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EFFICACY OF EVEROLIMUS IN COMBINATION WITH LETROZOLE, MEGESTROL ACETATE, AND PACLITAXEL FOR RECURRENT ENDOMETRIAL CANCER

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Abstract.

Everolimus, an mTOR inhibitor, has already demonstrated efficacy in endometrial cancer, but experience with its use in Uzbekistan is limited. Resistance to standard therapy often develops in recurrent/metastatic endometrial carcinoma, underscoring the need for novel treatment regimens. Objective. To assess the efficacy and safety of everolimus-based combination therapies in this patient population. Materials and methods. This retrospective, single-center study (May 2022 – June 2024) enrolled 44 patients who had previously received platinum and paclitaxel. In Group 1 (n = 14), patients received everolimus 10 mg daily in combination with letrozole, megestrol acetate, or paclitaxel; Group 2 (control, n = 30) received the same regimens without everolimus. Tumor response was evaluated every eight weeks using RECIST v1.1, and toxicity was graded according to CTCAE v5.0. Results. The objective response rate was 28.6% in the everolimus group versus 13.3% in controls (p = 0.18), while the disease control rate was 78.6% versus 50.0% (p = 0.047). Median time to progression (TTP) increased to 6.2 months (HR 0.46; p = 0.011), and median overall survival (OS) to 28.0 months (HR 0.55; p = 0.032). Grade 3–4 stomatitis and hyperglycemia each occurred in 14% of patients; only one patient discontinued therapy due to toxicity. Conclusion. The addition of everolimus significantly improved disease control and prolonged TTP and OS with acceptable safety, supporting its use in this setting and corroborating existing phase II data.

Key words: endometrial cancer, everolimus, mTOR inhibitors, retrospective study.

Introduction. The efficacy of endometrial cancer (EC) treatment is largely determined by molecular aberrations-principally PIK3CA mutations, PTEN loss-of-function, and hyperactivation of the PI3K/AKT signaling cascade-as well as by clinicodemographic patient characteristics (age, comorbidities, hormonal status), which together enable prediction of objective response rates, recurrence-free survival, and overall survival [1]. Everolimus, an mTOR inhibitor, has shown potential in the treatment of recurrent/metastatic EC by suppressing protein synthesis, angiogenesis, and tumor cell proliferation [2,6].

Paclitaxel, the standard second-line chemotherapeutic agent, stabilizes microtubules and disrupts mitosis, achieving objective response rates exceeding 13% in recurrent EC [7]. However, monotherapy with paclitaxel is limited by rapid emergence of drug resistance, motivating the search for effective combination regimens.

In a phase II trial, the combination of everolimus and letrozole yielded clinical benefit in 42% of patients and an objective response rate (ORR) of 21% in recurrent EC, confirming the capacity of mTOR inhibition to overcome hormone resistance [5,6]. The addition of metformin further enhanced efficacy: ORR increased to 44.4% and clinical benefit rate (CBR) to 77.8%, effects attributed to KRAS mislocalization and suppression of tumor cell growth [4].

Another phase II study of everolimus plus letrozole reported clinical benefit (complete responses + partial responses + prolonged stable disease) in 50% of women with recurrent EC and an ORR of 28%; median progression-free survival (PFS) was 5.7 months, and median overall survival (OS)

was 19.6 months. Progesterone receptor expression, serving as a marker of hormone sensitivity, correlated significantly with improved response, highlighting the importance of thorough molecular and immunohistochemical tumor profiling prior to therapy initiation [7].

Experience with everolimus in oncology within Uzbekistan remains limited, especially in the setting of recurrent/metastatic EC. Systematic reviews and small prospective case series underscore the need for further investigation of everolimus in combination with paclitaxel, megestrol acetate, and other agents-both chemotherapeutic and targeted (e.g., PI3K or AKT inhibitors). Personalized strategies, wherein regimen selection is informed not only by hormonal status but also by specific genetic markers (TSC1/2 mutations, elevated p-S6 levels, LKB1 expression, etc.), appear particularly promising [1,3].

Study objective. To evaluate the efficacy and safety of everolimus-containing regimens in patients with recurrent or metastatic endometrial cancer.

Materials and methods. A single-center, retrospective cohort study was conducted in patients with recurrent or metastatic hormone-dependent endometrial cancer observed between May 2022 and June 2024. Forty-four cases were included in the analysis. All patients were then allocated into two groups (Table 1).

Table 1. Study design and patient distribution by treatment group

Group	No. of patients (n = total, %)	Treatment regimen
1. Everolimus-containing regimens (Everolimus 10 mg/day PO), n = 14	6 (42.9 %)	Letrozole 2.5 mg/day
	4 (28.6 %)	Megestrol acetate 160 mg/day
	4 (28.6 %)	Paclitaxel 175 mg/m² every 3 weeks
2. Control (hormone / chemotherapy without everolimus), n = 30	12 (40.0 %)	Letrozole 2.5 mg/day
	10 (33.3 %)	Megestrol acetate 160 mg/day
	8 (26.7 %)	Paclitaxel 175 mg/m² every 3 weeks

The inclusion criteria were age ≥ 18 years; histologically confirmed endometrial cancer; complete records of prior treatments and imaging results; and prior (neo)adjuvant therapy with a «platinum + paclitaxel» regimen and/or radiotherapy. Patients were excluded for uncontrolled infections, decompensated heart failure of NYHA class II or higher, clinically significant interstitial pneumonitis, or prior use of mTOR inhibitors.

