Analysis of treatment outcomes in patients with progressive locally advanced non-resectable and disseminated medullary thyroid cancer receiving vandetanib outside of clinical trials (Russian experience)

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The study objective *is to perform retrospective analysis of the efficacy and safety of vandetanib for metastatic and non-resectable medullary thyroid cancer in routine clinical practice.*
Materials and methods. *We analyzed treatment outcomes in 46 patients treated with vandetanib. We also evaluated progression-free survival, overall survival, time to progression, and frequency of adverse events.*
Results. *At a median follow-up time of 27.4 months (range: 2.5–106.5 months) and median duration of vandetanib therapy of 21 months, disease progression was registered in 32.6 % of cases, whereas stable disease was observed in 28.3 % of cases and 8.7 % of study participants demonstrated partial response. One patient had complete response to treatment. Almost one-third of patients (28.2 %) died, including 2 individuals whose death was not associated with cancer. The one-year and three-year progression-free survival rates were 67.3 % and 33.3 %, respectively; the two-year and five-year overall survival rates were 82.4 % and 29.4 %, respectively. The efficacy of therapy was confirmed by a 79.4 % decrease in the serum level of calcitonin after treatment initiation. Side effects were observed in 33.9 % of patients (primarily skin and gastrointestinal toxic reactions) and were easily managed in most of the cases. Eight individuals (17.4 %) required cessation of vandetanib due to adverse events.*
Conclusion. *Our findings suggest high efficacy and acceptable safety profile of vandetanib in the treatment of progressive locally advanced non-resectable and disseminated medullary thyroid cancer*

Key words: *medullary thyroid cancer, vandetanib, tyrosine kinase inhibitors, survival, adverse events*

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Анализ результатов лечения вандетанибом прогрессирующего местно-распространенного неоперабельного и диссеминированного медуллярного рака щитовидной железы вне клинического исследования (российский опыт)

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Цель исследования *– ретроспективный анализ эффективности и безопасности применения вандетаниба в клинической практике с целью лечения метастатических и неоперабельных форм медуллярного рака щитовидной железы.*
Материалы и методы. *Проанализированы результаты лечения вандетанибом 46 пациентов. Оценивали выживаемость без прогрессирования, общую выживаемость, срок до прогрессирования и частоту нежелательных явлений.*
Результаты. *При медиане длительности наблюдения в 27,4 мес (диапазон 2,5–106,5 мес) и медиане длительности приема вандетаниба в 21 мес прогрессирование было зафиксировано в 32,6 % случаев, стабилизация – в 28,3 %, частичный ответ – в 8,7 %. У 1 пациента получен полный ответ на лечение. Смертельный исход произошел в 28,2 % случаев, в том числе в 2 случаях*

по не связанным с опухолью причинам. Однолетняя и трехлетняя выживаемость без прогрессирования составила соответственно 67,3 и 33,3 %, а двухлетняя и пятилетняя общая выживаемость – соответственно 82,4 и 29,4 %. Эффективность лечения подтверждена снижением уровня кальцитонина в крови после начала терапии на 79,4 %. Побочные эффекты зарегистрированы у 33,9 % пациентов (чаще кожные и гастроинтестинальные токсические реакции) и в большинстве случаев легко поддавались коррекции. В 8 (17,4 %) случаях в связи с возникновением нежелательных явлений терапия вандетанибом была прекращена.

Заключение. *Полученные результаты свидетельствуют о высокой эффективности и приемлемой безопасности вандетаниба в лечении прогрессирующего местно-распространенного неоперабельного и диссеминированного медуллярного рака щитовидной железы.*

Ключевые слова: *медуллярный рак щитовидной железы, вандетаниб, ингибиторы тирозинкиназ, выживаемость, нежелательные явления*

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Background

Medullary thyroid cancer (MTC) is a rare malignant tumor that originates from calcitonin producing parafollicular C-cells. MTC accounts for 1.7% to 5% of all thyroid cancers, while the incidence of all variants of thyroid carcinoma in Russia is 6 cases per 100,000 [1–5].

