

# A Dramatic Response to Long-Acting Octreotide in Metastatic Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a relatively uncommon malignancy in the United States, affecting approximately 19,000 people in 2004.<sup>1</sup> HCC is more commonly observed in eastern and southeastern Asia and sub-Saharan Africa, due to the association between HCC and infection with the hepatitis virus, which is endemic in these areas. The incidence in the United States is increasing, however, due to a rise in the prevalence of the hepatitis C virus (HCV). Other liver diseases associated with HCC include alcoholic liver disease, genetic hemochromatosis, and tyrosinemia.

Unfortunately, the diagnosis of HCC is most often made late in the course of the disease process. The diagnosis can be aided by a combination of imaging analysis (ultrasonography, computed tomography [CT], and magnetic resonance imaging) and an elevated  $\alpha$ -fetoprotein (AFP) level. The median survival following diagnosis is approximately 6–20 months; however, there are wide variations in prognoses.<sup>2</sup> Risk factors for a poor prognosis include the extent of tumor metastases and the severity of the underlying hepatic disease. If the disease is not resectable, the prognosis is quite poor, with a median survival of approximately 8 weeks.<sup>3</sup>

Surgical resection and liver transplantation remain the only chances for a cure. Unfortunately, because of advanced cirrhosis, bilobar disease, and extrahepatic metastases, only 9–27% of HCC cases are amenable to surgical resection.<sup>3</sup> In unresectable HCC, numerous clinical trials have investigated a wide variety of therapies: direct ablation with ethanol or acetic acid, transarterial chemoembolization, radiation, and systemic chemotherapy. Although some trials have shown limited success with these techniques, none have been proven to decisively prolong the median survival of patients with metastatic HCC when compared to observation alone. There remains no standard treatment for advanced HCC.

Here, we present a patient with advanced HCC with bilateral lung metastases and a large liver mass. After treatment with long-acting octreotide (Sandostatin, Novartis), the patient had a dramatic regression at all disease sites, with a corresponding decrease in his AFP.

## Case Report

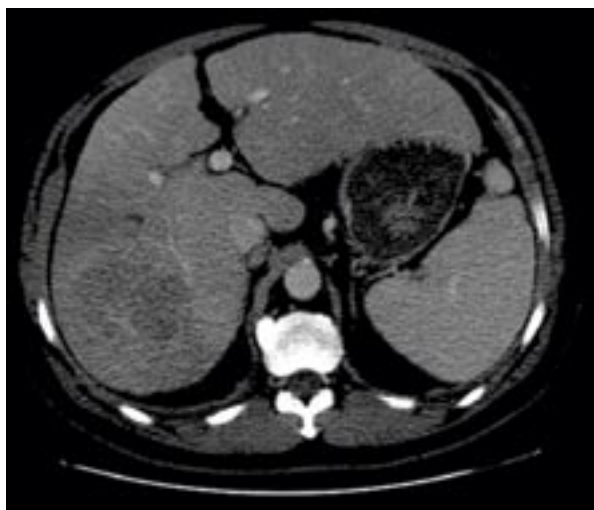
A 53-year-old white male patient with a past medical history of untreated HCV and compensated cirrhosis presented to the emergency department with a 3-week history of progressive dyspnea, a productive cough, and an unintentional 10-lb weight loss. In addition, he reported intermittent fevers, chills, and abdominal pain. He drank alcohol only occasionally and had no known history of exposure to tuberculosis.

On examination, he was afebrile with normal vital signs except for mild hypoxia, which corrected with supplemental oxygen by nasal cannula. He was anicteric and had no palpable lymphadenopathy. Bibasilar rales were auscultated and tenderness over the right upper quadrant was demonstrated without frank organomegaly. No peripheral edema, bone tenderness, or neurologic deficits were detectable.

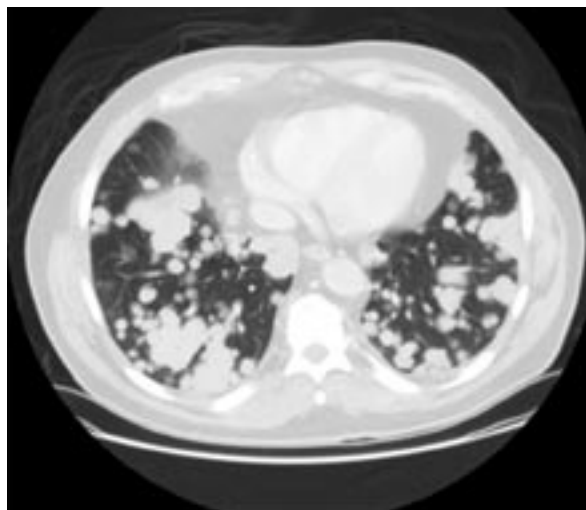
The admission blood work revealed a normal complete blood count with differential and normal renal function. The liver enzymes (alkaline phosphatase 141, AST 677, ALT 633, LDH 370) were elevated and the total bilirubin (0.4) was within the normal range. In addition, the AFP was elevated to 217,000 ng/mL.

