# Personalizing Medical Care for GEP-NETs

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This activity is designed to inform physicians about the current and developing strategies in treating patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

**Target Audience:**
This activity is directed towards medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with GEP-NETs. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other health care providers are also invited to participate.

**Learning Objectives:**
After participating in this CME/CE activity, learners should be better prepared to:

- *Describe the biologic features of GEP-NETs and the rationale behind different approaches in medical intervention depending on disease characteristics*
- *Explain the development history leading to the approval of targeted therapies in GEP-NETs*
- *Discuss emerging treatment options and clinical data for GEP-NETs*

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## Introduction

Neuroendocrine tumors (NETs) encompass a widely heterogeneous group of solid tumors with multiple primary anatomic sites and manifestations, including the pancreas, gastrointestinal (GI) tract, and lungs. Collectively, gastroenteropancreatic neuroendocrine tumors (GEP-NETs) comprise the diversity of tumors arising from neuroendocrine cells anywhere along the gut.[1] While generally considered rare, the incidence of GEP-NETs has been steadily increasing over the past several decades. In 2008, more than 31,000 patients with GEP-NETs were reported to the Surveillance, Epidemiology and End Results program of the National Cancer Institute; approximately 15,000 patients had foregut NETs, 9000 had midgut NETs, and 7000 had NETs of the hindgut.[2] In 2011, the incidence rate for GEP-NETs was determined to be 3.65 cases per 100,000 people, a 3.6-fold increase from 1973.[3] This is likely primarily attributable to the increase in available and routine detection technology, including gastroscopies, colonoscopies, and capsule endoscopies—notably, the increase in rectal NETs at age 50 corresponds to the onset of recommended colonoscopies in the United States at this age.[3]

GEP-NETs can be classified by multiple systems, but they are primarily considered by anatomic site of origin and histological grade. NETs of the foregut include those that arise in the thymus, lungs, esophagus, stomach, duodenum, proximal jejunum, and pancreas; NETs of the midgut include those that arise in the distal jejunum, ileum, appendix, and right-sided colon; and NETs of the hindgut include those that arise in the left-sided colon and rectum.[4–6]

In 2010, the World Health Organization (WHO) updated the grading system for NETs to unify multiple classification systems that had arisen. The updated grading system is based on proliferation rate as defined by mitotic rate and Ki67 index. The mitotic rate is measured by the number of mitoses observed per high-power field, or per 2 $mm^2$, and the Ki67 index by the percentage of tumor cells that immunolabel positively for the Ki-67 antigen.[6,7] Low-grade, or G1, NETs have 2 mitoses per 2 $mm^2$, and a Ki67 index ≤2%; intermediate-grade, or G2, NETs have 2-20 mitoses per 2 $mm^2$ and a Ki67 index of 3% to 20%; and high-grade, or G3, NETs have >20 mitoses per 2 $mm^2$ and a Ki67 index >20%.[6,7] A summary of the WHO classification appears in **Table 1**.

GEP-NETs are commonly treated with multiple modalities and lines of treatment. Because GEP-NETs are sometimes considered a chronic condition, management of disease burden and symptoms are necessary. Standard approaches to treatment of GEP-NETs include cytotoxic chemotherapy, targeted therapies, radiation therapy, and surgical resection.

## Evolution of Targeted Therapies

Generally, systemic chemotherapy can be used to cytoreduce pancreatic NETs, but the vast majority of GI NETs have been shown to be nonresponsive to cytotoxic drugs, primarily due to their slow proliferation.[8–10] In recent years, multiple approvals and advancements have been made in the use of targeted therapies to treat NETs of multiple origins.

