Acute Liver Necrosis Induced by Iodine-131-MIBG in the Treatment of Metastatic Carcinoid Tumors

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Iodine-131-metaiodobenzylguanidine (MIBG) is used in the treatment of carcinoid tumors. Temporary palliation with complete subjective symptomatic response has been reported in these patients. This treatment is usually well tolerated and side-effects are generally limited to nausea, mild hepatic toxicity with spontaneous recovery and temporary myelosuppression. Our case report shows that repeated treatment with [131I]MIBG in a patient with extensive carcinoid liver metastasis may cause severe hepatic toxicity leading to death. Factors such as concomitant use of 5-fluorouracil and the progressive nature of the disease may have contributed to this event.

Key Words: iodine-131-MIBG; carcinoid tumor; acute liver necrosis; therapy

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Carcinoid tumors are slow-growing neoplasms arising from the amine precursor uptake and decarboxylation cells of the diffuse endocrine system. The use of [131I]metaiodobenzylguanidine (MIBG) in neural crest and other potentially [131I]MIBG-concentrating tumors for both diagnostic and therapeudic purposes has been developed after successful application of [131I]MIBG in the localization of pheochromocytoma (1). In contrast to neuroblastoma and pheochromocytoma, the role of [131I]MIBG in the treatment of metastatic carcinoids is mainly palliative. The cumulative results of [131I]MIBG treatment in metastatic carcinoid tumors indicate a palliative effect in 65% and tumor reduction in 15% (2–6). To date, reported toxicity has been limited to nausea and vomiting and transient myelosuppression. Besides these effects, transient mild hepatic dysfunction 1 wk after treatment with full recovery after conservative therapy has been reported in one of four patients with liver metastases due to a carcinoid tumor (7). We treated 12 patients with [131I]MIBG (1 with pheochromocytoma, 2 with medullary thyroid carcinoma and 9 with carcinoid tumors) at our hospital. The present case demonstrates an unexpected, severe complication of [131I]MIBG therapy for carcinoid with widespread liver metastasis.

CASE REPORT

Two years before a liver metastasis appeared, our patient underwent a radical pancreaticoduodenectomy for a primary pancreatic carcinoid. The initial diagnosis was made when he presented with attacks of flushing and diarrhea. At that time, no distant metastasis was known, especially no liver metastasis. Shortly
before liver metastases were detected, his condition deteriorated, his diarrhea increased and he lost weight. Since he was known to have liver metastases, he received palliative treatment with four [131I]MIBG administrations (two doses of 3.7 GBq and two doses of 7.4 GBq over 1.5 yr). One day before treatment with [131I]MIBG, potassium iodate (170 mg/day) was started and continued for 10 days to block thyroid uptake of free 131I (less than 5%). Iodine-131-MIBG was purchased from commercial sources and administered through a running intravenous drip in 0.9% saline over 2 hr through an infusion system equipped with a pump. The specific activity was 0.74 GBq/mg. Thus, a 7400-MBq dosage will contain 10 mg MIBG. This amount of unlabeled MIBG will not contribute to the antitumor effect (8). Moreover, in the last year, continuous 5-fluorouracil (5-FU) 300 mg/m2/day, intravenously was used. 5-FU is one of the known effective chemotherapy regimens for palliative carcinoid treatment. Both the [131I]MIBG and 5-FU therapies were well tolerated and gave subjective improvement. The patient's fatigue diminished, his appetite increased and he had, during this period, no complaints of diarrhea or flushes. In the time of admission for his fifth [131I]MIBG therapy, he was 53 yr old. Preceding this renewed [131I]MIBG course of treatment, he experienced increasing pain in the liver area, general fatigue, nausea, vomiting and increasing dyspnea. Physical examination showed ascites and a very large, irregular, rock-hard liver that was tender by palpation. During the preceding 3 mo, blood chemistry demonstrated a rising serum liver enzyme concentration (see Fig. 1 for serum bilirubin and alanine aminotransferase (ALT) values during the course of the disease under [131I]MIBG). Previ-}

**FIGURE 1.** Serum bilirubin and ALT values of a patient with liver metastasis from a carcinoid tumor of the pancreas during repeated intravenously administered [131I]MIBG therapy.

...ously, pre- and post-therapeutic [131I]MIBG scintigrams showed multiple liver metastases (Fig. 2). These lesions were confirmed by CT examination of the liver (Fig. 3), which also showed progressive liver metastasis from the pancreatic carcinoid, but also a considerable remaining normal liver tissue. Based on volumetric CT measurements, this patient had 52% normal liver tissue and 48% necrosis and metastatic liver tissue. The second day after the fifth [131I]MIBG therapy (7400 MBq), the patient became increasingly confused and dull. Complementary blood chemistry demonstrated rapidly progressive liver insufficiency (as shown by the serum bilirubin and ALT values in Fig. 1), resulting in a hepatorenal syndrome (urea 58.6 mmol/liter, creatinine 230 μmol/liter, sodium 160 mmol/liter, potassium 5.5 mmol/liter).

