

Prolonged survival in the setting of metastatic cecal carcinoid tumor treated with combined gemcitabine-carboplatin chemotherapy regimen

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ABSTRACT

Gastrointestinal carcinoid tumors are rare. They constitute approximately two-thirds of all carcinoid tumors. Numerous therapeutic modalities have been used to treat metastatic carcinoids, including hepatic artery embolization and chemoembolization, surgical resection, radio-frequency ablation, chemotherapy, and the use of Octreotide combined with interferon-alpha. We report a case of sustained symptomatic control in a patient with cecal carcinoid metastatic to the liver using a combination of gemcitabine and carboplatin (G&C). We believe that this case illustrates the potential clinical value of the G&C combination in the setting of metastatic gastrointestinal carcinoid tumor. Larger clinical trials will be required to fully elucidate the clinical efficacy and side effects of similar regimens.

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INTRODUCTION

Gastrointestinal carcinoid tumors are rare, although their incidence has been rising over the last 30 years.^{1,2} They constitute approximately two-thirds of all carcinoid tumors.² Only about two-thirds of patients with gastrointestinal carcinoids survive five years from the time of initial diagnosis, regardless of tumor site.² Numerous therapeutic modalities have been used to treat metastatic carcinoids, including hepatic artery embolization and chemoembolization^{3,4}, surgical resection⁵, radio-frequency ablation⁶, chemotherapy^{4,7}, and the use of Octreotide combined with interferon-alpha.⁸ We report a case of sustained symptomatic control in a patient with cecal carcinoid metastatic to the liver using a chemotherapeutic combination consisting of gemcitabine and carboplatin (G&C).

CASE REPORT

A 78-year-old man presented to our institution with several weeks of generalized weakness. He stated that he was unable to perform daily tasks at home, including lifting objects and ambulating. The patient also noted right upper quadrant discomfort, increased abdominal girth, paresthesias in his arms and hands, and occasional fevers to 102°F. His past medical history included type II diabetes with diabetic neuropathy and prostate cancer diagnosed five years prior to the current presentation.

At the time of the current presentation, his physical exam demonstrated mild abdominal distention and hepatomegaly.

Neuromuscular evaluation showed proximal muscle weakness in all extremities and diminished deep tendon reflexes. The patient also had mild sensory loss to pinprick in all four extremities.

The patient underwent an extensive investigation into the cause of his symptoms. A right upper quadrant ultrasound showed multiple hepatic lesions suspicious for metastatic disease. His leukocyte count was 11,600/mm³ (85% segmented forms). While his CPK and TSH were normal, the erythrocyte sedimentation rate was elevated at 112. His carcinoembryonic antigen (CEA) level was normal at 0.6 ng/mL. Neuron-specific enolase (NSE) was elevated slightly at 12.9 ng/mL (normal range, 0.0-12.5 ng/mL).

Computed tomography (CT) of abdomen and pelvis confirmed the presence of multiple, rounded, low-attenuation lesions in the liver, most likely metastatic in nature. Thickening of the cecum and the appendix was also noted. Subsequent colonoscopy showed a lesion in the cecum, with features characteristic of a carcinoid tumor. A whole-body nuclear scan showed no evidence of osseous or other extrahepatic metastases.

The patient subsequently underwent right hemicolectomy and a wedge biopsy of the liver. The procedure was uneventful. Operative pathology demonstrated carcinoid tumor of the terminal ileum extending through the bowel wall into the adjacent fatty tissue and lymph nodes. The appendix was also involved with carcinoid. There was widespread lymphatic invasion into the mesentery and microscopic satellite carcinoid tumors in the adjacent bowel wall. The liver biopsy specimen confirmed metastatic carcinoid tumor.

Patient had an uneventful postoperative recovery and felt significantly better following tumor resection. His residual carcinoid-related symptomatology was treated effectively with octreotide. At that time, the patient opted not to receive any chemotherapy because of minimal residual symptoms and because of significant drop in postoperative 5-HIAA levels (**Figure 1**, page 13).

The patient was followed in the office on one-monthly basis. He was relatively symptom-free, and was continued on Octreotide. However, approximately two years following surgical resection of his carcinoid, his symptomatology worsened significantly, and he required four re-admissions to the hospital. This coincided with significant worsening of the tumor spread on magnetic resonance imaging (MRI) and concurrent increase in serum 5-HIAA levels. There was now significant new disease in the liver (**Figure 2**), retroperitoneum and mediastinum. It was decided that patient would undergo a course of chemotherapy with gemcitabine (1000 mg/m²) and carboplatin (AUC of 5 mg/ml-min).

Following the initial weekly treatments with G&C, patient improved significantly, with weight gain, remission of carcinoid-

related symptoms, increase in overall strength and stamina. After 5-HIAA levels stabilized following initial chemotherapy, the patient was transitioned to bi-weekly G&C chemotherapy sessions. He continued to tolerate his treatment very well and made a continuous sustained clinical improvement with stable radiographic appearance of the disease.