An abdominal CT scan showed an enhancing 8.3-cm mass within the posterior right lobe of the liver with invasion of the left hepatic vein. The left lobe and caudate displayed an irregular surface consistent with cirrhosis (Figure 1). In addition, numerous enlarged lymph nodes were seen within the region of the celiac axis. A chest radiograph and CT scan revealed innumerable well-margined pulmonary nodules suspicious for metastases present bilaterally in all lobes. The largest measured 2.6 × 1.6 cm (Figure 2).

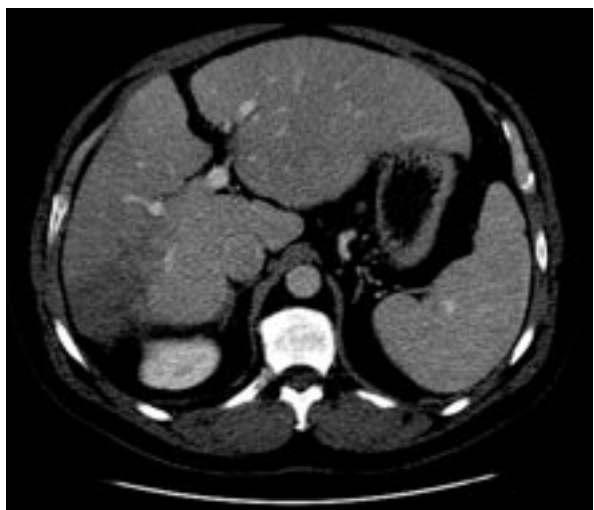
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**Figure 1.** Abdominal computed tomography scan showing the 8.3 cm liver mass pretreatment (August 2003).



**Figure 2.** Chest computed tomography scan showing the numerous bilateral pulmonary nodules consistent with metastatic disease (August 2003).



**Figure 3.** Abdominal computed tomography scan revealing the regression of the hepatoma 4 months after octreotide initiation (January 2004).



**Figure 4.** Chest computed tomography scan displaying the decrease in tumor load in the lungs 4 months after initiation of octreotide (January 2004).

The patient was seen in consultation and given the preliminary diagnosis of stage IVB HCC. Participation in a phase II clinical trial with long-acting octreotide was discussed and the patient was discharged home to return to the medical oncology clinic to participate in the trial.

Upon presentation to the medical oncology clinic 4 weeks later, the patient had an Eastern Cooperative Oncology Group performance status of 4, was cyanotic without supplemental oxygen, and was severely dyspneic. An urgent CT of the chest with protocol was obtained. He had no evidence of pulmonary embolism, but did have

massive coalescent pulmonary metastases that involved over 50% of his lung parenchyma. The patient was not eligible for the study due to his limited life expectancy and poor performance status. Instead, he was administered octreotide off-study. A test dose of 100 µg of octreotide was administered first, followed the next day by 30 mg of long-acting octreotide intramuscularly (IM).

Three days following the administration of the long-acting octreotide the patient began to notice an improvement in his shortness of breath and coughing. His energy level began to pick up along with his appetite. Two weeks

later, the patient was reassessed in the clinic with dramatic findings. He was off supplemental oxygen, felt remarkably better, was able to take walks greater than a mile, and had returned to work. A chest radiograph revealed a significant improvement in his lung metastases. One month later, CT scan confirmed these findings; a cluster of nodules in the base of the right lung had decreased from 5.1 cm to 2.8 cm. Additionally, CT of the abdomen revealed that his primary liver mass had withered and retracted its invasion of the hepatic vein.

Subsequent CT scans continued to show a decline in his tumors at 4 and 6 months after initiation of his treatment (Figures 3 and 4). Further regression of pulmonary metastases were noted on these scans, as well as a near complete response in the liver. AFP levels over the first 4 months of treatment improved from 217,000 ng/mL to 181 ng/mL. The patient continued on treatment for 9 months, until a worsening of the disease state was demonstrated on CT, along with an increased AFP level. Although the patient remained asymptomatic, octreotide treatment was discontinued due to disease progression.

