Lanreotide treatment of metastatic hepatocellular carcinoma resulting in partial regression and more than 3 years of progression-free survival

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Abstract

We describe the case of a 54 years old woman, with hepatitis B, in whom the diagnosis of a 6 cm hepatocellular carcinoma (HCC) in the left liver was made in 2001. Alpha-foeto-protein (AFP) was 63 ng/mL (Nl < 10 ng/mL). After work-up including liver and tumor biopsy confirming HCC and only fibrosis in the non-tumoral liver, left hepatectomy was performed. Final pathology showed a well differentiated HCC with tumoral portal vein thrombosis. Unfortunately, lung and mediastinal adenopathies were detected by CT scan 17 months later. Mediastinal nodes were punctured by endosonographic ultrasound, confirming HCC. The patient started treatment with Lanreotide 30 mg twice a month (Somatuline PR®, Ipsen). Three months later, CT showed decrease in size of the mediastinal nodes and complete disappearance of the lung nodes. This objective response lasted for 42 months. The treatment was without any significant side effect. Retrospectively, immunohistochemistry was performed to detect somatostatine receptors (sstr) 2. Both the primary tumor and the node showed intense membranous and cytoplasmic staining for sstr2. In 2006, AFP rose and CT showed the appearance of a new mediastinal node. At that time, octreoscan® was performed and showed uptake in the new node, although insufficient for metabolic radiotherapy. This case suggests that, although a number of randomized controlled trials did not show a benefit of somatostatin analogues in the treatment of advanced HCC, a subset of patients could benefit from treatment provided their tumor expresses sstr2, on which the existing drugs are efficient. (Acta gastroenterol. belg., **2012**, 75, **270-273**).

Key words : hepatocellular carcinoma, somatostatine analogue, lanreotide, metastasis, treatment.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver (1) and is characterized by a poor prognosis, with median survival times of only 3-6 months in most studies of advanced disease. Global incidence is rising as prevalence of viral hepatitis infection increases (2), but surgical cure is possible only in a minority of patients. Extra-hepatic metastases from HCC are found most frequently in the lung, abdominal lymph nodes, and bone, and are often refractory to surgical resection. Currently the only standard medical therapy for metastatic or locally advanced HCC is sorafenib (3).

Somatostatin and its synthetic analogs exert regulatory or suppressive effects in various tumor types, and play an established role in the management of gastroenteropancreatic neuroendocrine tumors (4). In patients with advanced HCC, however, recent randomized controlled trials conducted to assess efficacy of somatostatin analogs on tumor progression and survival have given conflicting results (5-8). As these studies have different study populations with respect to etiology, liver function, or tumor stage (6), it is not clear whether there are subsets of patients who would benefit most from somatostatin analog therapy, for example those with less advanced disease, a different disease etiology, or those patients whose tumors express somatostatin receptors. Single case reports may help to define the patient subgroup that should be selected to participate in larger trials.

A recent case study of a patient with multifocal intrahepatic recurrence of HCC, but no distant metastasis, showed complete and long-standing regression of HCC after treatment with the somatostatin analog, lanreotide (9). As lanreotide treatment is generally well tolerated without major side effects, it represents an attractive option for treating inoperable HCC. In this case report, we describe the use of lanreotide to treat advanced metastatic HCC.

Case report

In May 2001, a 54-year-old woman with active hepatitis B was diagnosed with HCC. The diagnosis was based on the presence of a 6 cm tumor in the left part of her liver. The patient's serum alpha-fetoprotein (AFP) level was 63 ng/mL (normal level, < 10 ng/mL). Assessments including liver and tumor biopsy confirmed the diagnosis of HCC, and identified significant fibrosis (F2 on the METAVIR scale) in the non-tumoral part of the liver. Left hepatectomy (of segments 1-4) was performed. Histologic examination showed a well-differentiated 6 cm HCC with tumoral left portal vein thrombosis. Serum AFP level decreased to 5.2 ng/mL postoperatively.

The patient attended regular follow-up appointments and, 17 months later (October 2002), multiple supracentimetric lung and mediastinal metastases were detected by thoracic computed tomography (CT) scan (Fig. 1a).

