Treatment of Metastatic Carcinoid Tumors With Radiolabeled Biologic Molecules

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Abstract
Treatment options in advanced-stage neuroendocrine tumors are limited. A promising new category of therapy was recently introduced for these tumors in which radioactive atoms are attached to molecules that target and bind to neuroendocrine cancer cells. 90Yttrium-DOTA-Phe1-Tyr3-octreotide and radioactive drugs which targets cells by binding to somatostatin receptors. 131Iodine-metaiodobenzylguanidine also targets neuroendocrine tumors using the amine transporter system. Both agents, along with the somatostatin analogue 177Lutetium-DOTATATE, have shown objective response rates in approximately 30% of patients with progressive metastatic disease. Symptomatic improvement is observed in most patients receiving these drugs and evidence of survival benefit is also mounting. Serious side effects are uncommon. (JNCCN 2009;7:760–764)

Neuroendocrine tumors typically synthesize and secrete various bioactive monoamines and peptides that can cause debilitating symptoms. Therapy of metastatic neuroendocrine malignancies, including the large subset of carcinoid tumors, was enhanced dramatically with the introduction of the somatostatin analogue octreotide into clinical practice over a decade ago. Unfortunately, nearly all of these tumors will eventually become resistant to the clinical effects of octreotide, and therapeutic options are limited for patients with disseminated disease who reach this point. Fortunately, a relatively new form of treatment is becoming available for these patients, involving the use of radiolabeled somatostatin analog peptides.

Because of the presence of somatostatin receptors (SSTRs) on cell surface membranes, most (> 95%) carcinoid tumors will bind certain peptide analogs of somatostatin. 90Yttrium (90Y)-DOTA-Phe1-Tyr3-octreotide (90Y-DOTATOC) is a radiopharmaceutical that targets these receptors and has proven promising in clinical trials for treating patients with carcinoid tumors.1–5 This molecule is similar in structure to 111Indium (111In)-pentetreoctreotide, which is used in routine clinical practice to image and detect all types of neuroendocrine tumors. Unlike 111In, which emits gamma rays, 90Y emits beta particles, which have the potential to kill tumor cells by indirectly and irreparably damaging the structure of DNA.

Other radiolabeled somatostatin peptide analogs, some with even better tumor-targeting properties and different beta-emitting radionuclides (most notably 177Lutetium [177Lu]-DOTATATE), have also proven efficacious for treating patients with advanced-stage carcinoid tumors.6 The concept of using beta-emitting radiolabeled peptide molecules to target corresponding cancerous cell receptors is often referred to as peptide receptor radionuclide therapy (PRRT).

Results have been encouraging from clinical trials investigating 90Y-DOTATOC in patients with metastatic carcinoid tumors. Published data for these patients, including those from the authors’ experience, indicate an overall response rate (partial + complete remissions) ranging from approximately 20% to 35%, with a substantial fraction of additional patients experiencing disease stabilization (Figure 1).1,3,5 Moreover, good evidence shows that in addition to tumor shrinkage, PRRT leads to a significant reduction in morbidity with improved quality of life (Figure 2). Several studies have found that 60% to 70% of individuals experience notable improve-
therapy is limited by tumor radiation dose levels that are achievable without causing substantial toxicity to normal organs. Currently, radiation exposure to the kidneys is the dosage-limiting factor for nearly all PRRTs, including treatments using $^{90}$Y-DOTATOC. This is because the kidney tubules efficiently reabsorb and retain these radiolabeled peptides. Cationic amino acid solutions infused at treatment inhibit this reabsorption leading to a corresponding reduction in renal radiation exposure of approximately 20% to 30%.

A small fraction of patients who have undergone PRRT with concomitant amino acid infusion have developed renal insufficiency, usually beginning 6 to 12 months after the last therapy cycle. Compelling data has supported a significant survival benefit for patients with advanced-stage carcinoid tumors treated with this radioactive drug.

As expected, tumors that show the greatest uptake on a diagnostic imaging study with $^{111}$In-pentetreotide, or similar diagnostic radiolabeled peptide, are more likely to respond to therapy with $^{90}$Y-DOTATOC. Interestingly, larger tumors seem to respond better to $^{90}$Y-labeled agents and smaller tumors to $^{177}$Lu-labeled peptides. This finding is consistent with the longer particle path length of the higher-energy beta radiation coming from $^{90}$Y compared with $^{177}$Lu.

