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Efficacy and Toxicity of Anti-Vascular Endothelial Growth Factor (VEGF) Receptor Tyrosine Kinase Inhibitors (TKIs) in Neuroendocrine Tumors (NETs) – A Systematic Review and Meta-Analysis

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BACKGROUND

Although anti-VEGF RTKIs have been tested in patients with NETs over the last 2 decades, no study to date has benchmarked efficacy and toxicity of these drugs in this patient population.

METHODS

A literature search was performed to identify all phase II and phase III studies of anti-VEGF RTKIs in patients with NETs published between January 1, 2000 – July 31, 2021. Major trial databases (e.g. Medline, EMBASE, Cumulative Index of Nursing and Allied Health Literature, Web of Science, Cochrane Database of Reviews and others) were searched in August 2021 for relevant studies. The primary objectives of the meta-analysis were to compare objective response rate (ORR) and progression-free survival (PFS) between patients with pancreatic (p) NETs and extra-pancreatic (ep) NETs and the incidence rate ratio (IRR) of adverse events (AEs) between patients receiving anti-VEGF RTKIs vs control drugs.

RESULTS

Of 92 potentially relevant studies, 17 studies with 8 distinct anti-VEGF RTKIs were included the meta-analysis. A total of 1611 patients were available for the analysis; 1194 received anti-VEGF RTKIs. ORR in pNETs was 18% (95% CI 13-25%) while ORR in epNETs was 8% (95% CI 5-12%); test for differences between pNETs and epNETs ($x_1^2 = 8.47$, $p < .01$). Median PFS in pNETs was 13.9 months (95% CI 11.43-16.38 months) while median PFS in epNETs was 12.71 months (95% CI 9.37-16.05 months); test for differences between pNETs and epNETs ($x_1^2 = .32$, $p = .57$). With regards to common grade 3/4 AEs, patients who received anti-VEGF RTKIs were more likely to experience hypertension (IRR 3.04, 95% CI 1.63-5.65) and proteinuria (IRR 5.79, 95% CI 1.09-30.74) relative to those who received control.

There was no difference in IRR for rare serious AEs (e.g. cardiac dysfunction, cerebrovascular accident, myocardial infarction, non-central nervous system bleeding, non-central nervous system emboli and gastrointestinal tract perforation) between patients who received anti-VEGF RTKIs and those who received control.

CONCLUSIONS

Anti-VEGF RTKIs demonstrate anti-tumor effect and safety in both pNETs and epNETs, supporting their development in both patient populations. The true determining factor for efficacy of agents within this drug class may be the baseline disease characteristics of the tested population in a randomized clinical trial; a trial including patients with more aggressive baseline disease will demonstrate greater benefit from the anti-VEGF RTKI given poorer outcomes anticipated in the control arm.

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