### *Somatostatin Analogues*

Certain NETs express somatostatin receptors (SSTRs) in variable amounts. SSTRs are G protein linked receptors that, once bound to somatostatin, activate the downstream inhibition of multiple pathways, including angiogenesis, cell growth, and neurotransmission. These pathways include the inhibition of cell proliferation, limiting cancer growth, and the secretion inhibition, reducing carcinoid symptoms. Binding of somatostatin and its analogues (SSAs) to SSTRs targets both of these mechanisms.[11]

The SSA octreotide has been approved since 1998 for use in patients with carcinoid symptoms. Administered as a subcutaneous injection, octreotide-LAR (long-acting repeatable) is approved for the management of severe diarrhea and flushing episodes associated with NETs.[12]

Lanreotide, another SSA, was approved for the treatment of patients with unresectable, locally advanced, or metastatic GEP-NETs in December 2014.[13] This approval was based on results from the phase III CLARINET trial. In this double-blind, placebo-controlled study, 204 patients with advanced, well- or moderately-differentiated, nonsecretory, SSTR-positive G1 or G2 NETs were randomized to receive 120 mg of lanreotide depot/autogel or placebo every 28 days for 96 weeks.[14] The primary endpoint of this study was progression-free survival (PFS). Secondary outcomes included overall survival (OS), quality of life, and drug safety.

Lanreotide was associated with a significantly improved PFS, with a 24-month PFS rate of 65.1% (95% CI, 54.0%-74.1%) compared with 33.0% (95% CI, 23.0%-43.3%) for placebo. The median PFS for patients receiving placebo was 18.0 months, and had not been reached for patients receiving lanreotide at time of initial publication.[14] Subsequent analysis has reported a median PFS of 30.8 months for patients receiving lanreotide.[15] There was no significant difference in

**TABLE 1. WHO 2010 Classification of GEP-NETs[7]**

| Grading | Mitotic Count (per 2 $mm^2$) | Ki67 Index (%) |
|---|---|---|
| G1 | 2 | ≤2 |
| G2 | 2-20 | 3-20 |
| G3 | >20 | >20 |

G1, G2, G3 indicate low-, intermediate-, and high-grade neuroendocrine tumors, respectively.

quality of life or OS reported between the 2 groups.[14] Treatment-related adverse events (AEs) included diarrhea in 26% of patients receiving lanreotide, abdominal pain (14%), and gallstones (10%).[14]

Since its initial approval, lanreotide has received an expanded indication for the symptom control of carcinoid syndrome, based on results of the phase III ELECT trial.[16] In this trial, 115 patients were randomized to receive lanreotide depot/autogel or placebo every 4 weeks, with access to rescue octreotide. Patients receiving lanreotide had a significantly lower percentage of days in which rescue octreotide was needed, 33.7% (95% CI, 25.0%-42.4%) compared with patients receiving placebo, 48.5% (95% CI, 39.6%-57.4%).[17]

***Tryptophan-Hydroxylase Inhibitor***

Telotristat ethyl is an agent in a novel class of drugs, tryptophan hydroxylase inhibitors. Tryptophan hydroxylase converts tryptophan to 5-hydroxytryptophan, and is the rate-limiting enzyme in the synthesis of serotonin.[18] The phase III TELESTAR study randomized 135 patients experiencing 4 or more bowel movements per day while on an SSA for symptom control 1:1:1 to 250 mg telotristat ethyl 3 times daily, 500 mg telotristat ethyl 3 times daily, or placebo. Reductions in bowel movement frequency, the primary endpoint, at week 12 were –0.9, –1.7, and –2.1 for patients receiving placebo, 250 mg, and 500 mg, respectively.[19] Response to treatment was predefined as a reduction in bowel movement frequency ≥30% for at least half of the trial's duration. This level of response was observed in 44% and 42% of patients receiving 250 mg and 500 mg, respectively. Further, treatment with telotristat ethyl was associated with a reduction in urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels of 40.1 mg/24 hours and 57.7 mg/24 hours in the 250-mg and 500-mg groups, respectively. Conversely, the mean u5-HIAA levels increased in the placebo group by 11.5 mg/24 hours by week 12.[19] Based on results from this trial, telotristat ethyl (250 mg, 3 times daily) in combination with an SSA has been approved for adult patients with carcinoid syndrome–induced diarrhea that SSA therapy has not adequately controlled.[20]

***mTOR Inhibitor***

Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), has repeatedly demonstrated activity in patients with NETs, and is now approved for the treatment of nonfunctional NETs, regardless of site of origin, with unresectable, locally advanced, or metastatic disease, based on results from the RADIANT-2, -3, and -4 trials.