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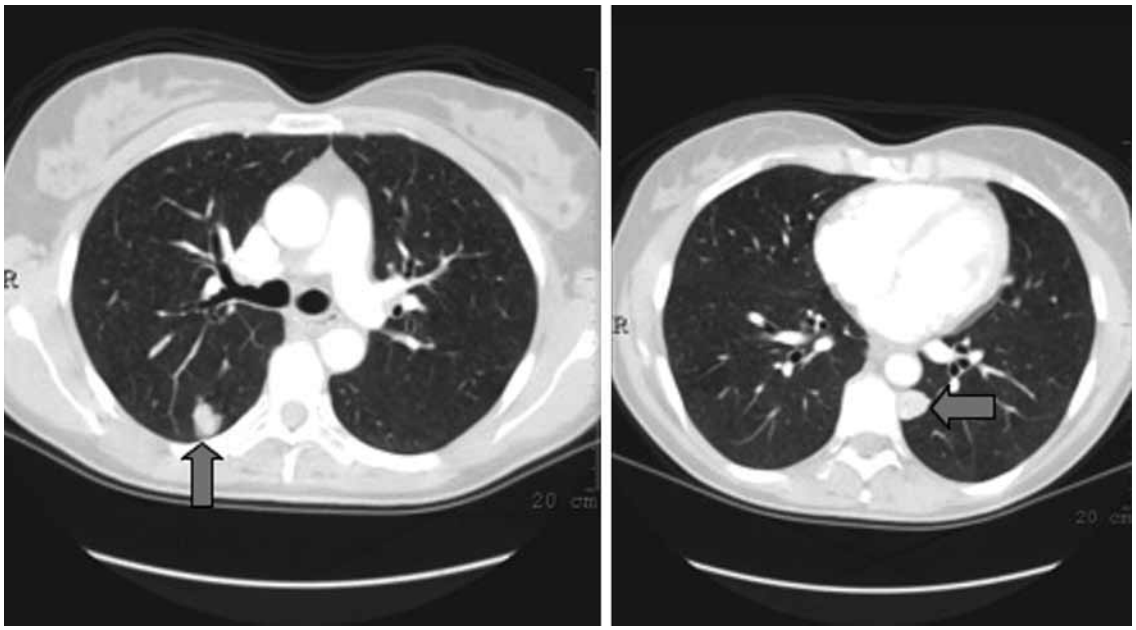