Despite treatment of the hepatorenal syndrome (volume expansion with salt/glucose, lactulose syrup 30 ml/hr, oral neomycin 4 × 1000 mg and fresh frozen plasma), the patient died from acute liver cell necrosis 8 days after [131I]MIBG administration.

A postmortem liver scintigram showed multiple [131I]MIBG-concentrating lesions as well as normal liver tissue (Fig. 4). Postmortem examination confirmed death by acute liver failure due to metastasized carcinoid. Signs of veno-occlusive liver disease, frequently observed in cases of radiation hepatitis, were absent.

**FIGURE 3.** Contrast-enhanced CT of the liver shortly before the fifth [131I]MIBG therapy demonstrates multiple solid tumors of the liver beside normal liver tissue.

**FIGURE 2.** (A) Iodine-131-MIBG scintigraphy 4 wk before the fifth [131I]MIBG therapy (7400 MBq) reveals multiple abnormal tumor uptake of the liver. (B) The 99mTc-colloid scintigram demonstrated nonfunctional liver tissue corresponding to the [131I]MIBG-avid areas beside normal colloid-avid tissue.
FIGURE 4. Postmortem scintigram (coronal SPECT slices) of the liver show multiple lesions with \(^{131}I\)MIBG uptake.

**DISCUSSION**

Less than 5% of the carcinoid tumors arise from the pancreas. Carcinoid tumors generally metastasize to the liver and may involve this organ extensively, with minimal metastatic disease elsewhere. This typical metastatic pattern was also found in our patient, as shown by \(^{131}I\)MIBG scintigraphy.

Significant symptomatic relief is described in patients with a metastasized carcinoid, after treatment with \(^{131}I\)MIBG (9). Response duration is 3–24 mo and tends to improve with increasing administered dose (4). However, only 60% of the carcinoid tumors concentrate MIBG (10). In addition, \(^{131}I\)MIBG uptake is often variable in tumors at different sites in the same individual, with relative sparing of some metastases, and this evidently limits therapeutic response. Therefore, the consensus is that \(^{131}I\)MIBG therapy should only be considered for patients in whom every tumor site is known to concentrate MIBG. Our patient satisfied these criteria.

In general, MIBG treatment is well tolerated with side effects limited to nausea 48–72 hr postinfusion, mild hepatic dysfunction with spontaneous recovery and temporary myelosuppression 4–6 wk post-therapy (7,11). Ackery et al. (12) reported three cases of hypoparathyroidism. We report on a patient who developed severe liver failure and a lethal hepato-renal syndrome after repeated \(^{131}I\)MIBG therapy. The acute onset of the hepatic failure makes it very unlikely that this event was due to tumor progression only. Therefore, it must be concluded that the deterioration of this patient was due to a combination of factors, including the repeated \(^{131}I\)MIBG treatment. 5-FU may have had an additive effect to this toxicity. 5-FU has been recognized as a potential clinical radiosensitizer (13,14) with no hepatotoxicity of its own. In general, concomitant continuous infusion of 5-FU and external beam radiotherapy might improve patients’ survival, but drug uptake by adjacent or dose-limiting normal tissue could limit the therapeutic gain for radiosensitization of tumor compared with normal tissue (15–17).

Because only animal dosimetric data are available for the treatment of carcinoids metastasized to the liver, no firm conclusions have been made with regard to the role of \(^{131}I\)MIBG in this particular patient. Reported estimated absorbed radiation doses to the liver from a \(^{131}I\)MIBG dosage range from 0.152–1.9 mGy/MBq and are mainly based on data from children with neuroblastoma (8).

**CONCLUSION**

Severe hepatic toxicity and hepato-renal syndrome can result after repeated therapeutic administration of \(^{131}I\)MIBG for metastatic carcinoid tumor of the liver, despite previously well tolerated \(^{131}I\)MIBG therapy. Although hepatic toxicity is a rather uncommon event after \(^{131}I\)MIBG treatment, physicians should be aware of this complication in patients with extensive liver metastases. In retrospect, no final conclusion can be drawn for the acute liver failure in this patient, but presumably the concomitant use of a radiosensitizing agent (5-FU), previous \(^{131}I\)MIBG administrations and the progressive nature of the disease (progressive liver metastasis on CT and slightly increase of liver enzyme values) contributed to the toxicity. Therefore, we believe that \(^{131}I\)MIBG therapy under such conditions has to be seriously reconsidered. Moreover, more exact dosimetric calculation (quantitative SPECT) is desirable to define optimum dosage schedules to prevent lethal side-effects in patients receiving multiple therapeutic dosages of \(^{131}I\)MIBG (18).

**REFERENCES**