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Efficacy of trastuzumab in treatment of disseminated HER2-positive ductal adenocarcinoma of the submandibular gland (a case report)

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Ductal adenocarcinoma of the gland is a rare malignancy characterized by high rate of metastasis and poor survival. Immunohistochemical findings indicate that 40 % of patients demonstrate overexpression of the human epidermal growth factor receptor 2 (HER2) (2–3+). In patients with distant metastases, targeted anti-HER2 therapy is the only effective method.

This article describes our experience of successful targeted therapy in a patient with HER2-positive ductal adenocarcinoma of the submandibular gland.

Keywords: submandibular gland, ductal adenocarcinoma, epidermal growth factor receptor type 2, distant metastases, trastuzumab, paclitaxel

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Introduction

Ductal adenocarcinoma accounts for 3–9 % of all gland cancers [1, 2]. This disorder is characterized by rapid progression and poor outcomes. The 3-year mortality rate reaches 3 % [3]. The efficacy of standard chemotherapeutic regimens for recurrent and metastatic disease is relatively low with an objective response rate of 20–30 % [4].

Parotid gland cancers encompass various histological variants with a wide range of genetic impairments that affect treatment strategy [4, 5]. One of these impairments is overexpression of human epidermal growth factor receptor 2 (HER2). Malignant HER2-positive tumors resemble breast ductal adenocarcinomas in their structure, which was first described in 1968 by O. Kleinsasser et al. [6]. Both tumors demonstrate HER2 overexpression.

HER2 overexpression is observed in many different tumors, including breast cancer, ovarian cancer, bladder cancer, gland cancer, endometrial cancer, and lung cancer [4, 7]. Approximately 20–40 % of patients with ductal adenocarcinoma have HER2 overexpression [8–12].

Of note, other tumors of the glands rarely demonstrate HER2 overexpression. Despite the fact that this disorder is associated with a poor prognosis, it is an indication for therapy with HER2 inhibitors.

Gland tumors account only for 5 % of all head and neck tumors. Therefore, there is still no consensus on the role of pharmacotherapy in the treatment of disseminated disease [4, 13–18]. We found several studies comparing the efficacy of trastuzumab for ductal and non-ductal adenocarcinomas of the glands [17, 19]. One of these studies included 14 patients, one of whom had partial response for 45 months and other two had stable disease for 19 and 36 months. It was impossible to evaluate the effectiveness of trastuzumab due to small number of patients.

Numerous studies identified high levels of HER2 expression in ductal carcinomas (mucoepidermoid and

squamous cell) in contrast to non-ductal carcinomas (adenoid cystic, acinous cell, myoepithelial carcinomas and adenocarcinoma). Glisson et al. detected HER2 overexpression in 12 (83 %) of patients with ductal adenocarcinoma with 9 of them having +3 status [19]. HER2 expression was identified using immunohistochemistry and fluorescence *in situ* hybridization (FISH). Such results can be explained by morphological and immunophenotypic similarities of ductal carcinomas of the and mammary glands, since these disorders are characterized by a desmoplastic reaction of the stroma. Both tumor types exhibit HER2 overexpression, which suggests potential effectiveness of HER2 inhibitors (trastuzumab, etc.) in the treatment of ductal adenocarcinoma of the glands [13, 17, 19].

Recently, much attention has been paid to therapy based on molecular targets and, as a result, the widespread use of targeted cancer therapy to improve outcomes.

We report a case of successful anti-HER2 therapy with trastuzumab in combination with docetaxel and carboplatin in HER2-positive disseminated ductal adenocarcinoma of the submandibular gland.