Fig. 1a. — Lung metastases, shown by gray arrows, before lanreotide start

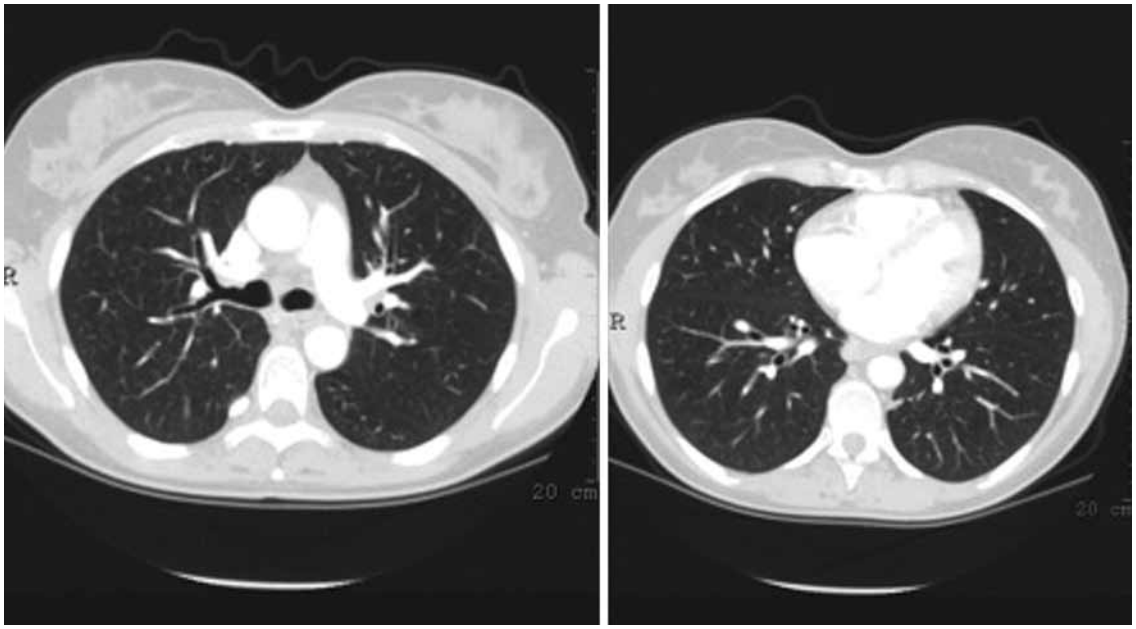

Fig. 1b. — disappearance of the lung metastases, 3 months after treatment start

Mediastinal nodes were punctured by endosonographic ultrasound with fine-needle aspiration, and the histology profile confirmed metastasis of the primary HCC tumor. As no evidence-based treatment was available at the time, the patient gave informed consent to the initiation of treatment with the somatostatin analog, lanreotide (Somatuline® 30 mg PR®, Ipsen, Belgium) at a dose of 30 mg every 2 weeks, administered intramuscularly. Three months after the initiation of lanreotide treatment, CT scans showed complete disappearance of the lung nodes (Fig. 1b), and, while the mediastinal nodes persisted, they were diminished in size. This favorable response continued for 42 months and during this time there was no hepatic tumor recurrence. Treatment was well tolerated except for mild pain at the injection sites. In February 2006, with the availability of a new long-acting aqueous formulation, lanreotide Autogel® (Ipsen, Belgium), the patient was switched onto this formulation at an initial dose of 120 mg administered subcutaneously every 28 days.

In May 2006, the patient's serum AFP levels increased to 107.8 ng/mL and a new mediastinal node was detected by CT scan. At that time, OctreoScan® (Mallinckrodt Medical, UK), performed with the aim of potentially

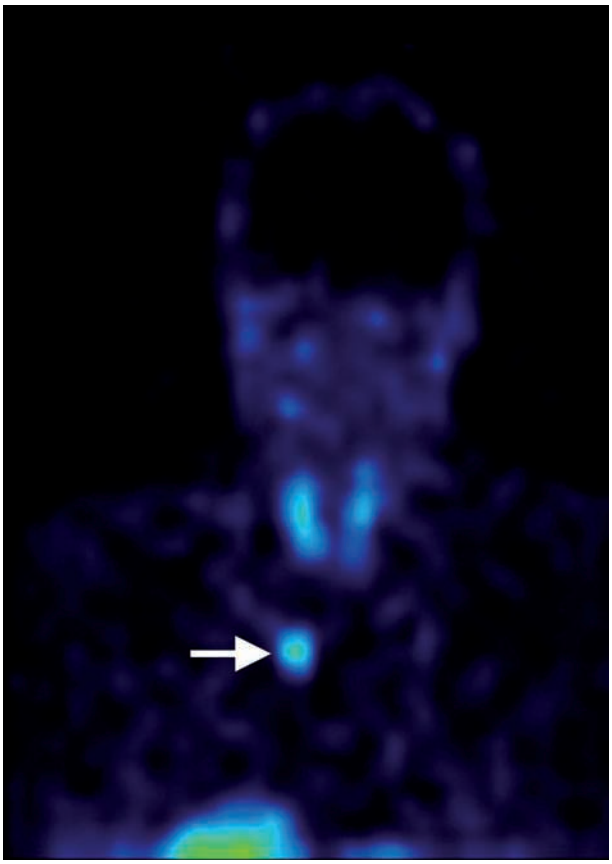

Fig. 2. — positive octreoscan of the new mediastinal lymph node (white arrow).

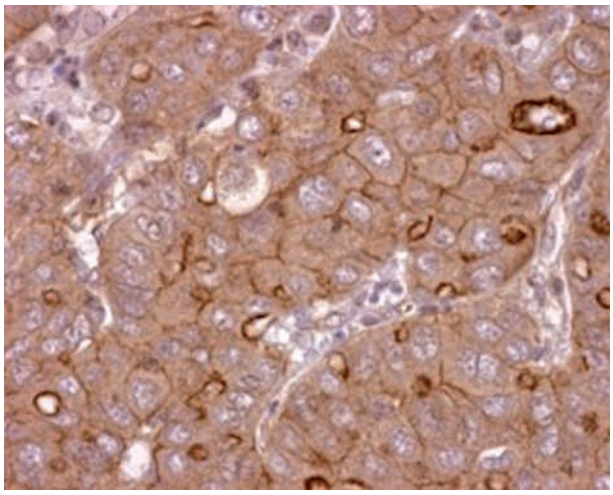

Fig. 3a. — Immunostaining with anti-SSTR2 antibody (DAKO, 1/50) of the resected HCC. Note intense membranous and cytoplasmic staining.