In general, the efficacy of targeted radionuclide therapy is limited by tumor radiation dose levels that are achievable without causing substantial toxicity to normal organs. Currently, radiation exposure to the kidneys is the dosage-limiting factor for nearly all PRRTs, including treatments using $^{90}$Y-DOTATOC. This is because the kidney tubules efficiently reabsorb and retain these radiolabeled peptides. Cationic amino acid solutions infused at treatment inhibit this reabsorption leading to a corresponding reduction in renal radiation exposure of approximately 20% to 30%.

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Figure 1 A) Metastatic carcinoid tumor (t) in liver on baseline CT. B) Follow-up CT at the same level after 3 treatment cycles with $^{90}$Y-DOTATOC shows nearly complete resolution of the hepatic metastases with overall reduction in liver volume. The right kidney is now visible where there once had been tumor. C) Baseline single-photon emission computed tomography (SPECT) axial image at the level of the CT slices shows tumor targeting with the diagnostic radiopharmaceutical $^{111}$In-pentetreotide in the lesions seen on baseline CT. Tumor is also observed on SPECT image (arrow) at a site in the liver not seen on baseline CT. Notice that all tumor sites show $^{111}$In-pentetreotide uptake levels greater than surrounding normal liver, a criteria used to determine appropriateness of therapy. Abbreviations: K, kidney; S, spleen; T, tumor.

Figure 2 Patient with progressive metastatic disease to the liver with clinical carcinoid syndrome which had become resistant to the effects of octreotide. A) Baseline MRI depicts 2 (white arrows) of 13 total hepatic metastases. B) Follow-up MRI after completion of 3 cycles of $^{90}$Y-DOTATOC shows no significant changes in the lesions. C) Axial single-photon emission computed tomography (SPECT) image with $^{111}$In-pentetreotide at the same level as the MRI depicts uptake greater than adjacent normal liver in the tumor sites (black arrows). Clinical symptoms of diarrhea and flushing were much improved after therapy despite the lack of objective response on MRI. Abbreviation: S, spleen.
treatment with radiolabeled SSTR peptides over a population of patients. Consequently, an individualized assessment of expected kidney radiation exposure before the actual treatment makes it possible to maximize the administered radioactive peptide dosage for a given individual while limiting the likelihood of renal radiation toxicity.16

Acute or subacute side effects from PRRT are minimal and consist largely of mild reversible bone marrow suppression and occasional short-term nausea or vomiting largely associated with the amino acid solution. Some patients may also feel lethargy, fatigue, or malaise for a few days to a week after a treatment cycle because of the generalized effects of radiation on the body.

The procedure associated with PRRT typically consists of first performing a scan to determine if the tumor sites concentrate sufficient radiotracer to achieve therapeutic radiation levels with a subsequent treatment. Currently, this is most often accomplished using 111In-pentetreotide. If the scan does not show adequate tumor targeting, then the individual is not treated. Intravenous infusions are delivered over 15 to 20 minutes. Treatments generally consist of anywhere from 2 to 4 cycles separated by 6 to 9 weeks each to allow for bone marrow recovery. Amino acid solutions are administered concomitantly over 4 hours at 90Y-DOTATOC infusion to help minimize renal radiation exposure to this organ. Therapy with both the 90Y- and 177Lu-labeled SSTR peptides are typically performed on an outpatient basis.

A distinctly different radiopharmaceutical, 131Iodine (131I)-metaiodobenzylguanidine (131I-MIBG), has been used successfully for many years to treat neuroblastoma in children and pheochromocytoma in adults, but it has also been used to a lesser extent to treat metastatic carcinoid tumors.17 This radioactive drug is concentrated in tumor cells through the same amine uptake and transporter system used for norepinephrine. Overall response rates for 131I-MIBG seem similar to those observed with PRRT in patients with carcinoid tumors, but less experience has been reported with this agent.17,18 Importantly, data also indicates improved survival for patients with advanced-stage carcinoid tumors treated with 131I-MIBG.18

Unlike with 90Y-DOTATOC or 177Lu-DOTATATE, renal toxicity does not occur with 131I-MIBG. Bone marrow suppression is the dose-limiting event observed with this agent. Patients may also experience lethargy or malaise for a few days after treatment with 131I-MIBG. Similar to PRRT, multiple treatment cycles consisting of intravenous drug delivery over 15 to 20 minutes are often used with 131I-MIBG for treating neuroendocrine malignancies. Radiation safety concerns are somewhat different for 131I-MIBG, necessitating inpatient treatment with this drug, as opposed to with 90Y-DOTATOC or 177Lu-DOTATATE, which are delivered on an outpatient basis. Finally, similar to the standard procedure for PRRT, tumor imaging with 131I-MIBG must first be performed to establish adequate tumor targeting before any therapy with 131I-MIBG.