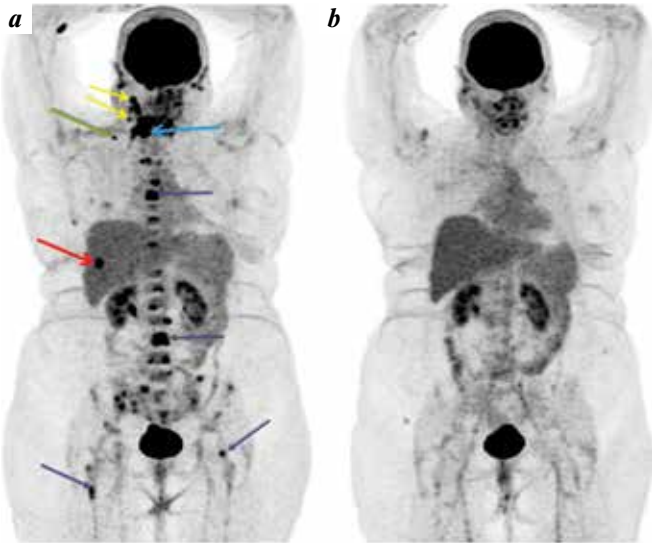

Fig. 1. *^{18}F-fluorodeoxyglucose positron emission tomography scan: a – maximum intensity projection (MIP), frontal view before treatment. Focal accumulation of radiopharmaceutical in the tumor of the right submandibular gland (blue arrow), cervical lymph nodes (yellow arrows), right supraclavicular region (green arrow), liver (red arrow), and bones (purple arrows); b – MIP after treatment. Regression of metabolically active lesions*

Case report

A 45-year-old female patient considered herself sick since June 2019, when she first noticed a nodular formation in the right submandibular region, which gradually increased in size. The patient underwent examination in N.N. Blokhin National Medical Research Center of Oncology.

Contrast-enhanced computed tomography (CT) of the neck performed on 06.07.2021 revealed an enlarged (29 × 24 × 28 mm) right submandibular gland with uneven edges, tuberous contour, and increased density (+40 HU). The adjacent subcutaneous fat was cord-like and infiltrated; enlarged lymph nodes (LNs) (up to 8 × 13 mm) actively accumulating contrast agent were visualized around the gland; enlarged LNs were also seen on the opposite side. The tumor accumulated radiopharmaceutical in a heterogeneous manner with a maximum during the delayed scanning phase. On 08.07.2019, the patient underwent trepanobiopsy. Pathomorphological examination revealed ductal carcinoma of the gland. Immunohistochemical examination demonstrated expression of HER2 (3+), as well as expression of SC7, GATA-3, estrogen receptors (score 3), and androgen receptors (score 7) in tumor cells, but no expression of progesterone receptors (score 0); tumor cell proliferation index (Ki-67) was 8 %.

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) performed on 18.07.2019 revealed an enlarged right submandibular gland (33 × 28 × 29 mm) with a heterogeneous structure and heterogeneous enhancement pattern (standardized uptake value maximum (SUV_{max}) up to 26.3). Multiple enlarged LNs with an increased radiopharmaceutical accumulation were visualized on the scan: superior cervical and middle jugular, submandibular on both sides with those on the right measuring up to 19 × 17 mm (SUV_{max} = 16.3) (middle jugular), on the left measuring up to 15 × 14 mm (SUV_{max} = 5.5) (submandibular), supraclavicular on the right measuring up to 12 × 9 mm (SUV_{max} = 5.8). A 21 × 16 mm formation with unclear contours accumulating radiopharmaceutical in the right lobe of the liver in the S6 segment (SUV_{max} = 11.8). Multiple metastatic lesions of a mixed nature (in the right scapula, manubrium, sternal end of the right clavicle, vertebrae of all departments, anterior segment of the VII rib on the left, sacrum, pelvic bones, and distal femoral bones) with radiopharmaceutical hypermetabolism were visualized (right half of the sacrum is up to 20 × 19 mm in size (SUV_{max} = 13.9), the body of the L3 vertebra is 31 × 25 mm in size (SUV_{max} = 14.9)) (fig. 1, a).

The patient was diagnosed with stage IVC T3–N2c–M1c ductal cancer of the right submandibular gland with bilateral metastases to cervical LNs, bones, and liver.

