

Brief Opinion

Lutetium Lu-177 Dotatate Flare Reaction

Andrew L. Salner, MD,^{a,*} Bette Blankenship, MS,^a
Hayley Dunnack, BSN, RN, OCN,^b Christopher Niemann, PharmD,^c and
Helaine Bertsch, MD^a



Departments of Radiation Oncology,^a Oncology Nursing,^b and Oncology Pharmacy,^c Hartford HealthCare Cancer Institute at Hartford Hospital, Hartford, Connecticut

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Abstract

Purpose: Lutetium Lu-177 dotatate is the first peptide receptor radionuclide therapy approved by the US Food and Drug Administration. Well-designed studies in Europe have shown dramatic effectiveness in improving progression-free survival in patients with gastroenteropancreatic neuroendocrine tumors, which are progressive and generally metastatic. This therapy is a molecular targeted therapy linking a beta-emitting radioisotope to dotatate, which binds tightly to somatostatin receptors on neuroendocrine tumors cells. Various adverse effects of this therapy have been reported in the literature, including potential toxicity to renal, hepatic, and hematologic tissues and risk of second malignancy. Our study sought to explore acute adverse effects in this patient population.

Methods and Materials: We tracked adverse effects and patient experience in our first year of therapy experience with this new agent.

Results: In our first 12 patients who received Lutetium Lu-177 dotatate, tumor flare reactions occurred in 5 patients due to worsening symptoms of bone or soft tissue metastasis. This flare reaction can be mitigated with short course of corticosteroid therapy or other strategies.

Conclusions: Flare reaction is common in patients with progressive metastatic gastroenteropancreatic neuroendocrine tumors and can be managed successfully with several strategies.

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Introduction

The advent of peptide receptor radionuclide therapy (PRRT) has provided clinicians with new therapeutic strategies to treat patients with neoplasms for which treatment is less effective and where fewer options remain.¹ These therapies offer a molecularly targeted means of delivering precise radiation therapy to the

tumors, which are frequently metastatic and resistant to other conventional therapies. Gastroenteropancreatic neuroendocrine tumors (GEP NETs) exemplify a group of tumors that are challenging due to a high likelihood of recurrence and metastasis, and relatively few active therapies that can cause meaningful progression free survival.² The first of these therapies approved by the US Food and Drug Administration is Lutetium Lu-177 Dotatate (TM Lutathera), an agent that includes a dotatate moiety, which binds tightly to somatostatin receptors on NET cells, and the beta-emitting radionuclide Lutetium-177, with a half-life of 6.7 days and a maximum beta range of 2 mm in tissue. This agent has been used in Europe for many years, and landmark studies have

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* Corresponding author: Andrew L. Salner, MD; E-mail: andrew.salner@hhchealth.org

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demonstrated substantial improvements in response rates and progression free survival in the GEP NET patient population.^{3,4} There have also been demonstrable improvements in quality of life.⁵ Several adverse reactions to this therapy have been reported, including renal, hepatic, and hematologic injury, and increased risk of late organ injury and secondary neoplasms.^{3,6-10} In this report, we document a flare reaction in 5 of our initial 12 patients treated and suggest therapeutic strategies to help mitigate this reaction. Although various toxicities including renal, hematologic and gastrointestinal have been reported in the literature, flare reaction and suggested mitigation strategies have not been widely reported. Palliative external radiation therapy has been frequently associated with pain flare in patients with bony metastasis.¹¹⁻¹³ The temporary use of corticosteroids has been successfully used to diminish this acute effect.^{14,15}

Methods and Materials

As the flagship teaching hospital of one of the largest hospital systems in our state with a high volume of patients with cancer, we have closely followed the research related to PRRTs. We have also been excited about a potential therapeutic strategy to manage patients with progressive NETs. Upon lutetium Lu-177 dotatate approval by the US Food and Drug Administration, our clinical team expressed interest in initiating a program to serve patients with GEP NETs in our system, and as well as those from other hospitals and oncology programs in the state. Delivery of this agent is complex, due in particular to the need for the infusion of amino acid solution as a renal protectant. This solution is highly emetogenic, requiring pretreatment with a group of antiemetic therapies which include ondansetron, aprepitant, and dexamethasone (12-mg single dose). All patients received their monthly somatostatin analog (SSA) dose

after completion of their 7-hour amino acid solution infusion. We initiated this program in 2018 through a collaborative effort of radiation oncology, radiation safety, nuclear medicine, oncology nursing, and pharmacy. We developed standard protocols, procedures, and consent; staff and patient educational materials, and documentation standards for lutetium Lu-177 receipt, administration, and patient release. These include monitoring of hematologic, renal, and hepatic function as well as patient adverse effects. By protocol, a total of 4 doses are delivered at 8-week intervals and each dose is followed by the administration of SSA to avoid competition for tumor binding sites.

