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The Efficacy of Low-dose vs Standard-dose Everolimus in Patients with Advanced Neuroendocrine Tumors

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BACKGROUND

Everolimus is an oral mTOR inhibitor with significant anti-cancer activity in patients with gastroenteropancreatic and lung well-differentiated neuroendocrine neoplasms. Although 10 mg once daily has been approved by the FDA, in clinical practice this dose can lead to significant toxicity and requires dose modification in most patients. Previous data from phase 1 trial in solid tumors and multicenter real-world retrospective data in breast cancer and NETs evaluated everolimus at 5 and 10 mg daily and suggested comparable efficacy, but better safety of 5 mg. This study aimed to compare the efficacy and safety of 5 vs 10 mg everolimus in NET patients.

METHODS

This is a multicenter retrospective study aimed to compare the efficacy and safety of standard 10 mg (higher dose [HD]) vs 5 mg (lower dose [LD]) everolimus in patients with advanced NETs. A chart review of patients treated with everolimus at Mayo Clinic and University Hospitals Seidman Cancer Center from January 1st, 2015, to May 28th, 2025, was performed to obtain data points. Progression-free survival (PFS) and overall survival (OS) were measured from the start date of everolimus therapy. Analyses were performed on an intention-to-treat (ITT) basis. Treatment-related adverse events (TRAEs) were graded per CTCAE v4.03. Kaplan-Meier estimates and Cox regression were used to evaluate outcomes.

RESULTS

A total of 170 patients were eligible for the study including 49 (29%) treated with 5 mg daily and 121 (71%) treated with 10 mg daily. Median age at diagnosis was 59 years; 77 (45%) were male. There was no significant difference in OS between the 10 mg and 5 mg groups in multivariable analysis (HR = 0.70, 95% CI 0.39–1.26; p=0.24). Similarly, PFS did not significantly differ (HR = 0.78, 95% CI 0.50–1.22; p=0.27). In multivariable models, higher age at diagnosis (HR=1.05, p=0.0002), higher WHO grade (G3 vs G1: HR=3.15, p=0.0008), and more prior lines of therapy (HR=1.39, p=0.017) were significantly associated with worse outcomes. The 5 mg group experienced fewer TRAEs, including hyperglycemia (6% vs. 25%; p=0.005), hypercholesterolemia (2% vs. 15%; p=0.014), stomatitis (6% vs. 15%; p=0.19) and fatigue (47% vs. 54%; p=0.50). Grade 3–4 TRAEs occurred in 21 patients (17%) receiving 10 mg daily and in 7 patients (14%) receiving 5 mg daily.

CONCLUSIONS

These results suggest that LD everolimus may provide similar efficacy to the HD everolimus while reducing toxicity and having lower treatment cost. Prospective randomized trials are needed to confirm these findings.

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