RADIANT-2, a randomized, double-blind, placebo-controlled phase III study, compared everolimus in combination with octreotide-LAR versus octreotide-LAR alone in patients with low- or intermediate-grade NETs.[21] A total of 429 patients were randomized between the 2 groups. Patients receiving everolimus had a median PFS of 16.4 months (95% CI, 13.7-21.2) compared with 11.3 months (95% CI, 8.4-14.6) for patients receiving octreotide-LAR alone. Median OS was not reached in either group at the time of primary analysis, but a posthoc follow-up reported a median OS of 50.6 months (36.4-not reached) for patients receiving everolimus compared with 35.8 months (95% CI, 8.3-29.5) for patients receiving placebo.[22] AEs were mainly low grade, but included stomatitis in 62% of patients receiving everolimus, rash (37%), fatigue (31%), and diarrhea (27%).[21]

RADIANT-3, also a randomized, double-blind, placebo-controlled phase III study, evaluated the use of everolimus to treat pancreatic NETs specifically.[23] A total of 410 patients with advanced-, low-, or intermediate-grade pancreatic NETs were randomized between the 2 groups. Median PFS for patients receiving everolimus was 11.0 months (95% CI, 8.4 months -13.9 months) compared with 4.6 months (95% CI, 3.1 months-5.4 months) for patients receiving placebo. The 18-month PFS rates were 34% (95% CI, 26%-43%) and 9% (95% CI, 4%-16%), respectively. In a final analysis, median OS was 44.0 months (95% CI, 35.6%-51.8%) compared with 37.7 months (95% CI, 29.1 months -45.8 months) for patients receiving everolimus and placebo, respectively.[24] Treatment-related AEs were mostly grade 1 or 2 and included stomatitis in 64% of patients receiving everolimus, rash (49%), diarrhea (34%), fatigue (31%), and infections (23%). High-grade AEs included anemia (6%) and hyperglycemia (5%).[23] Based on the results from RADIANT-3, everolimus was approved for use in patients with NETs of a pancreatic origin in May 2011.[25]

Finally, the RADIANT-4 trial, a randomized, double-blind, placebo-controlled phase III study, evaluated the use of everolimus to treat patients with NETs of the lung or GI tract.[26] A total of 302 patients were randomized 2:1 to receive everolimus or placebo. Median PFS was 11.0 months (95% CI, 9.2 months-13.3 months) for patients receiving everolimus compared with 3.9 months (3.6-7.4) for patients receiving placebo. At the time of the initial report, everolimus was associated with a 36% reduction in estimated risk of death, relative to placebo. Complete OS analysis has not been made available at this time.[26] Overall, results from the RADIANT-4 and the RADIANT-2 trials resulted in the approval for everolimus for NETs of the GI and lung in February 2016.[25] Results from the 3 RADIANT trials can be found in **Table 2**.

## Peptide Receptor Radionucleotide Therapy

Peptide receptor radionucleotide therapy (PRRT) is a targeted radiation therapy that utilizes an SSA bound to a radiation-emitting isotope, typically yttrium-90 or lutetium-177.[27] The radiolabeled SSA is able to deliver highly targeted radiation directly to SSTR-expressing tumor cells. Used commonly in Europe and Australia, PRRT has been experiencing rapid clinical development in the United States.

In the phase III NETTER-1 trial, 229 patients with well-differentiated metastatic midgut NETs were randomized to receive 7.4 GBq (gigabecquerel) of lutetium-177–labeled dodecanetetraacetic acid–tyrosine-3-octreotate ($^{177}$Lu-Dotatate) every 8 weeks in combination with octreotide-LAR or octreotide-LAR alone.[28] PFS at 20 months was 65.2% (95% CI, 50.0%-76.8%) for patients receiving $^{177}$Lu-Dotatate compared with 10.8% (95% CI, 3.5%-23.0%) for patients receiving the control. Overall response rates were 18% and 3%, respectively. High-grade AEs included lymphopenia in 9% of patients receiving $^{177}$Lu-Dotatate, thrombocytopenia (2%), and neutropenia (1%).[28]