### Discussion

HCC is a relatively chemotherapy-refractory disease. The previously studied treatments for advanced HCC have all met with low success rates. Currently, it is considered ethical to perform clinical trials on advanced HCC using a no-treatment control arm to compare treatment efficacies.

Proposed mechanisms for resistance to chemotherapy include an elevated expression rate of drug-resistance genes, such as P-glycoprotein, glutathione-S-transferase, and p53 mutations.<sup>4-7</sup> In addition, the toxicity of chemotherapeutic agents can reduce the liver function in patients who are already cirrhotic, leading to difficulties in administering treatment. Many chemotherapeutic agents are not metabolized and excreted properly due to the poor liver function, leading to thrombocytopenia and leukopenia. Doxorubicin (Adriamycin, Pfizer), 5-fluorouracil, gemcitabine (Gemzar, Lilly), recombinant interferon- $\alpha$ , and combination chemotherapy regimens have all been investigated, and none have proven to be reliable treatments (Table 1).

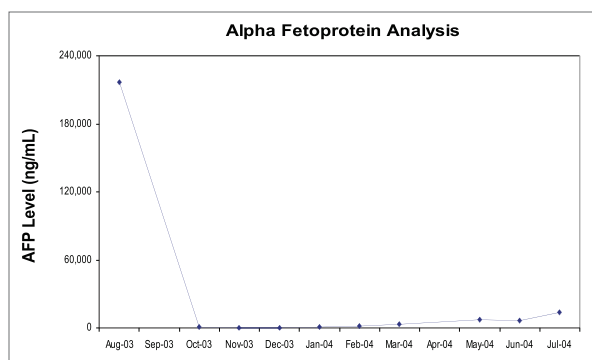
Hormonal therapies such as tamoxifen and octreotide have also been targets of investigation as treatments for advanced HCC. Given that one third of hepatomas express estrogen receptors, tamoxifen has been studied for its antagonistic properties. Unfortunately, 3 studies of tamoxifen have all failed to show an increased median survival or improved functional status due to treatment.<sup>30-32</sup> In addition to estrogen receptors, various concentrations of somatostatin receptors (SSTRs) have also been shown to be present in some hepatomas. Octreotide, a synthetic analog of the octapeptide of

**Table 1.** Systemic Chemotherapeutic Agents for HCC

Antineoplastic Agent	Patients, N	Objective Response Rate, %	Median Survival, Months
Doxorubicin <sup>8</sup>	52	11	4
Gemcitabine <sup>9</sup>	30	0	7
Paclitaxel <sup>10</sup>	20	0	3
$\gamma$ -Interferon <sup>11</sup>	15	0	Not Reported
Cisplatin/Mitoxantrone <sup>12,13</sup>	61	11	3-4
Irinotecan <sup>14</sup>	14	7	8
Etoposide <sup>15,16</sup>	39	4	2-3
Epirubicin <sup>17</sup>	14	0	4
Mitoxantrone	34	0	3-4
Fludarabine <sup>18</sup>	16	0	Not Reported
Ifosfamide <sup>19</sup>	15	0	3
Vindesine <sup>20</sup>	14	0	5
Flutamide <sup>21</sup>	22	0	2-3
Megestrol acetate <sup>22</sup>	32	0	4
5-FU/IFN- $\alpha$ <sup>23</sup>	28	14	15
5-FU/leucovorin <sup>24</sup>	15	7	3-8
Doxorubicin/IFN- $\alpha$ <sup>25</sup>	31	3	10
Gemcitabine/doxorubicin <sup>26</sup>	34	12	4-5
Doxorubicin/cisplatin <sup>27</sup>	37	19	7
Eniluracil/5-FU <sup>28</sup>	45	0	12
Uracil/tegafur <sup>29</sup>	26	4	Not Reported

5-FU = 5-fluorouracil; HCC = hepatocellular carcinoma, IFN = interferon.

somatostatin, has been studied to target these receptors. In a placebo-controlled, randomized clinical trial by Kouroumalis et al,<sup>33</sup> patients given octreotide subcutaneously (SC) at 250  $\mu$ g twice daily had a significant increase in median survival (13 vs 4 months,  $P=.002$ , log-rank test). In a similar trial using long-acting octreotide 30 mg monthly by Yuen et al,<sup>34</sup> no survival benefit was shown (1.93 vs 1.97 months,  $P$ =not significant, log rank test). However, the survival of the patients in the latter trial was quite poor and may have accounted for the lack of efficacy. In a trial performed by Dimitroulopoulos et al,<sup>35</sup> octreoscan scintigraphy-positive patients with advanced HCC were treated with 0.5 mg of octreotide administered SC every 8 hours for 6 weeks. Long-acting octreotide 20 mg at the end of weeks 4 and 8 and long-