The multidisciplinary consilium decided to initiate combinational targeted chemotherapy. Between 25.07.2019 and 07.11.2019, the patient received 6 courses of polychemotherapy plus targeted therapy according to the following scheme: docetaxel at a dose of 75 mg/m^2, carboplatin AUC 6, trastuzumab at a dose of 6 mg/kg, and zoledronic acid at a dose of 4 mg with each cycle lasting 21 days. The patient tolerated the treatment (controllable toxicity). After 6 courses of targeted chemotherapy, we observed clinically significant positive dynamics. From 28.11.2019, the patient started to receive supportive targeted therapy with trastuzumab at a dose of 6 mg/kg every 21st day.

Follow-up ^{18}F-FDG PET/CT performed on 10.12.2019 showed that the right submandibular gland (33 × 19 × 32 mm in size) was metabolically active with SUV_{max} = 3,66

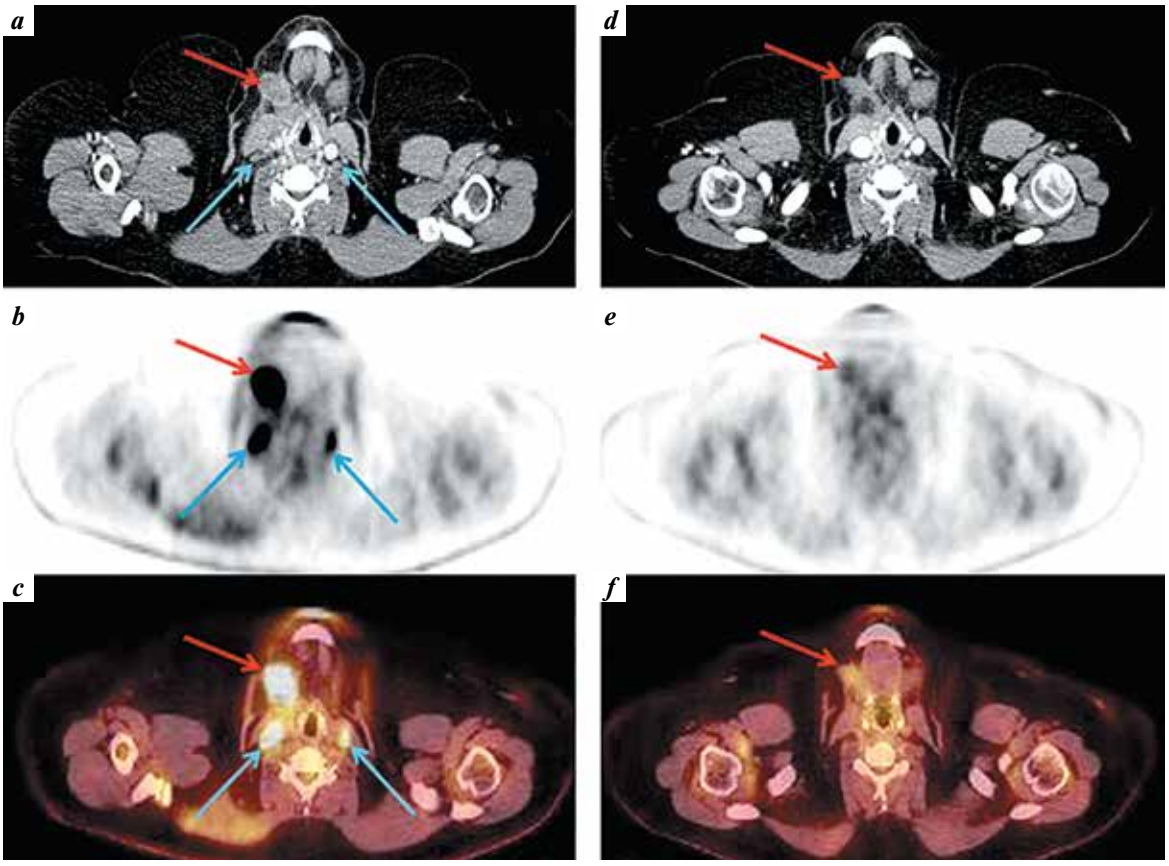

Fig. 2. *^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography scan. Tumor of the right submandibular gland (red arrows) and metastases in the cervical lymph nodes (blue arrows) before (a–c) and after (d–f) treatment. Reduced size of the primary tumor and reduced metabolic activity; tumor regression in the cervical lymph nodes*