Unlike well-differentiated cancers, MTC is characterized by poor prognosis due to biological properties of the tumor and inability to use hormone suppression therapy and radioiodine therapy [6, 7]. Surgery remains by far the most effective treatment for patients with MTC [3]. Radical surgery performed in patients with stage I–III disease ensures high five-year and ten-year survival rates (95% and 75% respectively) [8, 9].

However, in approximately 25% of cases, operation is impossible due to locoregional tumor spread or distant metastases [8]. Treatment of disseminated and locally advanced non-resectable MTC is believed to be one of the most challenging tasks in oncology, which had been a stumbling block until recently. The results of ZETA randomized controlled trial, published in 2012, have raised hopes to address this challenge. Median progression-free survival (PFS) in patients receiving vandetanib was 30.5 months, whereas in the placebo arm, median PFS was 19.3 months ($p = 0.001$). Vandetanib prevented not only structural, but also biochemical progression of MTC: patients in the vandetanib arm demonstrated a 69% decrease in serum calcitonin level, while the controls had only a 3% decrease ($p = 0.001$). Hazard ratio for PFS was 0.46 (95% confidence interval (CI) 0.31–0.69; $p < 0.001$) [10]. Further studies have also demonstrated high efficacy of vandentanib in the treatment of non-resectable locally advanced or metastatic MTC [11–14]. Since 2013, vandetanib has been the only targeted drug registered in the Russian Federation for the treatment of MTC [15].

Nevertheless, due to the difficulties associated with patient recruitment in such studies (as MTC belongs to orphan disease), the trials evaluating vandentanib efficacy are ongoing since there are still a number of important issues to be analyzed. In particular, it is necessary to assess the impact of vandetanib on the overall survival (OS) of patients. There are very few publications that evaluated OS and their results are controversial. One of retrospective studies performed by Russian researchers in 2018 demonstrated that targeted therapy with vandetanib alone or in combination with external beam radiotherapy (EBRT) was more effective than EBRT alone in patients with non-resectable progressive MTC. Median survival was 48 and 50 months in patients receiving combination therapy ($n = 16$) and vandetanib alone ($n = 36$) respectively, whereas in the group of EBRT alone ($n = 26$), the survival was only 14 months ($p < 0.001$) [16]. However, in a systematic review published in February 2019, no significant differences were found in the overall survival of patients receiving vandetanib and placebo (50% versus 52%; hazard ratio 0.99, 95% CI 0.72–1.38; $p = 0.975$). Result interpretation in this study was complicated because it was a crossover trial and some patients in the placebo arm who had disease progression were transferred to the vandetanib arm [17]. We are still expecting the results of two trials: NCT01945762 and NCT00410761.

The aim of this study was to perform retrospective analysis of the efficacy and safety of vandetanib for metastatic and non-resectable MTC in routine clinical practice.

Materials and methods

In this study, we performed retrospective analysis of data for 64 patients (29 females (45.3%) and 35 males (54.7%)) with non-resectable locally advanced and/or metastatic MTC who could benefit from vandetanib. Upon the initiation of targeted therapy with vandetanib, patients' age varied between 17 and 83 years (median 55 years; mean 52.5 years).

In all cases, the diagnosis was confirmed by both pathological examination and blood testing (high level of calcitonin, which varied between 71 and 33.884 pmol/L (mean value 2258.4 pmol/L; median value 1068.6 pmol/l)).

Twenty-three out of 64 patients had sporadic MTC, whereas in 3 patients, it was a manifestation of multiple endocrine neoplasia (type 2B in 2 patients and type 2A in 1 patient). Thirty-eight patients were not tested for mutations in the *RET* gene.

