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ЭFFICACY AND TOLERABILITY OF LENVATINIB IN RADIOIODINE-REFRACTORY DIFFERENTIATED THYROID CANCER.

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Introduction. The introduction of tyrosine kinase inhibitors into clinical practice has significantly improved treatment outcomes for patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC). Lenvatinib is recommended as a first-line drug for this category of patients.

Objective. To analyze the aggregated clinical experience of using lenvatinib in patients with RR-DTC.

Materials and Methods. Data obtained from December 2016 to September 2020 were analyzed. The study included 77 clinical cases of histologically verified DTC with proven resistance to radioactive iodine therapy and subsequent tumor progression according to the RECIST 1.1 (Response Evaluation Criteria in Solid Tumours 1.1) criteria.

Results. The median progression-free survival (PFS) among the patients included in the analysis (n = 72) was 26.1 months. In the subgroup of patients who responded to therapy (with complete and partial response), the PFS reached 36.2 months, exceeding the corresponding figure obtained in the updated analysis of the SELECT registration study (33.1 months). Safety analysis of lenvatinib therapy showed that adverse events were recorded in 87% of patients, while severe adverse events were observed in only 18.2% of patients. In 6.5% of cases, the development of adverse events led to discontinuation of the drug, and in 74% of cases, the dose of lenvatinib was reduced.

Conclusion. The results indicate the efficacy and good tolerability of lenvatinib in RR-DTC.

Keywords: lenvatinib, radioiodine-refractory thyroid cancer, clinical practice, progression-free survival.

Introduction. Differentiated thyroid cancer (DTC) is the most common malignant tumor of the endocrine system. According to the cancer registry, in 2022, the incidence of thyroid cancer in Uzbekistan was 1.0 per 100 thousand population, with an unacceptably high rate of advanced cases (III-IV stages) - 23.6% [1]. Patients with DTC who are resistant to radioactive iodine therapy fall into a separate clinical group with a poor prognosis [2]. Chemotherapy has demonstrated its ineffectiveness and high toxicity, and thus is not recommended as a systemic

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therapy for such patients [3]. The introduction of tyrosine kinase inhibitors into clinical practice has improved treatment outcomes with lower drug toxicity and better patient tolerability. Two tyrosine kinase inhibitors are used for the treatment of radioiodine-refractory DTC (RR-DTC): sorafenib in 2014 and lenvatinib in 2015. According to the results of international randomized phase III clinical trials, the response rates in terms of complete, partial regression, and stabilization of the tumor were 0%, 12.2%, and 42% respectively for sorafenib in the DECISION trial [4], and 1.5%, 64.7%, and 15% for lenvatinib in the SELECT trial [5]. The median progression-free survival (PFS) with sorafenib was 10.8 months (5.4 months with placebo), with a hazard ratio of 0.59 (95% CI 0.39-0.61, $p < 0.001$) in the DECISION trial [4]. The median PFS with lenvatinib was 18.3 months (3.6 months with placebo), with a hazard ratio of 0.21 (95% CI 0.14-0.31, $p < 0.001$) in the SELECT trial [5]. The National Comprehensive Cancer Network (NCCN) recommended lenvatinib as the first-line therapy for RR-DTC [6]. The Russian literature describes individual clinical observations of the use of this drug [7].

Objective. To analyze the aggregated clinical experience of using lenvatinib.

Materials and Methods. The study was conducted from February 2016 to September 2019. Clinical cases of lenvatinib treatment were included. Within clinical practice, patients with RR-DTC receiving lenvatinib were monitored from the time of radiologically confirmed tumor progression according to the RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumours 1.1) [8]. Inclusion criteria for the study were: patients over 18 years of age; histologically verified RR-DTC; tumor progression after radioactive iodine therapy; and initiation of lenvatinib treatment. Exclusion criteria were: presence of contraindications to lenvatinib as indicated in the drug's prescribing information. The primary endpoint of the study was the assessment of PFS, while secondary objectives included the evaluation of overall survival (OS), response rate and duration, and the profile of adverse events (AEs) and their management in patients with metastatic RR-DTC receiving lenvatinib. Medical data of the patients were formalized and entered into electronic spreadsheets. PFS was defined as the period from the start of lenvatinib therapy to the date of disease progression or patient death. OS was calculated from the start of lenvatinib therapy to the date of the last follow-up or patient death from any cause. Treatment response was assessed by the treating physician; for measurable tumor lesions per RECIST 1.1 criteria, an objective response was considered a complete or partial response. Tumor control was defined as disease stabilization for 2 months or more. Criteria for disease stabilization included no change in target lesions according to instrumental examination data and no increase in levels of tumor markers (thyroglobulin and antibodies to it). An adverse event was considered any unfavorable event, symptom, or disease, as well as the worsening of previously existing symptoms, occurring after the start of therapy. The severity of AEs was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [9]. The results were analyzed using standard statistical methods [10, 11] with commercially available statistical software packages. Survival was assessed by the Kaplan-Meier method. Cox univariate and multivariate regression analyses were used to identify prognostic factors significant for survival.