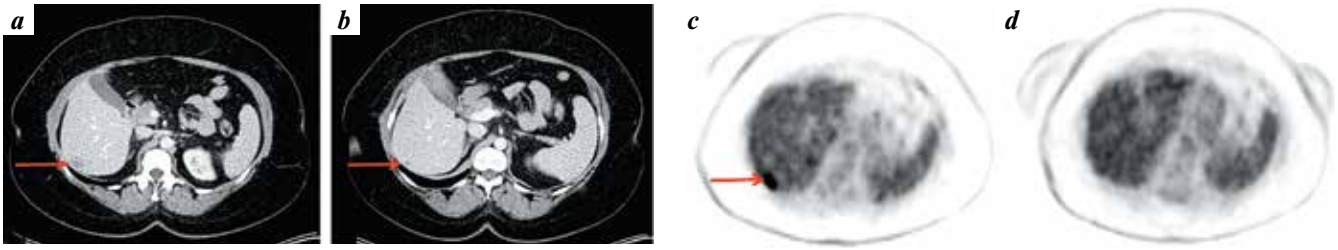

Fig. 3. *Results of patient examination: contrast-enhanced computed tomography (CT) scan before (a) and after (b) treatment; ^{18}F-fluorodeoxyglucose positron emission tomography scan before (c) and after (d) treatment; axial view. Metastasis in the right lobe of the liver in the S6 segment. Pretreatment scans demonstrate focal accumulation of radiopharmaceutical in a single hypovascular formation of the right lobe of the liver; posttreatment scans demonstrate reduced size of this formation (b) and no focal metabolic activity (d)*

(vs 33 × 28 × 38 mm and SUV_{max} = 26.3 at previous examination) (fig. 2). The scan also demonstrated a reduced number of metastatic lesions and complete regression of some of them (see fig. 1), lower metabolic activity of lesions in enlarged LNs that were earlier classified as active (see fig. 2), reduced size of lesions in the right lobe of the liver and less active radiopharmaceutical accumulation (fig. 3), reduced metabolic activity in the bones with increasing osteosclerotic changes (fig. 4). Regression of tumor lesions indicated complete clinical response according to the Response evaluation criteria in solid tumors version 1.1 (RECIST 1.1).

Between 10.02.2020 and 05.03.2020, the patient received a course of hypofractionated external beam therapy according to the following plan: single focal dose of 3 Gy and total dose of 54 Gy for the primary tumor and affected LNs; single focal dose of 2 Gy and total dose of 45 Gy for regional cervical LNs (levels Ia–V on both sides) along with trastuzumab therapy, followed by continued targeted therapy.

Follow-up ^{18}F-FDG PET/CT performed on 08.06.2020 showed that the right submandibular gland had the same size (up to 21.5 × 16 mm) with SUV_{max} = 7.7 (vs SUV_{max} = 3.7 at previous examination). A single 8-mm submandibular LN