Twelve individuals had primary inoperable MTC and 52 patients had undergone surgery for the primary tumor before the initiation of targeted therapy, namely hemithyroidectomy with subsequent thyroidectomy ($n = 4$) or thyroidectomy alone ($n = 48$). Thirty-two patients have also undergone surgery on regional lymph nodes: either unilateral ($n = 19$) or bilateral ($n = 13$) cervical lymphadenectomy. Twelve patients also had postoperative radiotherapy. Seven patients have undergone repeated surgery for cancer recurrence. Fifteen participants had disease progression and received a course of interferon therapy ($n = 14$) or targeted therapy with another multikinase inhibitor ($n = 1$) (Table 1).

Upon the initiation of vandentanib therapy, distant metastases were found in 59 patients, including 36 individuals with metastases in one anatomical area and 23 individuals with at least two anatomical areas affected by metastasis (Table 2).

Distant metastases were primarily located in the lungs (20.3%) and liver (20.3%) and less frequently in the bones and mediastinal lymph nodes. One patient had lesions in the palatine tonsil.

We evaluated PFS, OS, time to disease progression, and the incidence of adverse events (AEs) in patients receiving vandentanib.

Таблица 1. *Распределение пациентов с медуллярным раком щитовидной железы по видам лечения, проведенного до начала таргетной терапии вандетанибом*

Table 1. *Distribution of patients with medullary thyroid cancer by the type of treatment they received prior to targeted therapy with vandetanib*

Лечение Treatment	**Число пациентов, абс.** Number of patients, abs.
Не проводилось None	11
Хирургическое Surgery	29
Хирургия + лучевая терапия Surgery + radiotherapy	9
Хирургия + терапия интерферонами Surgery + interferon therapy	10
Хирургия + лучевая терапия + терапия интерферонами Surgery + radiotherapy + interferon therapy	3
Терапия интерферонами Interferon therapy	1
Хирургия + таргетная терапия Surgery + targeted therapy	1
Всего *Total*	*64*

Таблица 2. *Частота локализации отдаленных метастазов у пациентов с медуллярным раком щитовидной железы до начала таргетной терапии вандетанибом*

Table 2. *Location of distant metastases in patients with medullary thyroid cancer before the initiation of targeted therapy with vandetanib*

Локализация Location	**Частота, абс. (%)** Frequency, abs. (%)
Средостение Mediastinum	6 (10,1)
Печень Liver	12 (20,3)
Легкие Lungs	12 (20,3)
Кости Bones	5 (8,5)
Небная миндалина Palatine tonsil	1 (1,7)
Средостение + печень Mediastinum + liver	2 (3,4)
Средостение + печень + легкие Mediastinum + liver + lungs	3 (5,1)
Средостение + легкие Mediastinum + lungs	2 (3,4)
Средостение + кости Mediastinum + bones	3 (5,1)
Печень + легкие Liver + lungs	3 (5,1)
Печень + легкие + кости Liver + lungs + bones	1 (1,7)
Печень + кости Liver + bones	5 (8,5)
Легкие + кости Lungs + bones	2 (3,4)
Средостение + легкие + кости Mediastinum + lungs + bones	2 (3,4)

Data analysis was performed using the Microsoft Excel and Medcalc v15.8 software. OS and PFS were calculated according to real duration of life of each patient by the moment of study completion using the Kaplan–Meier method.

Results

Eighteen patients were excluded from the final analysis: 6 of them continue to receive vandentanib, but their follow-up time was <12 months; one patient discontinued vandentanib after 4.5 months because the drug was not available; eleven patients were lost to follow-up after they had been refereed to treatment to local clinics.