**TABLE 2. Results from RADIANT-2, -3, and -4 Trials Evaluating Everolimus in NETs**

| Trial | Setting | Progression-Free Survival (months) | | Overall Survival (months) | |
|---|---|---|---|---|---|
| | | Everolimus | Placebo | Everolimus | Placebo |
| RADIANT-2 | All NETs | **16.4** (95% CI, 13.7-21.2) | **11.3** (95% CI, 8.4-14.6) | **50.6** (36.4-NR) | **35.8** (95% CI, 8.3-29.5) |
| RADIANT-3 | Pancreatic | **11.0** (95% CI, 8.4-13.9) | **4.6** (95% CI, 3.1-5.4) | **44.0** (95% CI, 35.6-51.8) | **37.7** (95% CI, 29.1-45.8) |
| RADIANT-4 | Lung and GI | **11.0** (95% CI, 9.2-13.3) | **3.9** (3.6-7.4) | **NR** | **NR** |

GI indicates gastrointestinal; NET, neuroendocrine tumor; NR, not reached.

For more information on the targeted therapies discussed here, as well as an expert perspectives on how to integrate these therapies into practice, please see our interview with Alexandria T. Phan, MD, below.

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**AJHO®: What key distinctions do you make in your treatment of gastrointestinal (GI) neuroendocrine tumors (NETs) versus pancreatic NETs?**

*ATP*: There are several distinctions, but to put it simply, NETs that come from the GI tract versus pancreas behave differently. Treatment, therefore, has historically been developed to treat them in parallel fashion, or differently. NETs are classified by the origin of the tumor, or the primary sites, but are also classified by the embryonic origin of the primary site: midgut, foregut, and hindgut.

GI NETs are typically found in the midgut, and are typically more indolent. Even in the metastatic setting, their overall survival (OS) is longer than pancreatic NETs, which are considered foregut NETs, in the same category as lung NETs. That is why they are treated differently. Their biological behaviors—meaning that their OS, the natural history of disease—are different, and their responses to treatment are different. Typically, we consider pancreatic NETs to be more responsive to chemotherapy than GI NETs.

Further, pancreatic NETs typically present with local regional disease rather than metastatic disease. Still, they do have recurrence. Compare that with GI NETs, which typically present with metastatic disease. GI NETs are so indolent they will not produce symptoms until they're advanced or metastatic.

GI NETs versus pancreatic NETs are biologically different, respond to different treatments, and are prognostically different.

**Gastroenteropancreatic (GEP)-NETs have multiple approved treatment options. How do you determine first-line therapy and sequencing strategies for your patients?**

GEP-NETs have many treatment options, but GI NETs have fewer treatment options than pancreatic NETs. Let's start out broad, then go specifically based on their origin of disease.

The way I decide on the treatment of GEP-NETs is generally based on both cancer factors and patient factors. Patient factors include if they have anything that would predispose them to increased treatment-associated toxicity: their performance status, their organ function, their compliance to oral therapy, or whether they have a contraindication against therapy.

In terms of cancer characteristics, the 2 goals of treatment for NETs are symptom control and disease control. Symptom control consists of managing symptoms as the result of hormonal overproduction or burden of disease. Disease control involves slowing down cancer and reducing the risk of progression or tumor invasion.

The first thing I ask for patients with NETs, no matter what stage of cancer is, are they a surgical candidate? If it's surgical intervention, they go to surgery first. When they come back, then we discuss medical treatment options.

When considered medical or systemic treatment, you have to look at their disease. If they have an indolent disease, minimal disease burden, and no symptoms, that patient may be a good candidate for observation or treatment with a somatostatin analogue: lanreotide or octreotide.

Now if a patient has symptomatic, bulky disease, then the first treatment would be something to cytoreduce their tumor as fast as possible. For example, if a patient presents with borderline resectable pancreatic NETs we may want to cytoreduce; in that case, treatment would include temozolomide-based chemotherapy or streptozocin-based chemotherapy. For patients with bulky or moderate disease without

symptoms, we can consider treatment with either a somatostatin analogue or a targeted therapy.

These are the things I look for in the first-line setting: bulky disease, hormonal symptoms, and patient characteristics.

**What is the role of chemotherapy in this evolving treatment paradigm?**

If we're talking about chemotherapy, we're talking about cytotoxic chemotherapy drugs.