**Figure 5.** Analysis of the alpha fetoprotein level pretreatment and over the 9-month course of octreotide therapy.

acting octreotide 30 mg at the end of week 12 and then every 4 weeks was administered IM. This study showed a significant increase in the median survival of octreoscan-positive patients treated with octreotide compared to the octreoscan-negative patients who received no therapy (7.8 vs 4 months,  $P=.037$ ). In a randomized trial investigating the combination of tamoxifen and octreotide for the treatment of inoperable liver cancer in estrogen receptor-positive patients, the combination showed a prolonged median survival compared with those patients treated with the combination of 5-fluorouracil and mitomycin C (12.8 vs 5.5 months,  $P<.01$ ).<sup>36</sup> Additional trials are needed to determine the efficacy of octreotide treatment for patients with HCC.

Siveke et al<sup>37</sup> described a patient whose advanced HCC completely regressed with treatment with long-acting octreotide. This patient had numerous tumors of the liver visible on CT and the diagnosis of HCC was made after liver biopsy. The patient was treated initially with octreotide 250  $\mu$ g SC twice daily followed by long-acting octreotide 10 mg IM monthly. Four months after treatment began, a 50–70% decrease in size of the numerous liver tumors was observed on CT. Ten months after initiation of octreotide therapy, complete regression of the liver tumors was demonstrated, along with a normalization of the AFP level (7,615.3 vs 33.1 ng/mL).

The current case and the case mentioned above both demonstrate the ability of octreotide treatment to improve both the life span and quality of life of patients with HCC, although a response to treatment occurs in the minority of cases. The mechanism by which octreotide is able to regress hepatomas in some patients but not others has still not been identified. Kouroumalis et al<sup>33</sup> could not correlate the concentration of SSTRs with the efficacy of octreotide in the investigation previously discussed, but the concentration of the various isoforms in each individual case were not evaluated. The efficacy of octreotide may correlate not to the amount of SSTR

but, more importantly, to the proportion of the particular isoforms present in the tumor. Since octreotide has shown the greatest affinity for SSTR type 2 (SSTR2) compared to the other isoforms,<sup>38</sup> an increase in the proportion of this isoform could result in an increased efficacy for octreotide treatment. Alternatively, if the hepatoma expresses mostly SSTR1 or SSTR4 then octreotide may have a decreased efficacy, since octreotide binds these receptors with low affinity.<sup>39</sup>

Possible antineoplastic mechanisms for somatostatin analog include direct antimitotic effects via SSTRs on tumor cells, suppression of trophic hormone release (eg, growth hormone, insulin, prolactin, and gut peptides), direct or indirect inhibition of growth factors (eg, insulin-like growth factor-1, epidermal growth factor, platelet-derived growth factor), angiogenesis inhibition, apoptosis induction, and immune response modulation. Octreotide has been shown to induce apoptosis in several cancer cell lines, including the human hepatoma cell line BEL-7402.<sup>40</sup> In addition, the antiangiogenic effects of octreotide treatment were observed in nude mice bearing HCC xenografts.<sup>41</sup> Therefore, octreotide may perform its antineoplastic effects by a combination of these mechanisms, or through other pathways that remain to be identified.

To the best of our knowledge, no previous case has been published showing a near complete response in the setting of metastatic HCC following long-acting octreotide treatment. Such an effect is uncommon among patients receiving octreotide therapy; however, we propose an analysis of SSTRs in future studies to ascertain the usefulness of receptor status in predicting a response to octreotide therapy. Despite the low response rate, long-acting octreotide should be considered in patients diagnosed with HCC without other treatment options. The minimal risks associated with its administration are outweighed by the possibility of considerable improvement in disease and quality of life.

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## Review

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Hepatocellular carcinoma is one of the most commonly diagnosed malignancies on a worldwide basis, accounting for about 6% of all cancers. It is the fifth most common malignancy globally with an estimated incidence of approximately 500,000 cases per annum.<sup>1</sup> In the United States HCC is relatively uncommon, with the main predisposing factors being HCV infection and alcohol abuse, in contrast to HCC in Asia and Africa, where hepatitis B viral infection is the main underlying etiology.