Thus, long-term treatment outcomes were assessed in 46 patients with MTC (Table 3). The duration of follow-up period varied from 2.5 to 106.5 months (median

Таблица 3. *Исходы лечения вандетанибом пациентов с нерезектабельным местно-распространенным и/или метастатическим медуллярным раком щитовидной железы (n = 46)*

Table 3. *Treatment outcomes in patients with non-resectable locally advanced and/or metastatic medullary thyroid cancer after therapy with vandetanib (n = 46)*

Исход Outcome	Число пациентов, абс. (%) Number of patients, abs. (%)
Прогрессирование Disease progression	15 (32,6)
Стабилизация Stable disease	13 (28,3)
Частичный ответ Partial responce	4 (8,7)
Полный ответ Complete response	1 (2,2)
Смерть от прогрессирования Death due to disease progression	11 (23,9)
Смерть от иных причин Death due to other reasons	2 (4,3)

27.4 months); the duration of vandentanib therapy was between 2.0 and 106.5 months (median 21.0 months).

The objective response rate (ORR) was 43.5% with 1 patient having complete response. Two patients with stable disease died due to other reasons (pneumonia and acute myocardial infarction). Progressive disease was observed in 56.5% and led to death in 11 cases. The time to disease progression varied between 2 and 47 months (median 10.75 months and mean 15.54 months) (Fig. 1).

In more than half of the cases (53.8%), disease progression was registered 6 to 21 months after treatment initiation. By the moment of manuscript submission, the maximum duration of the progression free interval was 106.5 months; this patient continues to receive vandentanib with no deterioration of symptoms. It is important to mention that one patient had a 6-year interruption in vandentanib therapy due to acute myocardial infarction. Nevertheless, repeated administration of the drug after stabilization of the heart function gave a stable effect and ensured partial response.

The efficacy of vandetanib was also confirmed by a decrease in calcitonin levels. Upon treatment initiation, mean serum level of calcitonin was 2262.5 pmol/L (range: 220–22748 pmol/L); during therapy, it demonstrated a 79.4% decrease (mean level 488.9 pmol/L; range: 10.5–1855.8 pmol/L).

The one-year PFS rate was 67.3 ± 6.9 % with median PFS not reached (Fig. 2).

Due to the short follow-up period and the absence of disease progression during it, 10 out of 46 patients were excluded from the analysis of three-year PFS. The three-year PFS rate was 33.3 ± 7.8 % with a median PFS of 19.75 months (95% CI 10.25–35.0 months) (Fig. 3).

A total of 30 patients were included into the analysis of five-year survival. The five-year PFS rate was 13.3 ± 6.2%

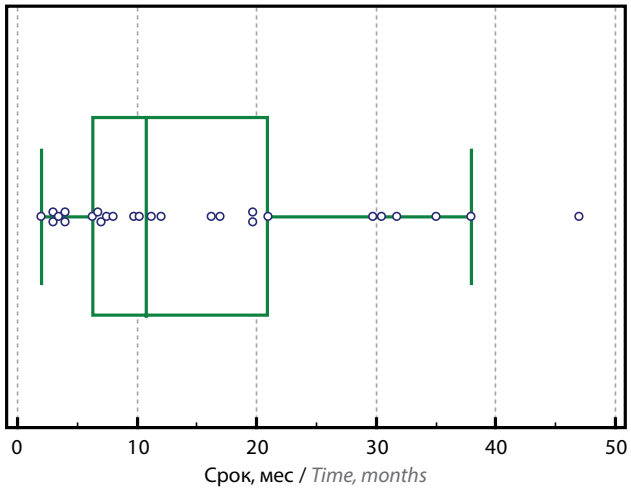

Рис. 1. *Срок от начала терапии вандетанибом до прогрессирования медуллярного рака щитовидной железы*

Fig. 1. *Time between the initiation of vandetanib therapy and progression of medullary thyroid cancer*

