Use of ^{90}Y SIR-Spheres in the Treatment of Unresectable Hepatic Metastases from Neuroendocrine Tumors

13

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Neuroendocrine tumors (NET), and their majority subset carcinoid tumors, are derived from peptide and amine producing or enterochromaffin cells which originate diffusely within the body. They produce an array of bioactive amines and peptides including neuron-specific enolases, 5-hydroxytryptamine, 5-hydroxytryptophan, synaptophysin, chromogranins A and C, ACTH, growth hormone, serotonin, and a number of others [1]. NET cannot be classified on histologic examination as malignant or benign; that distinction can only be achieved by the identification of metastatic lesions. These tumors will metastasize commonly to either the liver or the bone depending on their cells of origin. The carcinoid syndrome is another hallmark of malignancy since liver metastases are required to produce the characteristic cutaneous flushing, episodic hypertension, diarrhea, and asthma. Damage to the tricuspid and pulmonic cardiac valves arises from long-standing carcinoid syndrome. Foregut carcinoids, commonly originating in the bronchus, metastasize to bone but the appearance of the carcinoid syndrome is uncommon. Carcinoid tumors have the midgut as the most frequent site of origin and commonly (60%–87%) have the carcinoid syndrome. Midgut carcinoid tumors commonly arise in the small bowel, are multiple, and metastasize to the liver. Finally, hindgut carcinoids rarely have the carcinoid syndrome, arise in the colon or rectum, metastasize to bone, and are unusual, accounting for only 5% of the tumors. Carcinoid liver metastases present almost uniformly with the carcinoid syndrome and may show effects on the heart, due to fibrosis of the endocardium usually on the right side of the heart. However, large nodal metastases or metastases to other organs may cause the carcinoid syndrome due to direct venous drainage of the vasoactive products of the tumor and are responsible for up to 9% of patients presenting with carcinoid syndrome without liver metastases [2].

Demonstration of the site of origin of these tumors is a complex process involving computed tomography, magnetic resonance imaging, and nuclear medicine. Liver metastases may be imaged by use of either CT or MRI as space occupying lesions. With the advent of OctreoScans (Mallinckrodt Medical, Petten, The Netherlands), an indium-111 isotope bound to the somatostatin analogue, octreotide, the sensitivity of the discovery of the tumors has risen dramatically. These scans have very high sensitivity and demonstrate lesions that are not seen with any other imaging modality. PET scanning with standard agents has less sensitivity but when demonstrated to be positive, suggests that the tumor is more aggressive [3].

Given that midgut tumors smaller than 1 cm have a 15%–20% rate of metastases and in some series up to 69% of tumors smaller than 1 cm in diameter have metastases and virtually a certainty when the tumor is larger, the risk is extremely high that a carcinoid tumor will develop metastases sometime in the patient's lifetime. The risk of metastases is slightly lower in other sites of origin. Thus, palliation of the symptoms of carcinoid syndrome has been the backbone of treatment for this tumor when it is unresectable. With the development of the long-acting somatostatin analogues, octreotide and lanreotide, hormone levels and symptoms can be kept under reasonable control in roughly 80% of patients. It has also been noted that tumors may respond to the administration of these somatostatin analogues. However, there is no

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agreement on when, or if, patients should be started on chemotherapy as all regimens, either single agent or multiple, have response rates of around 30% at best with duration of response, at the longest, of 1 year.

Hepatic arterial bland and chemo-embolization have also been utilized. This therapy is based on the anatomic vascular distribution of the blood supply for hepatic tumors. The hepatic artery serves tumors in the liver almost exclusively while the portal vein serves normal hepatic parenchyma. There is some crossover but it is only approximately 10%. Bland embolization uses particles placed in the hepatic artery only while chemoembolization mixes these particles with a variety of chemotherapeutic agents and lipiodol, an iodinated poppy seed oil, which has been shown to increase the uptake into the cell via a pump in the cell wall. This therapy has been utilized for the last 20 years but eventual re-growth and recurrence have also uniformly occurred. Repeated embolizations are necessary to keep the disease in check and to palliate the patient's symptoms. The mean response to embolization is approximately 12–18 months with eventual occlusion of the hepatic arterial supply to the tumor after multiple embolizations. Response to embolotherapy has been dramatic for palliation of symptoms, with 63% of patients reporting a reduction in symptoms and an objective response seen on CT to be 76% either partial or minimal response, with an additional 16% reporting stable disease [4]. The embolotherapy will rid the patient of much of their tumor burden but isolated islets of viable tumor will remain after the procedure, accounting for the resurgence of disease.

With the advent of ^{90}Y particulate therapy, there is now a method of rapidly and effectively treating patients with unresectable hepatic metastases from carcinoid/neuroendocrine tumors combining the effects of hepatic arterial embolization and the use of high dose radiation to treat any remaining viable tumor sites.

Patients with unresectable metastatic carcinoid were referred to the Interventional Radiology Division for treatment with ^{90}Y SIR-Spheres® (Sirtex, Sidney, Australia). These patients had metastatic disease which was unresectable and had an ECOG performance score of 0 or 1. The treating agent is a 35-μm diameter resin sphere containing a pure beta particle emitter having a penetration depth of 2–4 mm with an energy of 0.9367 MeV. Since the particle is embolized into the hepatic artery, it will become lodged in the tumor arterioles and will irradiate only the tumor with minimal dose to the normal liver parenchyma. Previous work has demonstrated that the tumors receive up to 3000 Gray and are encompassed with the 1000 Gray isodose curve with the hepatic parenchyma receiving less than 50 Gray [5]. Prior to treating these patients, serology was performed to evaluate hepatic function as well as computed tomographic scanning and nuclear medicine scanning. Positron emission tomography scans were evaluated prior to treatment, as well as OctreoScans for those patients whose PET scans were not evaluable.

