

Systemic Treatment of Well-Differentiated Neuroendocrine Tumors

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Systemic therapeutic options for well-differentiated NETs include biotherapy (somatostatin analogs and interferon), targeted therapy (everolimus and sunitinib), and cytotoxic chemotherapy.

Somatostatin analogs have direct and indirect anti-proliferative effects. PROMID study showed that Octreotide LAR improves progression-free survival (PFS) in patients with metastatic G1 midgut NETs. CLINET study also revealed Lanreotide improves PFS in patients with metastatic, non-functional, G1 or G2 GEP-NETs. Somatostatin analogs are well tolerated, appropriate treatment for low-grade, indolent, and SSTR-positive NETs, and also palliative for functional symptoms. Interferon- α also has direct and indirect anti-proliferative effects on NETs. In patients with carcinoid tumor, Interferon- α treatment showed 68% symptomatic response and biochemical response 42%. Due to its limited well-conducted clinical trials and toxicities, interferon is appropriate used as second line agent for palliation of carcinoid symptoms after somatostatin analogs. Telotristat is a tryptophan hydroxylase inhibitor. In TELESTAR trial, among patients with carcinoid syndrome not adequately controlled by somatostatin analogs, treatment with telotristat was generally safe and well tolerated and resulted in significant reductions in bowel movement frequency and urinary 5-hydroxyindole acetic acid.

Everolimus works as an inhibitor of mTOR. In RADIANT-3 trial, everolimus, as compared with placebo, significantly prolonged PFS among patients with progressive pancreatic NETs and was associated a low rate of severe adverse events. In RADIANT-4 trial, treatment with everolimus was associated with significant improvement in PFS in patients with progressive lung and GI NETs. Sunitinib is an oral, small-molecule, multi-targeted receptor TKI. In SUN1111 trial, administration of sunitinib improved PFS, overall survival, and the objective response rate as compared to placebo among patients with advanced pancreatic NETs.

There is no panel consensus on which cytotoxic chemotherapy regimen is best. Cisplatin/etoposide, carboplatin/etoposide, or temozolomide, can be considered for intermediate grade/atypical NETs of GI tract, lung and thymus. The following anti-cancer agents can be considered in patients with bulky, symptomatic, and/or progressive PNETs: temozolomide, 5-FU, capecitabine, dacarbazine, oxaliplatin, and streptozocin.

Many therapeutic options are available, however, the treatment choice, sequencing, and duration of treatment are still questions to be answered. More new approaches and targets are ongoing, such as combination treatment, novel targets, and immunotherapy.