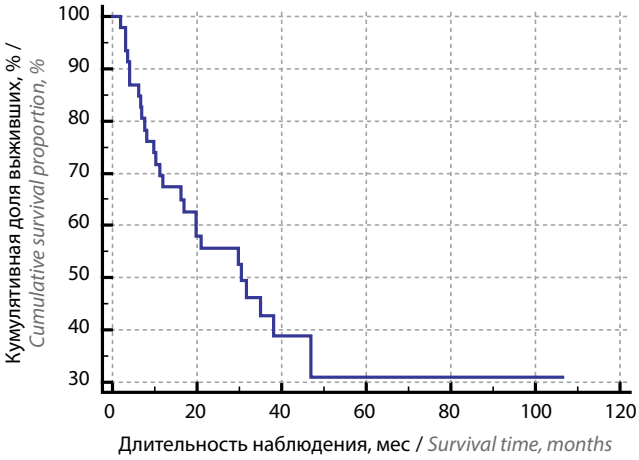

Рис. 2. *Кривая Каплана–Майера, отражающая выживаемость без прогрессирования на фоне терапии вандетанибом в когорте пациентов с нерезектабельным местно-распространенным и/или метастатическим медуллярным раком щитовидной железы (n = 46)*

Fig. 2. *Kaplan–Meier curve for progression-free survival in patients with non-resectable locally advanced and/or metastatic medullary thyroid cancer treated with vandetanib (n = 46)*

with a median PFS of 12 months (95% CI 7.5–29.75 months, mean PFS 27.6 months) (Fig. 4).

We have also evaluated two-year OS in 34 out of 46 patients receiving targeted therapy with vandetanib. Twelve patients were excluded from this analysis due to the short follow-up period, including 4 patients who refused to be treated and followed-up at N.N. Blokhin Russian Cancer Research Center after disease progression. In 6 out of 34 patients included in the analysis of OS, vandetanib was replaced with another multikinase inhibitor after disease progression (in 5 patients within 2 years; in 1 patient after 2 years).

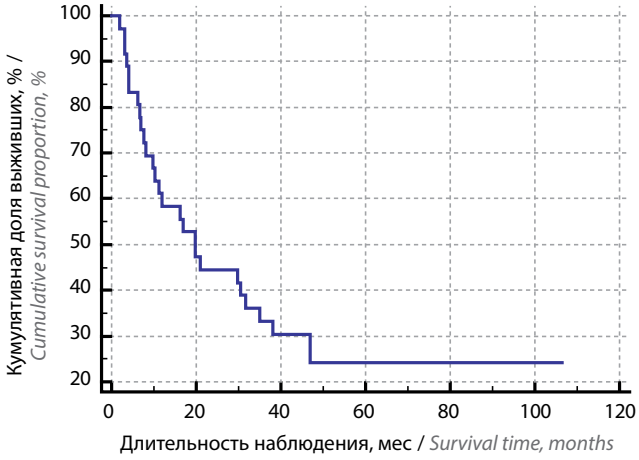

Рис. 3. *Кривая Каплана–Майера, отражающая выживаемость без прогрессирования на фоне терапии вандетанибом в когорте пациентов с нерезектабельным местно-распространенным и/или метастатическим медуллярным раком щитовидной железы (анализ после исключения 10 пациентов с отсутствием прогрессирования) (n = 36)*

Fig. 3. *Kaplan–Meier curve for progression-free survival in patients with non-resectable locally advanced and/or metastatic medullary thyroid cancer treated with vandetanib (after excluding 10 patients with no progression) (n = 36)*

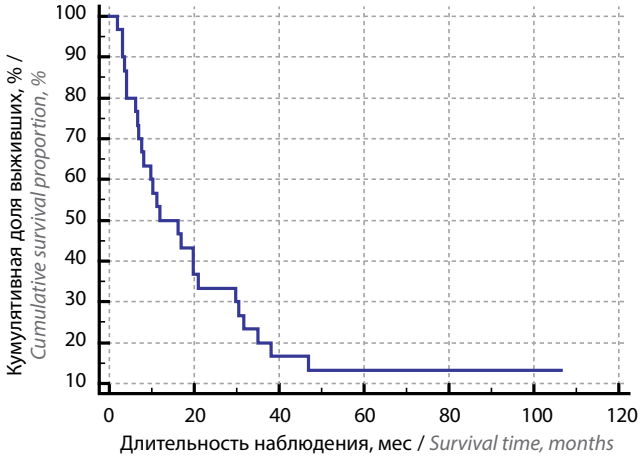

Рис. 4. *Кривая Каплана–Майера, отражающая выживаемость без прогрессирования на фоне терапии вандетанибом в когорте пациентов с нерезектабельным местно-распространенным и/или метастатическим медуллярным раком щитовидной железы (анализ после исключения 16 пациентов) (n = 30)*