Chemotherapy was studied in pancreatic NETs. We do not have robust prospective data of chemotherapy in patients with midgut NETs. So, at this point chemotherapy is only indicated for pancreatic NETs. Any chemotherapy given for midgut or GI NETs is usually a treatment of last resort when no other treatment is available.

**How do you classify high-grade NETs? What biological markers or histology do you look for? What changes do you make in your treatment approach for high-risk patients?**

Another classification of NETs is based on the grade of tumor. Tumor grade is defined by the proliferative index of the cancer cell. We measure the proliferative index by Ki67, an immunohistochemical stain, and by mitotic count, the number of mitoses observed in high-power field in histology tissue-staining. NETs can be low-grade, intermediate-grade, or high-grade. Low-grade NETs have less than 2% Ki67 and fewer than 2 mitoses per high-power field. High-grade NETs have a Ki67 greater than 20% and greater than 20 mitoses per high-power field. Intermediate-grade NETs are anywhere in between.

Patients with a high-grade NET are typically sicker. They'll present with constitutional symptoms including fevers, night sweats, or loss of weight. Low-grade NET patients typically have fewer symptoms and usually feel well.

High-grade NETs, by definition, are tumors with a rapid turnover or cell growth. Typically, their prognosis is worse because they are very aggressive tumors. Treatment for high-grade NETs are predominantly chemotherapy-based. High-risk status also includes increased risk from treatment itself.

While high-grade NET patients have poorer prognoses, they also have a high chance of response with treatment. Clinical studies with therapy for high-grade NETs have not been able to demonstrate survival improvement. There's a need to develop effective and less toxic therapy for patients high-grade NETs.

**How does the FDA approval of the oral tryptophan hydroxylase inhibitor, telotristat ethyl, affect your use of lanreotide and octreotide in the management of your patients with GEP-NETs?**

Tryptophan hydroxylase is a key enzyme involved in the pathway to convert tryptophan into serotonin. In some NET cells, serotonin is overproduced. Overproduction of serotonin has a negative effect on the body. Oversecretion can cause pulmonary fibrosis, valvular fibrosis, mesentery fibrosis, and, of course, diarrhea.

Telotristat is approved by the FDA for use in combination with lanreotide or octreotide for the management of patients with carcinoid syndrome that is serotonin-mediated. It is not currently being used as a single agent, as the study that led to approval involved combination therapy.

Telotristat is usually well tolerated. Its indication is for diarrhea, so knowing the different causes of diarrhea will help you be more effective in using telotristat and treating patients. Diarrhea of carcinoid syndrome is secondary to overproduction of serotonin by neuroendocrine tumor cells. Such diarrhea can be effectively controlled by inhibiting tryptophan hydroxylase with telotristat inside the cells, and by targeting somatostatin receptors with somatostatin analogues on the surfaces of the cells. Hence, by inhibiting both on the receptor surface (with a somatostatin analogue), and internally inhibiting the synthesis of serotonin (with telotristat), you can optimize the management of diarrhea from carcinoid syndrome.

**When do you elect to use antiangiogenic multitargeted tyrosine-kinase inhibitors (TKIs), such as sunitinib, for your patients with NETs? Does the development of cabozantinib or pazopanib impact this?**

Talking specifically about antiangiogenic targets, there are quite a few. Bevacizumab blocks the receptors at the surface, while the TKIs work downstream from the receptors. Sunitinib is currently the only FDA-approved TKI for the management of pancreatic NETs following disease progression. It is not approved for GI NETs or lung NETs; it is another very specific approval. In my practice, I usually select sunitinib for patients with pancreatic NETs who have progressive disease after observation, or after lanreotide. There have been several other antiangiogenic TKIs evaluated in NETs, but only sunitinib was FDA approved. Pazopanib was evaluated in a 2-armed parallel phase II study—1 arm for pancreatic NETs, 1 for midgut NETs. In this study, treatment with pazopanib did seem to have favorable outcome with prolonged progression-free survival (PFS) durations in both arms. Cabozantinib demonstrated impressive prolongation of PFS in patients with NETs, and is currently being developed for a multicenter clinical trial.

