBPMS, WRN and SDC4 are 5' partners. The EGF domain NRG1, located in the carboxy-terminal region, is necessary for the interaction of receptors. NRG1 mergers in NSCLC samples are detected in isolation from other known driver mutations [53; 54]. CD74-NRG1 mergers account for 1.7 % of lung adenocarcinomas and are most often found in invasive mucinous adenocarcinoma subtype of NSCLC, which accounts for 2 % to 10 % of all cases of lung adenocarcinoma [55]. CD74-NRG1 fusion causes activation of the PI3K ACT signaling pathway, which induces carcinogenesis.

Despite the small amount of data available, an in vitro study showed that lapatinib and afatinib inhibit the phosphorylation of HER2, HER3 and ERK produced by CD74-NERG1 fusion. In two cases of NSCLC carrying NRG1 fusion, a response to therapy with afatinib, an inhibitor of HER2, was noted. Median PFS with NSCLC carrying the fusion of SLC3A2-NRG1 and CD74-NRG1 was 12 months and 10 months, respectively. Recently, it was reported that a patient with CD74-NRG1-positive NSCLC reacted to the introduction of a monoclonal antibody against HER3 for 19 months [56].

CONCLUSION

Lung cancer is a heterogeneous group of malignant tumors with different genetic and biological characteristics. Molecular genetic studies determine the appropriate therapy for many patients with NSCLC by precision drug exposure to specific alterations. The list of genetic alterations is growing and expanding molecular profiling of patients with NSCLC is very important in the progression of the disease. Molecular genetic selection identifies specific groups of patients who benefit from targeted therapy and provides insight into the potential mechanisms of resistance. Despite the progress made, further studies are needed to clarify interactions with immune cells in the tumor microenvironment as factors affecting survival. In addition, it is becoming increasingly important to study targeted therapy in the context of multimodal treatment.

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