Hepatic arteriography with embolization of the gastroduodenal artery, as well as any other artery that could be supplying stomach or bowel, was performed utilizing stainless steel or platinum coils. Such partial embolization of the gastrointestinal tract is well tolerated since it has a rich collateral blood supply. Embolization of 2–4 mCi of technetium-99m macroaggregated albumin into the hepatic artery was performed in all cases. Nuclear medicine scanning with SPECT and planar scanning was utilized to determine the amount of hepatic artery to pulmonary artery shunting. The MAA was utilized as a surrogate for the SIR-Spheres even though the MAA particles are of a different size distribution. This screening has been demonstrated to replicate the actual treatment distribution of the SIR-Spheres. Patients who had greater than 20% of the spheres shunted to the lungs were excluded from this treatment as the lungs would receive greater than their tolerated dose. As an aside, the risk of radiation pneumonitis, the most serious complication of this procedure, has been all but eliminated do to this test. In the US, with over 2000 administrations of SIR-Spheres, there has not been a single documented case of radiation pneumonitis.

Exclusion criteria included:

1. A bilirubin greater than 2.0 mg/dl
2. Liver failure
3. Hepatic artery to hepatic vein shunt with pulmonary deposition of greater than 20% of the dose
4. An irreversible hepatic artery to gastrointestinal tract arterial deposition of MAA, as explained above

Note that the bilirubin level of 2 mg/dl or greater is an absolute contraindication. Since the bilirubin is being utilized as a marker for hepatic function, a level higher than 2.0 mg/dl denotes impaired hepatic function. Any increase over 2.0 should not be considered "marginal" and the patient treated because it will undoubtedly have dire consequences. The specifics of the preliminary screening examina-

tion and description of the treatment itself can be found elsewhere [6].

All patients were placed on somatostatin before the procedure to prevent a "carcinoid crisis" due to the massive release of serotonin during treatment. Additionally, an intravenous dose of steroids was administered immediately prior to the start of the procedure to help in reducing hepatic edema. Also given prior to the procedure was a proton pump inhibitor which would treat any small gastric ulcers in the unlikely event of non-target embolization of a gastric artery. All patients had a tapered steroid dose prescribed after the procedure lasting 1 week, as well as continued proton pump inhibitor, analgesic and antiemetic therapies for out-patient use. Patients were kept in the short stay unit for the day and overnight if symptoms persisted. Approximately 85%–90% of procedures were outpatient, i.e. patients were discharged to home the same day as the treatment. Follow-up to treatment was performed 4–6 weeks later. PET scans were performed 3 months after treatment and every 6 months thereafter.

The response of 84 patients, 43 males and 41 women, treated with this method were followed. All patients initially complained of liver referable symptoms and had unresectable hepatic disease. Of 84 patients 73 had carcinoid, eight had gastrinoma, and three had undifferentiated neuroendocrine tumors. Their average age was 58 with a range of 32–74 years. The tumors were universally extremely hypervascular. The more hypervascular a tumor is on angiography, the larger the dose is that can be administered safely since there are more tumor arterioles in which to deposit the spheres. The average dose administered was 2.1 GBq (56 mCi), which is about 30% more than hypovascular tumors. Two-thirds of the patients received sequential lobar treatment with first one lobe then the other treated approximately 1 month later. The remaining third had a whole liver treatment with the entire liver treated in one session with, usually, a repeat whole liver treatment 1 month later. Follow-up was 14 months on average.

There were no deaths from this therapy but there were 14 cases of grade 3 gastrointestinal toxicity with pain, nausea and vomiting which all resolved after appropriate medical therapy. Two patients developed ulcers, which were treated with medical therapy and resolved. There was no surgical treatment of ulcers.

PET/OctreoScan results demonstrated complete response in 20 patients (24%), partial response in 41 (43%) and stabilization occurring in the remainder. A total of 80% of patients noted symptomatic received relief from their symptoms with either reduction in their analgesic intake (37%) or complete elimination of analgesics (43%).

As with previous reports, CT scans were less sensitive than PET scans with no patients achieving a complete response, 32% having a partial or minimal response, and stabilization in 50% and progression in 18% [6]. The discrepancy between the PET/OctreoScan response and the computed tomographic response can be attributed to the greater specificity of the functional imaging studies. Consequently, all patients with activity demonstrated on nuclear medicine scans had treatment decisions made upon these scans.

Seven patients achieved a complete response for longer than 1 year as measured by PET scans. None of these patients required the administration of somatostatin analogues or other systemic therapy and are currently being followed with yearly PET scans. The longest current survivor is at 4 years without evidence of recurrent disease.

The use of ^{90}Y microspheres in hepatic arterial embolization demonstrates promise in dealing with neuroendocrine tumors with a high degree of effectiveness at low toxicity. Further studies are warranted to demonstrate its effectiveness in other treatment schemas.

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