Table 1. *Characteristics of patients with radioiodine-refractory differentiated thyroid cancer receiving Lenvatinib.*

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Characteristic	**Number of patients**	
	abs.	**%**
Gender:		
male	43	55,8
female	34	44,2
Eastern Cooperative Oncology Group performance status:		
0–1	67	87
2–3	10	13
Histological type:		
papillary	54	70
follicular	15	19
hurthle-cell	6	9
mucoepidermoid	1	1
unknown	1	1
Number of areas affected:		
1	17	22,1
2	34	44,2
3	15	19,5
4	7	9,1
5	2	2,6
6	2	2,6
Location of metastases:		
lungs	64	83,1
cervical lymph nodes	39	50,6
mediastinal lymph nodes	21	27,3
bones	21	27,3

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local recurrence	18	23,4
liver	6	7,8
brain	3	3,9
soft tissue	3	3,9
esophagus	2	2,6
adrenal gland	2	2,6

The current analysis includes data from 2016 to September 2020. According to the inclusion criteria, the study included 77 histologically verified clinical cases of RR-DTC with proven resistance to radioactive iodine therapy and tumor progression according to RECIST 1.1 criteria. All patients received lenvatinib as part of clinical practice. The age of the patients ranged from 40 to 79 years, with an average age of 62.0 ± 15.6 years. Among the patients, 34 (44.2%) were women and 43 (55.8%) were men (ratio 4:5). At the start of lenvatinib therapy, 67 (87%) patients had a satisfactory somatic status (0-1 point) according to the Eastern Cooperative Oncology Group (ECOG) scale, while 10 (13%) patients had a status of 2-3 points. The dominant histological type of tumor in 54 (70%) patients was papillary thyroid cancer, 15 (19%) patients had follicular thyroid cancer, 6 (9%) had Hurthle cell carcinoma, and 1 (1%) had mucoepidermoid carcinoma. The histological subtype of the tumor was unspecified in 1 (1%) patient. Metastases in two or more organs were present in 39 (50.6%) patients. Metastatic involvement of the lungs was diagnosed in 64 (83.1%) patients, cervical lymph nodes in 39 (50.6%) patients, and mediastinal lymph nodes in 21 (27.3%) patients. In 18 (23.4%) patients, the tumor was unresectable. The study also included 21 (27.3%) patients with bone metastases, 6 (7.8%) patients with liver metastases, 3 (3.9%) with brain metastases, 2 (2.6%) with esophageal metastases, 2 (2.6%) with adrenal metastases, and 3 (3.9%) with soft tissue (skin) metastases (Table 1). Total thyroidectomy was performed at the surgical treatment stage in 76 (98.7%) patients, while 1 case was deemed inoperable. During follow-up and treatment, 25 (32.5%) patients underwent repeat surgeries for recurrence or ongoing tumor growth. After total thyroidectomy, 5 (6.5%) patients received a course of external beam radiotherapy (irradiation of the thyroid bed and regional lymphatic drainage areas). Lenvatinib as first-line treatment for RR-DTC was received by 42 (55%) patients, while 35 (45%) received it as second-line treatment. In the latter case, the median duration of prior targeted therapy (usually sorafenib) before lenvatinib was 13.0 ± 11.7 months, ranging from 1 to 36 months. The primary reason for discontinuing prior targeted therapy was tumor progression (n = 30, 85.7%); in 5 (14.3%) cases, it was due to unacceptable toxicity (Table 2).

Table 2. *Characteristics of lenvatinib therapy in patients with radioiodinerefractory differentiated thyroid cancer.*

Characteristic	**Number of patients**	
	abs.	**%**

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Line of therapy, in which lenvatinib was used: 1st line 2nd line	 42 35	 55 45
Causes of cessation of first-line targeted therapy: disease progression intolerable toxicity	 30 5	 85,7 14,3

All patients were prescribed lenvatinib therapy at the recommended dose of 24 mg/day. Dose adjustments were made as necessary according to the drug's instructions for use [12]. Monitoring during the treatment course was conducted in accordance with local hospital standards every 2-3 months and included patient interviews, physical examinations, biochemical and complete blood counts, urinalysis, electrocardiography, and computed tomography (CT) or magnetic resonance imaging (MRI) of the neck and chest (and other areas as needed). Patients with bone metastases underwent bone scintigraphy, and those with brain metastases had head CT or MRI with contrast.