Treatment options for advanced HCC, especially in the context of metastatic disease, are very limited. When HCC remains confined to the liver, surgical resection and/or liver transplantation represent the only potential for cure. The presence of metastatic disease, bilobar disease, vascular invasion, or compromise conferred by the underlying predisposing cirrhosis, means that up to 90% of patients are not candidates for surgery.<sup>2</sup> Similarly, the scarcity of organs for transplantation severely limits the option for transplantation. Somewhat controversially, the option for live-donor liver transplantation has been suggested as a route of possible circumvention for a limited organ supply.

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In unresectable disease, numerous local therapies have been studied. These include transcatheter hepatic artery embolization with or without chemotherapy, percutaneous ethanol injection, thermal ablation, and cryosurgery. Local ablative therapies are generally only useful for patients with a limited number of tumors (2–3) or a tumor with a maximum diameter of 3 cm.<sup>3</sup> Systemic chemotherapy has also been investigated over the past 30 years but is largely considered to be ineffective. Single-agent chemotherapy with agents such as doxorubicin, 5-fluorouracil, cisplatin and etoposide as well as combination chemotherapy have all yielded disappointing results.<sup>4</sup> No chemotherapeutic agent or combination has been proven to offer a survival advantage over supportive care or to significantly affect the natural history of the disease. Single-agent doxorubicin is generally considered a controversial default standard of care.

In view of the dearth of efficacy of standard chemotherapy, the use of hormonal therapy has been long and actively investigated in HCC. One potential series of such agents has been somatostatin analogs, in particular octreotide and long-acting octreotide. The theoretical basis for the experimental use of these compounds stems from *in vitro* studies that demonstrate that octreotide is able to inhibit the proliferation of and induce apoptosis in HCC cells.<sup>5</sup> It has been postulated that these actions occur through direct receptor-mediated effects (which may involve the p53 pathway), stimulation of the reticuloendothelial system, or reduction of tumor blood flow.<sup>6,7</sup> Additional data to support the clinical use of somatostatin come from studies showing that cell membrane receptors for somatostatin are expressed on HCC cells. These SSTRs are responsible for the cellular effects of somatostatin and occur in subtypes (SSTR1–SSTR5). Analogs such as octreotide have high affinity binding to SSTR2 and lower affinity to SSTR5 and SSTR3 (SSTR5 > SSTR3). SSTR subtypes occur in a differential pattern on different HCC cells. No significant correlation has been observed between SSTR expression, histologic type of the tumor, presence of underlying cirrhosis, or the etiology of cirrhosis.<sup>8</sup>

As Deming and colleagues note, clinical trial data involving somatostatin analogs in the treatment of HCC have been mixed. Initial enthusiasm came from the study by Kouroumalis et al,<sup>9</sup> in which patients treated with octreotide had an increased median survival of 13 versus 4 months compared with patients randomized to observation ( $P=.002$ ). This study also evaluated SSTR expression on the patients' HCC cells and found no correlation between SSTR density (classified as "high" or "low") and clinical outcome. (It would be interesting to know in the case report of Deming et al whether or not their patient had a positive octreoscan and the differential receptor expression subtype.) The follow-up study by Yuen et al,

involving octreotide LAR, yielded less favorable results. There was no difference in the cumulative survival between patients randomized to octreotide versus those randomized to placebo (median survival, 1.93 vs 1.97 months,  $P$ =not significant).<sup>10</sup> Other studies have similarly failed to demonstrate any benefit to somatostatin therapy. Raderer et al<sup>5</sup> treated 21 patients with another long-acting analog, lanreotide 30 mg injection once every 14 days until documented disease progression. Only 1 out of 21 patients showed a partial response while an additional 8 patients had short-lasting stable disease. The median survival was only 4.2 months. The authors noted, however, that approximately 20% of patients had an improvement in World Health Organization (WHO) performance status while 25% had an increase in body weight of greater than 5 kg (not attributable to edema or ascites). Most recently, Lersch et al<sup>11</sup> treated 58 patients with either octreotide  $3 \times 200 \mu\text{g/day}$  for 2 months followed by octreotide LAR 20 mg every 4 weeks until death or progressive cachexia ( $n=30$ ), pravastatin ( $n=20$ ), or gemcitabine ( $n=8$ ). None of these treatments prolonged the patients' median survival compared to control groups reported by other authors.