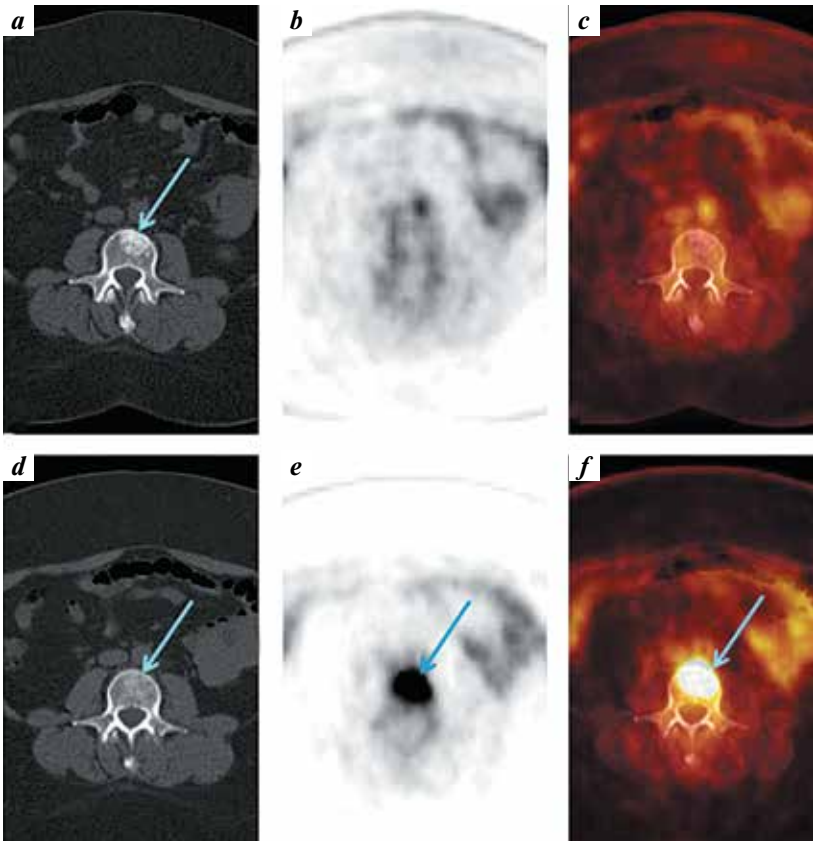

Fig. 4. *Results of patient examination: computed tomography (CT) scan (a, d); ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scan (b, e); PET/CT scan (c, f). Axial view. Metastasis in the L3 vertebra (blue arrows) before (d, e, f) and after (a) treatment. The pretreatment scans demonstrate a mixed focus of radiopharmaceutical accumulation in the body of the lumbar vertebra; the posttreatment scans demonstrate significantly increased density of the metastatic tumor with no radiopharmaceutical accumulation (below the accumulation of ^{18}F-fluorodeoxyglucose in intact bone tissue)*

with SUV_{max} = 7.7 was visualized (vs 8 mm and SUV_{max} = 4.1 at previous examination). Cervical LNs on the left side were not enlarged with no radiopharmaceutical accumulation. The liver was not enlarged with no signs of radiopharmaceutical hypermetabolism. The intrahepatic and extrahepatic bile ducts were not dilated. Several osteosclerotic foci with radiopharmaceutical accumulation and SUV_{max} = 8.5 were identified in the bones (spine, ribs, pelvic bones, femoral and humerus bones in the scanning area, shoulder blades) (vs SUV_{max} = 4,6 for the L5 vertebra at previous examination).

Between 09.01.2020 and 16.06.2020, the patient received 10 courses of chemotherapy. She had complete regression of metastases in the liver and bones, but cervical LNs were still affected by metastatic lesions, it was decided to perform radical surgery on the neck.

The patient underwent right-sided fascial-sheath excision of the neck on 10.07.2020. Histological examination demonstrated no viable tumor cells in the excised tissue. Since the patient was initially diagnosed with gland cancer, this finding can be interpreted as a sign of grade IV therapeutic pathomorphosis and complete regression of the primary tumor. The patient was recommended to continue supportive targeted therapy with trastuzumab.

The follow-up PET/CT performed 17 months after surgery (27.12.2020) demonstrated the development of a single 10-mm lesion with indistinct contours accumulating ^{18}F-FDG in the area of the right parotid gland (SUV_{max} = 6.83). Bone metastases demonstrated no dynamics. It was decided to continue follow-up while the patient was receiving targeted therapy.

PET/CT performed on 22.04.2021 revealed a lesion with indistinct contours in the area of the right parotid gland (fig. 5). The scan demonstrated positive dynamics reflected in lower metabolic activity (SUV_{max} = 3.19 vs SUV_{max} = 6.83 earlier) and reduced tumor size (7 mm vs 10 mm earlier). Bone metastases demonstrated no negative dynamics.