Fig. 4. *Kaplan–Meier curve for progression-free survival in patients with non-resectable locally advanced and/or metastatic medullary thyroid cancer treated with vandetanib (after excluding 16 patients) (n = 30)*

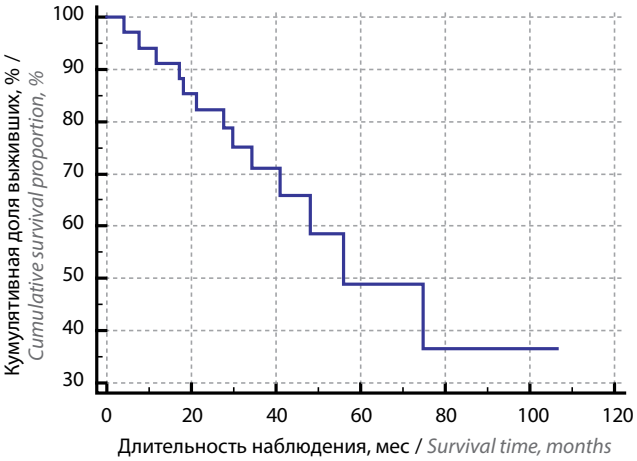

Рис. 5. *Кривая Каплана–Майера, отражающая общую выживаемость на фоне терапии вандетанибом в когорте пациентов с нерезектабельным местно-распространенным и/или метастатическим медуллярным раком щитовидной железы (n = 34)*

Fig. 5. *Kaplan–Meier curve for overall survival in patients with non-resectable locally advanced and/or metastatic medullary thyroid cancer treated with vandetanib (n = 34)*

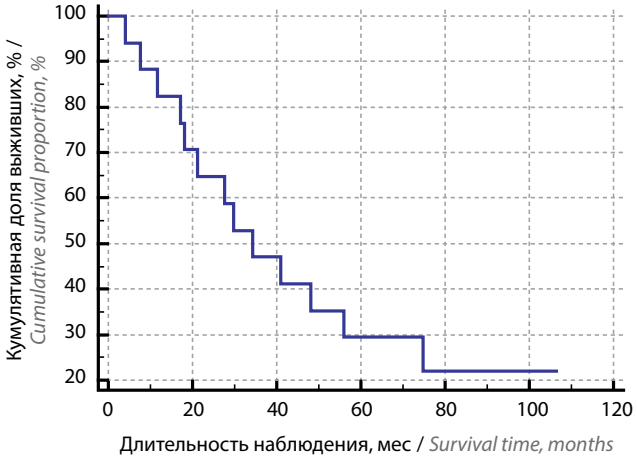

Рис. 6. *Кривая Каплана–Майера, отражающая общую выживаемость на фоне терапии вандетанибом в когорте пациентов с нерезектабельным местно-распространенным и/или метастатическим медуллярным раком щитовидной железы (анализ после исключения 17 пациентов) (n = 17)*

Fig. 6. *Kaplan–Meier curve for overall survival in patients with non-resectable locally advanced and/or metastatic medullary thyroid cancer treated with vandetanib (after excluding 17 patients) (n = 17)*

The two-year OS rate was 82.4 ± 6.5% with median OS not reached (Fig. 5).

Seventeen patients who had sufficient follow-up period were included into the analysis of five-year OS. The five-year OS rate was 29.4 ±11.1 % with median OS 34.2 months (95% CI 18.0–74.75 months; mean 47.5 months) (Fig. 6).