Targeted radionuclide therapy using the radiopharmaceuticals discussed in this article may be considered in any patient with an advanced-stage carcinoid tumor, particularly in the presence of progressive disease or significant tumor-related symptoms. It is essential as a prerequisite to therapy to show sufficient tumor targeting using diagnostic administration of the proposed therapeutic agent or its surrogate. The authors’ recommended approach involves initially imaging a patient with 111In-pentetreotide. If it is ascertained that tumor octreopeptide uptake is inadequate for a reasonable expectation of successful therapy with 90Y-DOTATOC or 177Lu-DOTATATE, imaging should next be performed with 123I-MIBG to determine whether treatment with 131I-MIBG might be effective. In general, levels of tumor uptake less than those seen in normal liver are considered inadequate for therapy. Exceptions to this may be made for tumors smaller than 1 cm in diameter.

Delivering radiation doses to carcinoid tumors from any of these radioactive drugs individually, at sufficient levels to cause a high percentage of objective anti-tumor responses, is challenging because of the dose limits imposed by damage to normal tissues. Taking advantage of the fact that the kidney is the radiation critical organ for 90Y-DOTATOC and 177Lu-DOTATATE in contrast with red marrow for 131I-MIBG, the authors introduced and validated the concept that tumor radiation doses can be substantially increased in certain patients through combining specific levels of 90Y-DOTATOC with 131I-MIBG (or 177Lu-DOTATATE with 131I-MIBG) while not exceeding critical organ radiation dose limits.19

Using 131I-MIBG with radiolabeled octreotide in combination therapy has other potential ad-
vantages. The cellular targeting mechanisms for \(^{131}\text{I}-\text{MIBG}\) and \(^{90}\text{Y}-\text{DOTATOC}\) or \(^{177}\text{Lu}-\text{DOTATE}\) are distinctly different. Some individuals with carcinoid tumors have been shown to have tumor sites with good octreotide uptake and poor MIBG uptake, and other tumor sites with good MIBG uptake and limited octreotide uptake.\(^{20}\) Clearly, the relative expression of the amine transporter and SSTRs, as determined through uptake of MIBG and octreotides, respectively, may be substantially discordant within some patients; hence, the value of delivering both agents.\(^{21–23}\)

Combining \(^{131}\text{I}-\text{MIBG}\) with \(^{90}\text{Y}-\text{DOTATOC}\) has another potential advantage. The maximum beta-particle energy for the emissions from \(^{131}\text{I}\) and \(^{90}\text{Y}\) are substantially different (0.6 and 2.3 MeV, respectively). Consequently, a notable difference also exists in the distance over which the electron energy is delivered in tissue. Therefore, the optimal tumor diameter for effective therapy is probably only an order of several millimeters for beta particles from \(^{131}\text{I}\), whereas it is an order of magnitude larger for particles from \(^{90}\text{Y}\).\(^{24}\) This has been confirmed in preclinical studies.\(^{25–27}\)

Unfortunately, clinical availability remains a problem for these agents. \(^{90}\text{Y}-\text{DOTATOC}\) and \(^{177}\text{Lu}-\text{DOTATE}\) are currently unavailable in the United States. However, both agents are being used at specialized medical centers in Europe, including Erasmus University Medical center in Rotterdam. \(^{131}\text{I}-\text{MIBG}\) is currently being given as part of a clinical trial at Duke University and is available at Emory University in Atlanta under a physician-sponsored Investigational New Drug application.

In summary, \(^{131}\text{I}-\text{MIBG}\), \(^{90}\text{Y}-\text{DOTATOC}\), and \(^{177}\text{Lu}-\text{DOTATE}\) are all effective in treating patients with metastatic carcinoid tumors that are progressing or no longer respond well to octreotide. Side effects are typically mild and reversible, with a low incidence of chronic renal insufficiency associated with the radiolabeled octreotides but not with \(^{131}\text{I}-\text{MIBG}\). The future of targeted radionuclide therapy might include using some combination of these agents to improve radiation dose-delivery and better treat multiple tumors of varying sizes. Combining these agents with selected chemotherapy drugs known to enhance the effects of radiation is another promising area for future investigation.

References