Fine-needle aspiration biopsy of the node located in the right parotid gland was performed on 06.05.2021. Cytological examination showed no metastasis.

An oncological consultation was conducted. Given the positive dynamics in response to targeted therapy with trastuzumab, it was decided to continue treatment and dynamic monitoring.

Discussion

Trastuzumab is effective for HER2-positive breast cancer both as a monotherapy and in combination with

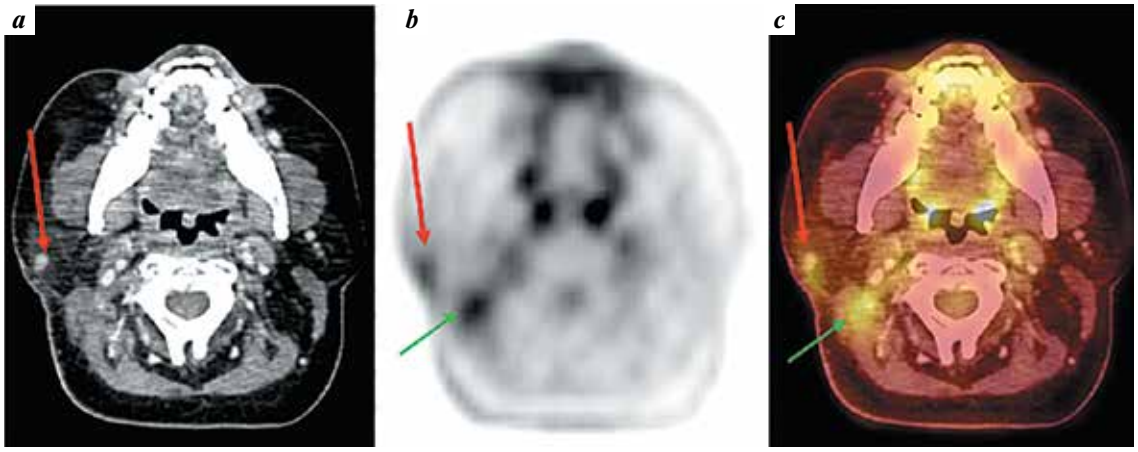

Fig. 5. *Results of patient examination: a – contrast-enhanced computed tomography (CT) scan; b – ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography scan; c – ^{18}F-FDG PET-CT scan. Axial view. Nodular formation in the right parotid gland (red arrows); nonspecific radiopharmaceutical accumulation in the upper third of the neck deeply in the postoperative scar (green arrows)*

chemotherapy. The overall efficacy of trastuzumab monotherapy for metastatic, HER2-positive stage IV breast cancer in newly diagnosed patients is 23 %. Combination therapy with trastuzumab and paclitaxel increases treatment efficacy to 62 % [20–22]. The median response duration varies between 6.6 and 9.1 months with 57 % of patients having no signs of disease progression within 12 months [23–25]. A complete clinical (pathological) response to preoperative chemotherapy in patients with aggressive breast cancer improves the disease prognosis [26].

What treatment strategy can be chosen for progressive disease in patients with HER2-positive tumors receiving supportive therapy with trastuzumab?

In 2014, trastuzumab emtansine (T-DM1; kadcyla), an antibody – drug conjugate and next-generation HER2-inhibitor was registered in Russia. This drug contains trastuzumab and the cytotoxic agent emtansine, which stabilizes microtubules, inhibits cell division and induces their death [27]. T-DM1 acts via the following mechanism: it reaches a HER2-positive target tumor cell and specifically binds to the HER2 receptor; then the cytotoxic agent (emtansine) is released inside the tumor cell, thus acting exclusively on cancer cells [28]. This approach was considered as a significant breakthrough in biotechnology. A large international randomized open-label phase III study EMILIA compared the efficacy trastuzumab emtanzine monotherapy versus a combination of lapatinib and capecitabine in the second-line anti-HER2 therapy. Findings of the study laid a ground for the registration of T-DM1 as a second-line treatment for advanced HER2-positive breast cancer [29].