**The mammalian target of rapamycin (mTOR) inhibitor everolimus is approved for use in NETs regardless of tumor location. How has this new indication impacted your treatment strategy decisions?**

The only mTOR inhibitor that has demonstrated benefit in NETs is everolimus, at 10 mg daily. Everolimus has been evaluated in 3 pivotal phase III trials, RADIANT-2, -3, and -4. RADIANT-3 was in patients with pancreatic NETs and demonstrated improved PFS with mTOR inhibition compared with placebo. This resulted in the first FDA indication of this drug in NETs.

The second indication came from a compilation of RADIANT-2 and -4. RADIANT-2 alone was insufficient to demonstrate a PFS benefit in GI NETs. Then, RADIANT-4, which included GI NETs and lung NETs, demonstrated that treatment with everolimus resulted in PFS benefit.

Unlike the antiangiogenic TKIs, this drug has a broad indication for NETs that are well differentiated. The objective response rate (ORR) is less than 7%. It's important to note that some long-term adverse effects (AEs) can be significant. Everolimus can cause elevated blood sugar and kidney failure, among other AEs. Due to its broad indication, it is commonly the drug of choice for most NETs after they fail frontline therapy, whatever that may be. Still, treatment-related AEs are notable and need to be carefully monitored.

So how does this new indication impact my treatment strategy decisions? There are important considerations to make every time I change treatment for a patient—whether it's in the frontline setting, after progression, or elsewise. You should consider the patient characteristics that are relevant, and whether this patient can manage or even tolerate this treatment in the long term. Then, you should consider what AEs you'll need to manage with patients if you put them new therapy. Goals of therapy are other important considerations when changing therapy.

In general, everolimus gives me another option for my patients with NETs. The obvious question is, how do you pick between everolimus and sunitinib? For now, that should be based on the AE profile of each of the drugs.

**Following up on that, can you discuss the AE profiles, and how that informs your decision?**

Sure! Let's start with somatostatin analogues. Common AEs include elevated blood sugar, gallstones, or gallbladder sludging. Another thing to be aware of is pancreatic insufficiency. Those are the 4 common AEs.

For antiangiogenic multitargeted TKIs, hypertension, leukopenia, DVT or clotting, and proteinuria are the 4 most important AEs. Then, for the mTOR inhibitor, everolimus, for me the most frequent AEs are stomatitis and blood-sugar elevation. Everolimus can also cause kidney dysfunction, swelling of the legs, and interstitial pneumonitis. Interstitial pneumonitis happens rarely, and sometimes symptoms don't even present until it becomes rather bad.

**FDA approval of peptide receptor radionuclide therapy (PRRT) is anticipated for later this year. How would PRRT impact your sequencing strategies? What barriers may exist in the implementation of PRRT for oncologists?**

PRRT has been used more commonly in Europe, the UK, and Australia, but without any prospective studies. Its use was primarily based on retrospective and historical studies—until PRRT was prospectively evaluated in the United States.

The first prospective study with PRRT, the NETTER-1 trial, was done in the United States. NETTER-1 was published in the *New England Journal of Medicine* in January 2017. The study only took patients with GI NETs who had progressed on frontline therapy, and randomized them to receive PRRT with octreotide at 30 mg or 60 mg. The primary endpoint was PFS. They also evaluated OS and ORR.

The ORR for GI NETs was significant at 19%. One potential implication of this study is that PRRT can be used to cytoreduce NETs that are borderline resectable. Second, risk of progression or death was reduced by 80% compared with high-dose octreotide. There is no other chemotherapy or targeted drug that is able to demonstrate that kind of impressive benefit.

How does this impact sequencing? Well, PRRT, once it's approved by the FDA, would be for use after progression of disease. PRRT hasn't been investigated in the frontline setting. I think that PRRT works best when the patient has less disease. So, we really should evaluate its role in the frontline setting or in patients who have borderline resectable disease who would benefit from cytoreduction. For now, data would support PRRT to be used after progression of another therapy. In the future, I think it should be a frontline treatment option or adjuvant following R1 surgical resection.