Results. With a median follow-up of 27 months (range 1–45 months), at the time of data analysis, 52 (67.5%) patients were still undergoing treatment, while 25 (32.5%) had completed therapy. The reasons for discontinuing treatment were: disease progression in 7 (9.1%) cases, death in 9 (11.7%) cases, and intolerable toxicity in 5 (6.5%) cases. Three (3.9%) patients completed therapy due to the unavailability of the drug, and treatment was discontinued in 1 (1.3%) patient due to achieving a complete response. The median duration of therapy in the group that completed treatment was 18.3 months (range 1–37 months). Tumor response to treatment was assessed in 72 out of 77 patients. According to RECIST 1.1 criteria, the maximum response was classified as complete in 2 (2.6%) patients, partial in 41 (53.3%) patients, stable disease in 25 (32.5%) patients, and disease progression in 4 (5.2%) cases. The response to treatment was not evaluated in 5 (6.5%) patients. The median time to the first treatment response was 4 months (range 2–8 months). The PFS was 26.1 months (95% CI 24.0–28.2 months). The median PFS in the subgroup of patients who responded to lenvatinib therapy (with complete and partial responses) was 36.2 months (95% CI 33.4–38.9 months) (Table 3). The median OS was not reached at the time of data analysis.

Table 3. *Treatment response in patients with radioiodine-refractory differentiated thyroid cancer receiving Lenvatinib.*

Characteristic	**Value**

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Best overall response, abs. (%): complete response partial response stable disease progressive disease not evaluated	 2 (2,6) 41 (53,3) 25 (32,5) 4 (5,2) 5 (6,5)
Time to objective response, months (95 % CI)	4 (2–8)
Progression-free survival in patients responded to treatment (partial and complete response) (*n* = 43), months, Me (95 % CI)	36,2 (33,4–38,9)
Progression-free survival in all patients receiving lenvatinib (*n* = 72), months, Me (95 % CI)	26,1 (24,0–28,2)

Note. *CI – confidence interval.*

In 28 (36.4%) patients, a reduction in the sum of the maximum diameters of target lesions during treatment by more than 50% was recorded. Additionally, in 23 (29.9%) cases, the sizes of target lesions decreased by 20–50% (on average by 34%). Adverse events were recorded in 67 (87%) observations, including grade III-IV severity in 14 (18.2%) patients. Hospitalization for the management of adverse events was required in 6 (7.8%) cases, including for uncontrolled hypertension in 5 (6.5%) and for diarrhea in 1 (1.3%). Discontinuation of the drug was necessary in 5 (6.5%) patients. The dose of lenvatinib was reduced in 57 (74%) patients: in 30 (39%) to 20 mg/day and in 27 (35%) to 14 mg/day or less (Table 4).

Table 4. *Incidence of lenvatinib-associated adverse events in patients with radioiodine-refractory differentiated thyroid cancer.*

Adverse events	**Incidence, abs. (%)**
Any	67 (87,0)
Grade III–IV	14 (18,2)
Required hospitalization	6 (7,8)
Required treatment discontinuation	5 (6,5)
Required dose reduction for lenvatinib:	

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by 1 step by 2 steps or more	30 (39,0) 27 (35,1)

In the structure of adverse events during lenvatinib therapy, the following dominated: arterial hypertension (in 62% of patients, including grade III in 26%), diarrhea (in 52%), and weight loss (in 49.4%). Asthenia was recorded in 38%, decreased appetite in 30%, stomatitis in 24.7%, nausea in 23.4%, proteinuria in 18.2%, headache in 18.2%, and hand-foot syndrome in 9.1% (Table 5). Adverse events that developed during lenvatinib treatment were mostly managed by dose reduction and symptomatic therapy. In 50 (65%) patients receiving lenvatinib, thyroid-stimulating hormone (TSH) production was suppressed at the start of therapy (level <0.1 mIU/mL), while in 27 (35%) patients, the TSH level did not reach target suppression values but was within reference ranges. During lenvatinib treatment, an increase in TSH levels was detected in 47 (61%) patients, necessitating an increase in the dose of levothyroxine sodium.