After approximately 20 months of chemotherapy, the patient began experiencing increasing side effects of chemotherapy, and it was elected to discontinue G&C. Meanwhile, he experienced progressively worsening weakness, decreased appetite, difficulty ambulating, and persistent right upper quadrant abdominal discomfort. His pain symptoms were well managed with mild opioid analgesic regimen. There was also evidence of worsening intraabdominal disease on MRI, with concurrent deterioration in 5-HIAA and serotonin levels (**Figure 1**, page 13).

The patient was continued on Octreotide for symptom relief, and continued on a declining clinical course thereafter, electing not to pursue any new therapeutic options. He died 4 years and 5 months after the initial diagnosis of the carcinoid tumor was made.



Figure 2. Computed tomogram showing multiple hepatic metastases from cecal gastrointestinal carcinoid primary.

DISCUSSION

Gastrointestinal carcinoid tumors are uncommon, although their incidence has been rising over the last 30 years.^{1,2} They constitute approximately two-thirds of all carcinoid tumors, and are considered a subset of neuroendocrine tumors of the digestive tract.^{2,9} The overall 5-year survival for all the carcinoid tumors, regardless of site, was 67.2% in a large retrospective study.² Numerous therapeutic modalities have been used to treat metastatic carcinoids, including hepatic artery embolization and chemoembolization^{3,4}, surgical resection⁵, radio-frequency ablation⁶, chemotherapy^{4,7}, and use of Octreotide combined with

interferon-alpha.⁸

Diagnostically, computed tomography and magnetic resonance imaging provide a reliable platform for short- and long-term follow-up, but ultrasonography can also be useful in diagnosis and follow-up on a limited basis. In terms of tumor markers, the current case demonstrates the usefulness of 5-HIAA and other tumor markers in long-term monitoring of the disease response to therapy. Others corroborate our experience, with reports of high 5-HIAA levels correlating with carcinoid syndrome and metastatic disease.^{1,5}

Hepatic resection for metastatic neuroendocrine tumors is safe and achieves symptom control in most patients.⁵ Surgical treatment of these tumors has been associated with prolonged survival and improved quality of life, despite an approximate 50% to 60% recurrence rate.^{1,5} In one series, radical resection of digestive tract carcinoid metastatic to the liver resulted in no perioperative mortality, low overall morbidity (7%), and at the median follow-up of 75 months, global survival rate of 89% despite high recurrence rate and only two of nine patients in complete remission.¹⁰ In another series, ten-year overall survival was 43% following surgical resection of metastatic disease.¹ Debulking extends survival, but the tumor nearly always recurs.⁵ Radiofrequency ablation has been performed safely and with promising results, especially in the setting of secondary hepatic tumors measuring less than 4 centimeters in size.⁶

To our knowledge, this is one of the few published reports of sustained symptomatic control in a patient with cecal carcinoid metastatic to the liver using a combination of gemcitabine and carboplatin. In general, the results of systemic antitumoral treatment in the setting of carcinoid with distant metastases are discouraging. A recent phase II trial of the combination of paclitaxel, carboplatin, and VP-16 examined 78 patients with histologically proven poorly differentiated neuroendocrine carcinoma.¹¹ The study included a variety of tumors with known primary sites (colon, rectum, esophagus, stomach), although a majority of patients had an unknown primary.¹¹ Fifty-three percent of patients showed major response, which was not significantly different when unknown and known primary sites were compared.¹¹ However, toxicity was significant, with grade 3/4 neutropenia being present in 82% of patients and three deaths attributed to neutropenic sepsis. Others reported on the efficacy of the combination regimen of cisplatin and irinotecan among 18 patients with advanced neuroendocrine tumors.¹² Only one radiological response was observed among four patients with poorly differentiated neuroendocrine tumors and no radiological responses were observed in 14 patients with well-differentiated tumors.¹² One Phase II trial of gemcitabine alone for metastatic neuroendocrine tumors showed disappointing results, with disease stabilization in 65% of patients and overall median survival duration of only 11.5 months.¹³ Efficacy of the oxaliplatin-based regimen FOLFOX-4 in 16 patients (8 low-grade and 8 high-grade) has been noted in 62.5% patients, suggesting that this regimen may be an option in tumors with highly aggressive potential.⁹ In another study, the combination of cisplatin and etoposide was shown to produce significant responses in patients with heavily pretreated and poorly differentiated/rapidly progressing neuroendocrine tumors. The toxicity was considerable, however, and nephrotoxicity appeared to be the dose limiting factor.¹⁴

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CONCLUSIONS

The case reported describes prolonged patient survival on combined G&C chemotherapy regimen for widely metastatic carcinoid tumor. Similar chemotherapeutic regimen for treatment of carcinoid tumors has been described in only a handful of reports. This case suggests that there may be clinical value of the G&C combination in this setting. A larger clinical trial will be required to fully elucidate the clinical efficacy and side effects of this regimen.

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Figure 1. Chronologic representation of various laboratory parameters (alkaline phosphatase, 5-HIAA levels, and serotonin levels) as well as patient weight (lbs). Heavy black vertical bars represent the starting and ending points for the gemcitabine and carboplatin chemotherapeutic regimen. The Y-axis displays the numeric value of each corresponding variable and the X-axis shows the time progression on two-monthly basis.