In an effort to select a subgroup that might benefit from treatment with octreotide, Dimitroulopoulos et al,<sup>12</sup> attempted to select patients with high levels of SSTR expression by octreoscan scintigraphy. Out of 28 patients who underwent scanning, 22 had scintigraphy findings positive for overexpression of SSTR in the liver parenchyma. One of these patients refused treatment and 6 others discontinued treatment from the third day. These 7 patients, together with the 6 patients with negative octreoscans, served as the control group. The treatment group received octreotide 0.5 mg SC every 8 hours for 6 weeks, while octreotide LAR was administered IM at 20 mg once at the end of weeks 4 and 8 and 30 mg at the end of week 12 and every 4 weeks thereafter. Compared with the control group, the treatment group had longer median survival (31 vs 16 weeks,  $P=.037$ ) and reported greater improvement in quality of life.

Aside from the current case report by Deming et al, there have also been several case reports that have described very robust responses to somatostatin administration in HCC. Raderer et al<sup>13</sup> described a 68-year-old man with stage IVA HCC who was treated with lanreotide 30 mg IM, primarily for the palliation of severe diarrhea. It was soon incidentally noted that his serum AFP level had declined and that he had experienced some weight gain and improvement in performance status. Lanreotide treatments were continued every 10 to 14 days until the 13th treatment, when they were discontinued at the patient's request. He ultimately experienced disease stabilization for 8.5 months and remained alive 11 months after initiation of treatment with progressive disease and

a WHO performance status of 1. Siveke et al<sup>14</sup> reported on a patient with advanced HCC and HCV, who received octreotide. Complete regression of the tumor was noted at 10 months, along with a normalization of AFP levels. However, a gradual increase in AFP after 13 and 19 months (from 37 to 223 ng/mL) and a new suspicious liver nodule by CT scan were noted. The patient remained in excellent health during the 22 months of treatment, without any symptoms due to the underlying disease or treatment side effects. Finally, Senturk et al<sup>15</sup> described a 53-year-old man with advanced HCC and heavy alcohol use who was treated with octreotide (initially 100 µg 3 times daily, subsequently changed to LAR formulation 30 mg monthly) and tamoxifen (10 mg twice daily). Over an 8-month period, the patient experienced normalization of his AFP level (from 330 to 2 ng/mL) and complete radiologic regression by CT scan. Unfortunately, the patient was diagnosed at that time with lung cancer and cerebral metastases. A fine-needle aspiration of the lung mass suggested squamous cell carcinoma and the patient died 1 month later. Given the lack of apparent clinical efficacy of tamoxifen from previous meta-analyses, the authors attributed the clinical benefit predominantly to octreotide.

On the basis of current available clinical trial data, there is certainly insufficient evidence to advocate for the routine use of somatostatin analogs in the treatment of advanced HCC. In addition, it is difficult even to advocate for further clinical studies of somatostatin analogs—at least without more careful selection of theoretically appropriate patients. While the overall trial data are mixed, the current case report by Deming et al corroborates observations by other clinicians that somatostatin analogs can have surprisingly potent effects and lead to sustained regression of advanced HCC and improvement in symptoms. Part of this heterogeneous response could be due to the differential expression of SSTRs on different HCC cells. Patients who do not respond to somatostatin therapy may have HCC cells that express low levels of SSTRs strongly targeted by the somatostatin analogs and/or express high levels of SSTRs for which the analogs have low affinity. Hence, a more rational and directed approach to the future use and study of somatostatin should involve the profiling of SSTR expression on a patient's HCC cells. Such profiling could involve either noninvasive methods such as octreotide scintigraphy or the use of immunohistochemical or polymerase chain reaction techniques to analyze HCC tissue samples obtained by biopsy. Only patients with high levels of SSTR expression—especially the SSTR2, SSTR5, and SSTR3 subtypes that soma-

tostatin analogs show affinity to—might be potential candidates for somatostatin therapy. Similarly, increasing the dosage of octreotide used or selecting new compounds that target the other SSTRs commonly expressed on HCC cells may lead to greater clinical benefit.

Advanced HCC remains a very challenging disease to treat, with few effective therapeutic options. Although the overall clinical evidence does not unequivocally endorse the clinical efficacy of somatostatin analogs, case reports such as the one by Deming et al suggest that some selected patients can experience profound clinical benefit from its use with minimal side effects. Our current understanding of the differential expression of SSTRs on different HCC cells dovetails with knowledge about the affinity of somatostatin analogs for certain SSTRs. On this theoretical basis, any further study of somatostatin therapy should select patients on the basis of their SSTR expression so that they might be most likely to benefit from such treatment.

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