Vandetanib-associated AEs were registered in 33.9% of participants (Table 4). The most common AEs included skin (36.9%), gastrointestinal (34.8%), and cardiovascular (26.1%) reactions. Mild AEs were observed in 34 patients (73.9%) and were easily managed. Grade II–III AEs were registered in 8.7% of cases. Moreover, 8 patients (17.4%) had to discontinue vandetanib therapy due to AEs.

Discussion

In this study, we performed retrospective analysis of the efficacy and safety of vandetanib in routine clinical practice outside of clinical trials. Median follow-up time was

Таблица 4. *Частота нежелательных явлений у пациентов с нерезектабельным местно-распространенным и/или метастатическим медуллярным раком щитовидной железы на фоне приема вандетаниба (n = 46)*

Table 4. *Frequency of adverse events in patients with non-resectable locally advanced and/or metastatic medullary thyroid cancer treated with vandetanib (n = 46)*

Нежелательное явление Adverse event	Число случаев, абс. (%) Number of cases, abs. (%)
Кожные, в том числе: Skin, including:	17 (36,9)
сыпь rash	13 (28,2)
ладонно-подошвенный синдром hand-foot syndrome	4 (8,7)
Гастроинтестинальные, в том числе: Gastrointestinal, including:	16 (34,8)
диарея diarrhea	14 (30,4)
потеря аппетита loss of appetite	1 (2,2)
тошнота nausea	1 (2,2)
Сердечно-сосудистые, в том числе: Cardiovascular, including:	12 (26,1)
артериальная гипертензия arterial hypertension	8 (17,4)
острый инфаркт миокарда acute myocardial infarction	3 (6,5)
увеличение интервала QT QT prolongation	1 (2,2)
Гипотиреоз Hypothyroidism	9 (19,6)
Слабость Fatigue	5 (10,9)
Маточное кровотечение Uterine bleeding	1 (2,2)
Депрессия Depression	1 (2,2)
Головная боль Headache	1 (2,2)
Пневмония Pneumonia	1 (2,2)

27.4 months; almost one-third of patients (32.6%) had disease progression, which led to death in 23.9% of patients. Our findings are consistent with the results of the phase III ZETA trial performed by Wells et al., in which at median follow-up time of 24 months, disease progression was observed in 37% of patients and 15% of patients died [10]. Our results also agree with the results of a French retrospective study evaluating vandetanib in clinical practice in terms of complete response rate (2.2% vs 2.0%) and median PFS at follow-up period <3 years (19.75 vs 16.1 months) [13]. Chougnet et al. reported higher ORR (77% vs 43.5%); however, their follow-up period was shorter than that in our study (20 vs 27.4 months). We should also mention that patients in our study had longer two-year OS (82.4% vs 60%), which can probably be attributed to the fact that 5 individuals received a second targeted drug.

In addition to that, unlike in other studies, we managed to estimate the five-year OS ($n = 17$) and PFS ($n = 30$) rates, which reached 29.4% and 13.3% respectively. However, the results should be interpreted with caution due to the small sample size.

The comparison of safety profile has shown that the frequency of treatment cessation in our study was 17.4% vs 12% in the ZETA trial [10] and 27% in the study by Chougnet et al. [13]. Such difference with ZETA results can be explained by strict selection of patients in the vandetanib arm regulated by the study protocol. The toxicity profile was similar to that reported in 2 previously published studies: the most common AEs included dermatological and gastrointestinal reactions. Nonetheless, in most of the cases, AEs were easily managed. Median duration of vandetanib therapy was 21 months, which is not contradictory to the literature and indicates the possibility of long-term treatment.

Conclusion

The results of this retrospective study suggest high efficacy and acceptable safety profile of vandetanib in routine clinical practice outside of clinical trials. Moreover, AEs registered in our study were similar to those reported by other authors; therefore, these AEs were expected, which is particularly important for practicing clinicians in their decision on drug administration.

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