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ASO PERSPECTIVES

Sequencing of Therapies in Progressive Neuroendocrine Tumors

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Patients with neuroendocrine tumors (NETs) generally have long survival, even when they present with advanced disease. There are many treatment options for advanced gastroenteropancreatic NETs (GEPNETs), including surgical resection of the primary and cytoreduction of metastases, somatostatin analogs (SSAs), targeted therapy (TT), chemotherapy (CT), hepatic embolotherapy, and peptide receptor radionuclide therapy (PRRT). For patients with advanced or metastatic NETs, SSAs are usually the first line of therapy, based upon the improvement found for progression-free survival (PFS) relative to placebo in the PROMID[1] and CLARINET trials.[2] An important unanswered question in these patients is the selection of the next treatment upon progression. This choice is influenced by many factors, including the type of tumor (pancreatic vs intestinal NET), tumor grade and differentiation, patient comorbidities, as well as the medical specialties and specific centers seeing the patient.

Since FDA approval of ^{177}Lu-DOTATATE in the United States in 2018, and for over two decades in Europe, PRRT has been an option for patients with progression of GEPNETs.[3–5] The efficacy of PRRT plus intermediate dose SSA for improving PFS of patients with advanced midgut tumors as compared to high dose SSA was established in the NETTER-1 trial, resulting in a median PFS of 25.0 and 8.5 months, respectively.[6, 7] In longer-term follow-up (median 76 months), the median overall survival (OS) was not significantly different between these 2 groups (48 and 36 months, respectively; $p = 0.30$), but 36% of patients in the high dose SSA group crossed over to receive PRRT.[8] Targeted therapies have also shown promise for treatment of progressive NETs. The mTOR pathway-targeted everolimus modestly improved PFS in lung, GI, and pancreatic NET patients,[9, 10] and the VEGF-directed tyrosine kinase inhibitor sunitinib led to PFS benefit in pancreatic NETs.[11] The chemotherapy regimen of capecitabine and temozolomide improved PFS in pancreatic NET patients over temozolomide alone, with response rates of 33%.[12] However, most experts acknowledge that there are no clear guidelines for which therapy should be used and in what order for patients with progressive GEPNETs.[13]

A recent paper by Pusceddu et al. retrospectively evaluated 508 patients with unresectable, locally advanced or metastatic GEPNETs who progressed on treatment with SSAs in 25 Italian centers between 2000 and 2020.[14] Of these, 329 were treated with PRRT on progression (45% with ^{177}Lu, 19% with ^{90}Y, and 33% with both isotopes), and 179 had targeted therapy or chemotherapy (TT/CT). The main endpoint of the study was to look at PFS in these two groups. Although overall survival is a desirable endpoint in many cancers, this has proven to be very challenging in NET studies. Patients often live for a long time, and therefore may receive many different therapies and follow-up must be long. Cross-over from one therapy to another is common, such as from PRRT to TT/CT or the reverse. Another confounder is that these studies are retrospective, leading to bias as to which therapy is given first, as well as other factors, such as whether patients are referred for primary tumor resection and/or cytoreduction of metastases. Given these limitations of a retrospective multi-institutional study, the authors sought to improve their comparisons by using propensity-matching based upon 18 patient, tumor, and treatment factors.

They found that the group receiving TT/CT had significantly more patients with pancreatic NETs, functional tumors, grade 2 and 3 tumors, and tumors with Ki-67 >

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10%, while the PRRT group had more patients undergoing surgery for their primary tumor. The groups compared by propensity-matching had 111 patients in each therapeutic category, median follow-up from diagnosis was 90 months, and median time to progression while on SSAs was 18 months in the unmatched and 13 months in the matched groups. The unmatched group receiving PRRT had significantly improved median PFS compared with the TT/CT group, at 2.5 and 0.7 years, respectively (HR 0.35; $p < 0.001$). The results were similar in the propensity-matched groups, with PFS of 2.2 and 0.6 years, respectively (HR 0.37; $p < 0.001$). However, there was no difference in OS from time of diagnosis in the unmatched groups (12.0 years in the PRRT group and 11.6 years in the TT/CT group, HR 0.81, $p = 0.11$). There was also no difference in OS in the matched group (median OS of 12.2 and 11.5 years, respectively, HR 0.83, $p = 0.36$). In subgroup and multivariable analysis, patients with functional and non-functional tumors, grade 1 and 2 tumors, and Ki-67 $\leq 10\%$ had improved PFS in the PRRT group. Patients with pancreatic NETs and intestinal NETs both had improved PFS with PRRT, with the former group having 1.6 years longer PFS than if treated with TT/CT on progression. Importantly, there was no significant improvement in PFS for PRRT over TT/CT in patients with grade 3 tumors or when Ki-67 was $> 10\%$.