Table 5. *Most common lenvatinib-associated adverse events in patients with radioiodine-refractory differentiated thyroid cancer.*

Adverse event	**Number of cases**	
	abs.	**%**
Arterial hypertension including grade >3	47 20	55 45
Diarrhea	40	52
Weight loss	38	49,4
Asthenia	29	38
Decreased appetite	23	30
Stomatitis	19	24,7
Nausea	18	23,4
Proteinuria	14	18,2
Headache	14	18,2
Hand-foot syndrome	7	9,1

Discussion. Currently, most patients with progressive RAI-R DTC receive lenvatinib as first-line targeted therapy. The effectiveness of lenvatinib was demonstrated in the multicenter, randomized, double-blind, placebo-controlled phase III SELECT trial . Based on the results of

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this study, lenvatinib was included in the clinical guidelines of the National Comprehensive Cancer Network (NCCN) as the preferred first-line treatment with a high level of evidence for efficacy. In the SELECT study, the primary endpoint was PFS, calculated for all participants regardless of response to therapy, and it was 18.3 months according to the main analysis. Later, in an updated analysis , the median PFS for patients receiving lenvatinib reached 19.4 months.

According to our study, the median PFS for patients included in the analysis (n = 72) was 26.1 months. This result surpasses the figures previously obtained in other well-known clinical trials involving patients with this disease. In the SELECT study, in the subgroup of patients who responded to lenvatinib therapy, the median PFS was 33.1 months. According to our analysis, this indicator was 36.2 months. When analyzing the incidence of adverse events (AEs) in patients participating in our study, it was found that treatment-related AEs were observed in almost all cases of lenvatinib intake (87% vs. 97.3% in the SELECT study). The incidence of severe AEs (grade III-IV) was significantly lower compared to the registration study (18.2% vs. 75.9%) . Therapy discontinuation was much less common (6.5% vs. 14.2%), and the frequency of dose reduction of lenvatinib was comparable to the data from the SELECT study (74% vs. 67.8%), which may partly be due to less intensive monitoring of treatment tolerance in clinical practice compared to clinical trials.

At the same time, the low incidence of patient complaints about AEs during lenvatinib treatment indirectly confirms the acceptable tolerability of the drug. The AE profile of lenvatinib in this series of observations did not differ from the previously known profile. No new types of AEs were noted with lenvatinib intake. The incidence of arterial hypertension was comparable to that in the SELECT study (62% and 67.8%, respectively), as was the incidence of diarrhea (52% and 59%), and weight loss (49.4% and 46.4%). However, other AEs occurred significantly less frequently compared to the SELECT study: asthenia (38% vs. 59%), decreased appetite (30% vs. 50.2%), stomatitis (24.7% vs. 35.6%), nausea (23.4% vs. 41%), proteinuria (18.2% vs. 31%), headache (18.2% vs. 27.6%), and hand-foot syndrome (9.1% vs. 31.8%). As mentioned earlier, this may be related to the low incidence of patient complaints. It should be noted that the ability to compare the obtained data with the results of the registration study is limited by differences in the designs of the randomized and observational studies, differences in the sample sizes of patients receiving lenvatinib, as well as differences in the baseline characteristics of patient populations.

At the time of data analysis, 52 (67.5%) patients continued treatment amid significant reductions in the sums of the diameters of target lesions (partial response to treatment or disease stabilization was recorded). More detailed patient interviews, monitoring of treatment tolerance, prevention, and timely correction of AEs allow lenvatinib therapy to be conducted with minimal impact on patients' quality of life.

Conclusion. According to the Russian multicenter observational study, lenvatinib therapy in patients with confirmed progressive RAI-R DTC is characterized by high efficacy, comparable to the results of the phase III SELECT registration study. In the sample of Russian patients, the median PFS was 26.1 months, and in patients who responded to treatment (complete and partial responses), this indicator reached 36.2 months. The tolerability profile of lenvatinib in clinical practice was somewhat better compared to that in the SELECT study. The proportion of

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patients who developed AEs was 87%. Severe AEs (grade III-IV) were observed in only 18.2% of patients. In 6.5% of cases, the development of AEs led to the discontinuation of the drug, and in 74% of cases, the dose of lenvatinib was reduced. It should be noted that these results may be related to the observational nature of the study and incomplete recording of AEs.

Thus, at present, lenvatinib is an effective drug for the systemic therapy of progressive RAI-R DTC with a well-studied and potentially manageable tolerability profile. The main task of physicians prescribing lenvatinib is to proactively inform patients about possible AEs, manage comorbid conditions before starting therapy, and promptly correct emerging AEs by prescribing necessary symptomatic therapy, reducing the dose, or temporarily discontinuing the drug. To prevent and manage severe AEs during treatment, it is necessary to involve cardiologists, internists, nephrologists, dermatologists, neurologists, and other related specialists to achieve the maximum treatment effect.

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