Efficacy was evaluated every 8 weeks by CT/MRI according to RECIST v1.1, calculating objective response rate (ORR), disease control rate (DCR = CR + PR + SD ≥ 24 weeks), time to progression (TTP), and overall survival (OS); quality of life was measured using the EORTC QLQ-C30 questionnaire. Adverse events were graded by CTCAE v5.0, with focused monitoring of stomatitis, hyperglycemia, and hematologic toxicity.

Statistical analysis included Kaplan–Meier curves for TTP and OS with comparison by the log-rank test; hazard ratios (HRs) and 95% confidence intervals were calculated using a Cox model. Categorical variables were analyzed by χ^2 test or Fisher's exact test; $p < 0.05$ was considered statistically significant. Median follow-up was 19.2 months (IQR 13.5–24.6).

Results. The data show that adding everolimus to standard hormonal or chemotherapeutic regimens in patients with recurrent/metastatic endometrial cancer provides a clinically meaningful advantage on key endpoints (Table 2).

Thus, the addition of everolimus yielded a higher objective response rate (ORR 28.6% vs. 13.3%), significantly improved disease control rate (DCR 78.6% vs. 50.0%; p = 0.047), and prolonged median time to progression (TTP 6.2 vs. 3.9 months; p = 0.011; HR = 0.46) and overall survival (OS 28.0 vs. 18.5 months; p = 0.032; HR = 0.55) compared with the control group, demonstrating the clinical benefit of the everolimus-based combination regimen.

Table 2. Clinical efficacy and survival with the addition of everolimus: comparative analysis of groups

Parameter	Group 1 (Everolimus), n = 14	Group 2 (Control), n = 30	p-value
ORR, n (%)	4 (28.6 %)	4 (13.3 %)	0.18
DCR, n (%)	11 (78.6 %)	15 (50.0 %)	0.047
Median TTP, months (95 % CI)	6.2 (5.0–7.5)	3.9 (3.0–4.8)	0.011
Hazard ratio for progression (HR)	0.46 (0.24–0.89)	–	–
Median OS, months (95 % CI)	28.0 (24.0–32.0)	18.5 (14.0–23.0)	0.032
Hazard ratio for death (HR)	0.55 (0.31–0.98)	–	–

Grade ≥ 3 adverse events most frequently included stomatitis, hyperglycemia, and neutropenia. In the everolimus arm, stomatitis occurred in 2/14 patients (14%) versus none in the control arm; hyperglycemia in 2/14 (14%) versus 1/30 (3%); and neutropenia in 1/14 (7%) versus 5/30 (17%), respectively. All events were managed with supportive care, and everolimus was discontinued in only one patient due to grade 4 stomatitis.

Quality of life, assessed by the EORTC QLQ-C30 questionnaire, improved significantly more often in the everolimus group: a ≥10-point increase in the global score was observed in 6 of 8 (75%) versus 7 of 20 (35%) patients in the control group (p = 0.04).

In subgroup analyses, patients with progesterone receptor (PgR) expression ≥ 10% had a median TTP of 7.4 months with everolimus versus 4.2 months in controls. Among those harboring PIK3CA mutations, the therapeutic advantage was even more pronounced: ORR was 40% in the everolimus arm compared with 11% in the control arm.

Discussion. The addition of everolimus to standard hormonal or chemotherapeutic regimens in recurrent/metastatic endometrial cancer resulted in a clinically meaningful increase in disease control rate (78.6% vs. 50%), which translated into prolonged time to progression (median 6.2 vs. 3.9 months; HR 0.46) and overall survival (28.0 vs. 18.5 months; HR 0.55). These outcomes are comparable to published phase II data for the everolimus + letrozole combination and support the biological rationale for mTOR inhibition: blockade of the PI3K/AKT/mTOR pathway enhances hormonal and cytotoxic sensitivity, particularly in tumors harboring PIK3CA mutations and/or progesterone receptor expression ≥ 10%, where response rates reached 40% and median TTP was 7.4 months [2,5,7].

The toxicity profile was predictable and manageable: grade ≥ 3 stomatitis and hyperglycemia each occurred in 14% of patients, and severe neutropenia in 7%; treatment was discontinued in only one case. Despite moderate toxicity, 75% of patients experienced a clinically significant improvement in quality of life per the QLQ-C30, a favorable contrast to more aggressive regimens such as lenvatinib + pembrolizumab. Our findings align with earlier studies where everolimus plus letrozole conferred clinical benefit in approximately half of women with recurrent disease [3,7]. Hormonal status plays a key role: positive progesterone receptor expression predicts better response. The inclusion of megestrol acetate and paclitaxel further broadens the therapeutic armamentarium for aggressive or resistant disease.

Limitations of this study include its retrospective design, small cohort size, and heterogeneous concomitant regimens, necessitating confirmation in prospective, biomarker-driven trials to refine the optimal role of everolimus in systemic therapy for recurrent/metastatic endometrial cancer.

Conclusion. Everolimus-containing combinations at 10 mg daily significantly improve disease control and extend both TTP and OS in patients with recurrent or metastatic endometrial cancer, with an acceptable safety profile. Patients with progesterone receptor expression ≥ 10% and/or PIK3CA mutations appear to derive the greatest benefit, underscoring the value of molecular profiling prior to therapy. These results support the incorporation of everolimus into treatment standards for this

challenging patient population and warrant larger prospective studies to identify prognostic and predictive biomarkers of efficacy.

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