What we learned from this paper was that patients with advanced GEPNETs that progress on SSAs generally have longer PFS if treated with PRRT vs targeted therapy or chemotherapy, but that did not translate into a benefit in overall survival. In the unmatched groups, patients with pancreatic NETs were treated with TT/CT 77% of the time, while 63% of patients with intestinal NETs had PRRT. This may be a reflection of practice patterns due to the larger number of TT/CT options for treating pancreatic NETs, as opposed to only everolimus being approved for intestinal NETs. This study suggests that more pancreatic NET patients might have had PFS benefit if they were treated with PRRT, at least for grade 1 and 2 tumors with Ki-67 $< 10\%$. It does not really answer the sequencing question, though, since nearly all of the patients received the other therapy when they progressed after PRRT or CT/TT, and overall survival was not affected by the sequence. The cumulative toxicity or quality of life was not measured in the two groups, nor whether PFS after PRRT was impacted by giving TT/CT beforehand, which could also affect the choice of therapy.[15]

For most patients with advanced GEPNETs, it makes sense to begin treatment with SSAs, because they are well-tolerated and most tumors grow slowly. At progression, it is still very hard to know the best choice for the next treatment. For intestinal NETs, an argument for choosing PRRT over everolimus might be that the PFS from the NETTER-1 trial for PRRT/SSA was 25 months as compared to only 11 months for everolimus in the RADIANT-4 trial.[7, 10] The ongoing COMPETE trial is currently looking at this very question in GEPNETs, with one group being randomized to ^{177}Lu-edotreotide PRRT and the other to everolimus.[16] For patients with pancreatic NETs, there are more choices available, which include PRRT, sunitinib, everolimus, and capecitabine/temozolomide, which may help explain why over three quarters of patients initially received TT/CT instead of PRRT in this study. Greater uncertainty remains in patients with higher-grade tumors, who did not appear to derive as much benefit from PRRT. The ongoing NETTER-2 trial (NCT03972488), which is randomizing patients with higher-grade GEPNETs (well-differentiated, grade 2 and 3 with Ki-67 10–55%) to PRRT (with 30 mg Sandostatin LAR, q 4 weeks) vs high-dose SSAs, will help determine the efficacy of PRRT in these patients. If a PFS benefit is found in NETTER-2, the question of whether this is superior to TT or CT will remain, especially for patients with PNETs. That question may be answered by the COMPOSE trial, comparing ^{177}Lu-edotreotide PRRT to best standard of care (including all TT and CT) in aggressive grade 2 and grade 3 GEP-NETs.[16] Another relevant trial just opening is Alliance for Clinical Trials in Oncology A022001 (ComPareNET; NCT05247905), which will randomize patients with progressive, advanced, well-differentiated grade 1–3 pancreatic NETs to PRRT (^{177}Lu-DOTATATE x 4 cycles) or 12 cycles of capecitabine/temozolomide.

Pusceddu et al. have given us valuable understanding of treatment patterns of patients with progressive pancreatic and intestinal NETs in Italy, and how PRRT may improve PFS in many patients. However, it also suffers from the same issues dogging all non-randomized studies in NETs. First is the concern with selection bias, which these authors addressed by propensity-matching. Second is the fact that patients usually live long enough to cross over to the other therapeutic arm. Since overall survival was not affected in this study, how can we be sure that giving PRRT before or after TT/CT is better for patients? We do know that PRRT with ^{177}Lu-DOTATATE is fairly safe, with low incidence of nephrotoxicity, a 2% rate of myelodysplastic syndrome or leukemia, and only 6% of patients having grade 3 or 4 adverse events.[8] Grade 3 or 4 adverse events leading to treatment discontinuation occurred in 12% of patients receiving everolimus in RADIANT-4,[10] and even more grade 3 or 4 adverse events were seen in pancreatic NET patients treated with sunitinib.[11] Time to deterioration of quality of life may be another important measure to be considered when choosing the next therapy on progression. This duration was significantly longer in the ^{177}Lu-DOTATATE group in NETTER-1.[15] Although the results of the current study would seem to favor PRRT as the next

best choice on progression, the volume of disease, rate of growth, and sites of metastases are also important factors in the choice of therapy. Clearly, additional studies are needed to determine the optimal sequencing of therapy when progression occurs in patients with GEPNETs treated with SSAs. The current retrospective evaluation provides many important insights, but the question of optimal sequencing of therapies will not be settled without randomized trials with careful stratification by tumor site, grade, and extent of disease.

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