Currently, T-DM1 is used only in breast cancer patients and is not agnostic, so its use in other malignancies with HER2 overexpression is an off-label therapy.

For a long time, treatment of tumors with different levels of HER2 (1–2+) expression, as well as FISH-negative tumors (HER2 – low) remained controversial, since neither tyrosine kinase inhibitors, nor monoclonal antibodies, nor T-DM1 conjugate demonstrated sufficient clinical efficacy for these cancers. Thus, such tumors were considered as HER2-negative.

The discovery of trastuzumab deruxtecan (T-DxD), a new generation antibody-cytostatic conjugate, became a significant advance in the treatment of HER2-low tumors. DESTINY-PanTumor02 trial demonstrated the efficacy of T-DXd in patients with HER2-positive tumors [30]. This study assessed the efficacy of T-DXd (at a dose of 5.4 mg/kg once every 3 weeks) with locally advanced or disseminated HER2-positive (3+/2+) breast and stomach cancer, non-small cell lung cancer with *HER2* mutations, and solid tumors expressing HER2.

The study involved 267 patients (including those who had earlier received systemic anti-HER2 therapy) randomized into groups by tumor location: endometrium, cervix, ovaries, bladder, bile ducts, pancreas, glands, etc. The median follow-up time was 12.7 months; the objective response rate among all participants was 37.1 % (n = 99) (95 % confidence interval (CI) 31.3–43.2). The median progression-free survival was 11.3 months (95 % CI 9.6–17.8); median overall survival was 13.4 months (95 % CI 11.9–15.5). Treatment-related grade III adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 scale were observed in 40.8 % of patients. Drug-induced interstitial lung disease was diagnosed in 10.5 % of cases; 3 patients died.

The results of this global multicenter phase II trial demonstrated high clinical efficacy of T-DxD, which provided long-term clinical benefit for newly diagnosed patients with solid HER2-positive tumors. The safety profile, including interstitial lung disease, was similar to that described in previous studies. These findings indicate high effectiveness of T-DxD for various types of tumors, which suggests its potential activity against HER2-positive ductal adenocarcinoma of the glands.

Another phase I trial conducted in Japan also demonstrated high efficacy and safety of T-DxD in patients with HER2-positive gland adenocarcinoma [31]. It included 17 patients with gland adenocarcinoma, of whom 14 patients had previously received anti-HER2 therapy and 13 patients had received radiation therapy. The median follow-up was 12 (2.3–34.8) months; the objective response rate was 58.8 %; the median response duration was 17.6 months; the median progression-free survival was 20.5 months. A total of 76.5 % of patients experienced grade III or lower treatment-related adverse events, most common of which included decreased appetite (94.1 % of cases), nausea (88.2 % of cases), neutropenia (76.5 % of cases). Drug-induced interstitial lung disease of varying severity was observed in 5 (29.4 %) patients.

All of the abovementioned findings indicate that patients with the gland adenocarcinoma, inclusing those with HER2 overexpression, are likely to benefit from treatment with next-generation anti-HER2 inhibitors. However, additional studies are needed to analyze the effect of this therapy on overall survival in both local and disseminated cancers.

Conclusion

Given that ductal adenocarcinoma of the glands is a relatively rare disorder, the choice of an optimal treatment strategy is highly relevant.

The case described in this article demonstrates high efficacy (complete pathomorphological response) of anti-HER2 therapy with trastuzumab in combination with traditional cytostatic therapy (docetaxel, carboplatin) in a patient with disseminated HER2-positive gland cancer. However, the rarity of this histological type of tumors necessitates additional studies to evaluate long-term outcomes of anti-HER2 therapy in such patients.

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Authors' contributions
A.M. Mudunov, I.M. Gelfand: obtaining data for analysis, analysis of the data obtained, article writing, editing;
O.D. Ryzhova, M.B. Pak: analysis of the data obtained, review of publications on the topic of the article, editing;
A.S. Tarakanova, I.O. Tarakanov, A.S. Morozova, H. Chen: review of publications on the topic of the article.

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