Barriers certainly exist in the implementation of PRRT. Not every institution will be able to offer PRRT, as the treatment requires the availability of a cyclotron and the availability of predictive diagnostic $^{68}$Ga-based PET scans. An institution needs to be within a certain perimeter of where the ligands are produced, due to their half-life, and once it's administered, the facility must have the ability to manage and monitor radioactive excretion of the material.

The barriers to any general cancer providers include access and understanding of its indication and timing for effective utilization of PRRT. Having a facility that can manage the radioactive safety of the compounds, and multidisciplinary clinical expertise, such as in a NET center of excellence, will go a long way in optimizing care for patients with NET. Providers should refer their patients to places with clinical expertise that are equipped to handle PRRT.

**What role might immunotherapy have in the treatment of GEP-NETs? What other emerging therapies are on the horizon?**

Immunotherapy has revolutionized the whole field of oncology. In NETs, its role is yet to be determined. NETs are hidden in the human body for so long that they may not be immunogenic. There are ongoing clinical trials with immunotherapy for the treatment of GEP-NETs, but we don't have any data. Still, I think immunotherapy is an exciting field of research for patients with NETs.

Other emergent therapies include CDK4/6 inhibitors and fibroblast growth factor inhibitors. There will be a lot focus on sequencing treatments and determining the role of PRRT after its FDA approval. More targeted therapies are on the horizon.

**What is the role of a multidisciplinary team in managing patients with GEP-NETs?**

Metastatic or unresectable NETs are an incurable cancer that mimics a chronic condition. With a chronic condition, if properly managed, a patient can have a prolonged life expectancy.

As a result, a multidisciplinary team is very relevant and significant to such a goal. The longer a patient lives, the more you're going to need a multidisciplinary team to manage their chronic illness. Whether it's an endocrinologist to manage their diabetes, which can result from treatment-related AEs—or just life—or a cardiologist to manage their cardiovascular disease, multiple specialties need to be involved.

The roles of a surgeon, interventional radiologist, radiation oncologist, and medical oncologist all are relevant in the management of a patient with a NET. Once you pursue one treatment option, it affects the availability of others. Given how long patients can live, it's not a decision that you can make in isolation.

Let's say you pursue surgery. If you take a patient to surgery, you still have to address the metastatic disease. You'll need medical oncologists to get involved. During the course of systemic therapy provided by medical oncologists, additional therapy may become necessary to control syndromic symptoms or palliative pain. An interventional radiologist giving liver-directed therapy, and a radiation oncologist giving palliative radiation, will be likely relevant and involved. Personally, I think that nowhere is the multidisciplinary approach deemed as relevant as much as in the management of patients with NETs.

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# Updates in Rare Hematology: Advancing Care and Improving Outcomes for Patients with Aplastic Anemia

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## Background and Disease Biology of Aplastic Anemia

Aplastic anemia is a rare heterogeneous disorder, characterized by hematopoietic stem cell (HSC) deficiency and bone marrow hypoplasia, resulting in significant reductions of red blood cell (RBC), white blood cell (WBC), and platelet levels. This "empty" bone marrow causes a combination of cytopenia, neutropenia, and thrombocytopenia, collectively referred to as *pancytopenia*. While calculated incidence rates vary, a 2008 report found this rare disease to occur in 2.34 per million people per year, meaning an estimated 750 new cases of AA could be reported in the United States in 2017.[1] Internationally, incidence rates vary, but have been found to be as high as 2- to 3-fold higher in Asia.[1,2] Aplastic anemia is more common in adolescents and young adults between age 10 and 25 years, as well as adults over age 60 years; it is further rarer in children, but can still affect approximately 1 per million per year.[1,3]

Aplastic anemia is caused by an immune-mediated destruction of HSCs, where autoreactive T cells are suspected to play a key role.[4] While the exact mechanism remains unclear, clinical evidence suggesting that AA is an immune-mediated disease dates to clinical observations first published in 1970, when Mathe and colleagues showed the immunosuppressive effect of antilymphocytic serum in patients with AA, restoring autologous bone marrow function in some patients.[5] Other early studies have documented long-lasting recovery of peripheral blood counts in 30% to 80% of patients receiving immunosuppressant agents, including antilymphocyte globulin, methylprednisolone, cyclosporine (CsA), or cyclophosphamide.[6-10] The pathogenesis of AA is thought to involve destruction of HSCs by cytotoxic T lymphocytes. Inflammatory cytokines such as interferon- and tumor necrosis factor- are overproduced, contributing to bone marrow failure. This results in reduced cell cycling, induced apoptosis, and a depletion of HSCs.[4]