Results

As seen in Table 1, we have treated 12 patients between December 2018 and April 2020. Eight were female and 4 are male. The age range at the time of treatment initiation was 45 to 77 years with a median of 66 years. All patients have GEP NETs with the exception of one patient with a NET arising from a dysplastic kidney, for whom we were able to gain authorization for treatment. All patients had documented progression of disease on SSAs. Some patients also had progression on chemotherapy or mTor inhibitors, palliative external beam irradiation, as well as prior therapy with bland, chemotherapy, or radioembolization of hepatic metastases. All patients had hepatic metastases, and most had metastasis to retroperitoneal or mesenteric nodes as well. Several patients also had bony metastases, pulmonary metastases, and other areas of metastatic disease, including subcutaneous metastases. Most patients had some symptoms of carcinoid syndrome. Some had symptoms emanating from areas of metastases, including bone pain, liver pain, small bowel dysfunction, early satiety, and neuropathic pain related to nerve

Table 1 Patient characteristics and flare reactions

Patient no./age/sex	Primary site	Prior therapy	Flare type (CTCAE score)	Mitigation success
1/69/f	Sm bowel	SSA, temozolomide	Cranial nerve dysfunction (2)	Fair
2/46/f	Sm bowel	SSA, pall RT	Bone pain (2)	Good
3/68/m	Pancreas	SSA, everolimus, Y90 and chemo emb		
4/57/f	Sm bowel	SSA		
5/68/f	Sm bowel	SSA, bland and Y90 emb	Epigastric pain (2)	Fair
6/56/m	Sm bowel	SSA, TACE	Small bowel dysfunction (2)	Fair
7/47/f	Sm bowel	SSA	pSBO (3)	Good
8/65/f	Kidney	SSA		
9/68/m	Sm bowel	SSA, Y90		
10/77/f	Sm bowel	SSA, TACE, ablation. Liver resection		
11/73/f	Sm bowel	SSA, TACE, everolimus, Y90		
12/45/m	Pancreas	SSA, everolimus		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; emb = embolization; pall = palliative; pSBO = partial small bowel obstruction; RT = radiation therapy; sm = small; SSA = somatostatin analog therapy; TACE = transarterial chemoembolization.

compression. All patients had documentation of avidity on gallium dotatate positron emission tomography scanning before treatment initiation.

Five patients exhibited flare reactions of symptoms during the first week after lutetium Lu-177 dotatate therapy. Two of these were related to bone metastases. In one patient with base of skull metastases, seventh cranial nerve dysfunction was noted. In another with spine metastasis, increased spine pain occurred. In a patient with extremely bulky left liver metastasis, increased epigastric pain and early satiety occurred. In 2 patients with extensive mesenteric metastases, increased bowel dysfunction and partial small bowel obstruction occurred. All of the flare reactions were quantified by Common Terminology Criteria for Adverse Events grades 2 (4 patients) or 3 (1 patient). Mitigation with a short course of oral corticosteroids was generally successful, as well as use of symptomatic medications. Steroid courses either included a methylprednisolone dose pack or a week of prednisone 40 mg daily. In patients who developed a flare reaction after the first of 4 lutetium Lu-177 dotatate administrations, we recommended a steroid course for subsequent courses, and also elected to arrange a phone or physical visit with their radiation oncologist or medical oncologist within the first week after administration to monitor and appropriately manage flare symptoms.

Discussion

Lutetium Lu-177 dotatate has become an additional effective therapy in the management of patients with GEP NETs.^{3,4} It is an excellent example of a targeted molecular therapy, as it binds avidly to the somatostatin receptors on NET cells, and delivers a high radiation dose via the beta emitting isotope Lutetium-177. Its use has been associated with a high likelihood of improving progression free survival. It is therefore not unexpected that flare reactions might occur similar to those which occur through the use of external radiation therapy. Flare reactions certainly occur on occasion in patients with symptomatic bony metastases who undergo palliative radiation therapy.^{11,12} This reaction might be treated with a temporary course of corticosteroids, or analgesics as appropriate.^{14,15}

In our patients with GEP NETs receiving Lutetium Lu-177 dotatate, we have observed flare reactions associated with bony metastasis and soft tissue deposits of disease, in the liver and small bowel mesentery. These flare reactions are presumably mediated by transient local edema or inflammation secondary to initial tumor cell injury. Therefore, one might conjecture that such a process could occur either in bone or soft tissue if the local environment is subject to swelling causing nerve pressure or other organ dysfunction. Given the risk of such side effects

recurring with subsequent doses of the Lutetium Lu-177 dotatate, we discovered that either a short prophylactic course of corticosteroids in subsequent courses was useful, or that close monitoring in the first week after therapy was warranted to manage adverse effects as needed. The single dose of 12 mg of dexamethasone administered on the day of treatment as an antiemetic was clearly not enough to prevent the flare reaction in these patients, likely owing to concomitant timing and lack of steroid presence on subsequent days when radiation was still present.

Mitigation of flare related symptoms with steroids or symptomatic medications as judged by patient report and MD assessment was fair to good. It is likely that a patient already focally symptomatic from a GEP-NET lesion, such as in bone or soft tissue, may be at increased risk for experiencing a flare reaction. Radiation oncologists are particularly adept at managing these symptoms owing to the fact that that they may commonly occur during courses of external beam irradiation. One potential benefit of having a radiation oncologist involved in radionuclide therapy for cancer is their expertise in dealing with adverse effects which are in some ways analogous to external radiation therapy.

Conclusions

Tumor flare reactions are common with the use of Lutetium Lu-177 dotatate in the management of GEP NETs. In our series of 12 patients, 2 had flare reactions characterized by bony metastasis causing spine pain and cranial nerve dysfunction due to skull base metastasis. An additional 3 patients had flare reactions due to soft tissue metastasis causing pain due to liver metastasis in one and bowel dysfunction in 2. All flare reactions were manifested in the first of 4 administrations. Management with a short course of corticosteroids and appropriate analgesics was generally successful. Use of such strategy for the 3 subsequent courses was helpful, as was close monitoring of the patient in the week after therapy to determine what interventions might be helpful.

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