Aplastic anemia can be broadly classified into acquired, or idiopathic, and inherited types.[11] Acquired AA, which accounts for 80% to 90% of AA cases, can be caused by the drug-, chemi-

cal-, virus-, or ionizing radiation-induced destruction of HSCs, but most patients lack any preceding etiologic exposure. Inherited AA is rarer, accounting for 10% to 20% of cases of AA. The main causes of inherited AA include Fanconi anemia (FA) and dyskeratosis congenita or telomere disorder, and less commonly, Shwachman-Diamond syndrome and congenital amegakaryocytic thrombocytopenia. While absence of these features does not rule out a diagnosis of inherited AA, screening for Fanconi anemia and telomere disease is recommended for all children and young adults to determine proper clinical management and potential donor selection, especially in those with a suggestive personal or family history.[11]

Clinical symptoms of AA in children and adults can range from mild cytopenia, often revealed by a routine blood count,[11,12] to symptomatic cytopenia expressed with pallor, infection, and mucosal bleeding. Thrombocytopenia can further lead to bleeding in major organs, while prolonged neutropenia increases susceptibility to infections. Blood transfusions are frequently required to treat and mitigate AA, exposing a patient to the risk of iron overload, further leading to dysfunctions in multiple organ systems; these include endocrinopathies, liver siderosis, and cardiomyopathy, usually after many years, if iron chelation therapy is not instituted.[13] Overall, AA is associated with significantly reduced quality of life, substantial morbidity, and an increased risk of premature death.[11,13]

## Diagnosis and Grading of Aplastic Anemia

Acquired AA is a diagnosis of exclusion; there is no single test that can diagnose idiopathic disease. As patients with both acquired and inherited AA present with similar symptoms of pancytopenia, a differential diagnosis for acquired AA necessitates evaluating for inherited causes. A careful personal and family history should be performed, including comprehensive physical examination, to evaluate for extrahematopoietic abnormalities suggestive of an inherited syndrome. For example, FA is characterized by short stature, predisposition to neoplasia, skin hyperpigmentation, and skeletal abnormalities, particularly those of the thumb. While FA most commonly presents in children, diagnosis can be delayed until adulthood in 30% to 40% of patients.[11] Fanconi anemia can be most effectively screened for by performing a chromosomal breakage analysis on peripheral blood, the diepoxybutane (DEB) assay.[11] Treatment guidelines suggest that clinical expertise be sought for patients with diagnostic uncertainty.[14]

Confirmatory diagnosis of AA also requires exclusion of other bone marrow disorders that may cause pancytopenia and hypocellularity, including hypocellular myelodysplastic syndrome (MDS) or leukemia, which can be determined with cytogenetic analysis and flow cytometry, respectively. Aplastic anemia can also occur in association with paroxysmal nocturnal hemoglobinuria (PNH), and is best evaluated by performing flow cytometry of peripheral blood for glycosylphosphatidylinositol (GPI)-anchored proteins. A bone marrow aspirate and trephine biopsy are both required for the confirmatory diagnosis of AA.[14] Two of the following clinical features must be present to confirm a diagnosis of severe AA: neutrophils levels $0.5 \times 10^9/L$, platelet count $20 \times 10^9/L$, and reticulocyte count $60 \times 10^9/L$.[15]

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**Learning Objectives**

Upon completion of this activity, you should be better able to:

1. Describe pathobiology of AA and evidence-based approaches for accurate diagnosis of patients with AA
2. Outline first and second-line treatment strategies to optimize clinical outcomes in patients with AA
3. Discuss potential treatment-associated adverse events and strategies to mitigate their occurrence and impact for patients with AA
4. Evaluate recent clinical trial results and apply these findings in the context of an evolving treatment landscape for management of AA

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