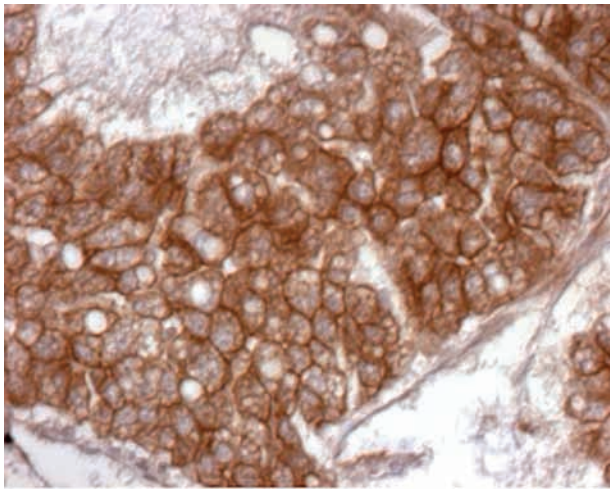

Fig. 3b. — Immunostaining with anti-SSTR2 antibody (DAKO, 1/50) of the mediastinal lymph node FNA. Note intense membranous and cytoplasmic staining.

initiating peptide-related radiotherapy using 177-lutetium-octreotate, showed the presence of somatostatin receptor 2 (SSTR2) in the new node (Fig. 2). Immunohistochemistry was then retrospectively performed in August 2006 using antibodies against SSTR2 and 5. Both the primary tumor (Fig. 3a ; × 40) and the punctured node (Fig. 3b ; × 40) showed positive membranous and cytoplasmic staining for SSTR2. Unfortunately, however, expression levels were not judged sufficient for metabolic radiotherapy using 177-lutetium-octreotate. Therefore the decision was taken to increase the lanreotide Autogel® dose to 2 × 120 mg/month, and further response was observed with the new node reduced in size. AFP level was 723 ng/mL. At the last visit (November 2007), 61 months after the start of the treatment, the patient was tolerating the treatment well, with persistent stabilization of tumor size. The AFP level had decreased to 560 ng/mL.

Discussion

To our knowledge, this is the first case report of partial regression and persistent stabilization of histologically proven, unresectable, metastatic HCC with the somatostatin analog lanreotide. These promising effects on tumor progression may be explained by the direct antitumor effects of somatostatin analogs, which are mediated through their binding with one of the two somatostatin receptors (SSTR2 and 5), expressed with varying density among different tumor types (10). HCC tumors express somatostatin receptors (11), with 41% of HCCs expressing SSTR2 (12), the main target of current somatostatin analogs, including lanreotide. Retrospective analysis of SSTR expression in this case showed that both the primary tumor and metastases were strongly positive for SSTR2, and this provides a rationale for the success of the treatment here.

Results of immunohistochemistry studies suggest that both the pattern and the level of SSTR expression might determine the antiproliferative efficacy of somatostatin analogs in HCC tumors, and therefore influence treatment response (12). Such findings may serve as an explana-

tion for the conflicting results regarding the clinical use of these compounds in the treatment of advanced HCC. Thus, there is a strong case for routine screening of SSTR expression to identify the exact SSTR subtype before initiating somatostatin analog treatment, an approach which has been successfully applied in one trial.

In addition to 5 years of tumor stabilization, the patient in this study had a progression-free period of 3.5 years. This is much longer than the 5.5-month time-to-progression period observed with sorafenib for HCC in the SHARP trial (3).

It is possible that lanreotide may exert a chemopreventive effect in HCC, as *in vivo* studies have shown an effect on carcinogenic transformation (13), and therefore lanreotide may be effective in patients in the early stages of HCC. As well as potential earlier initiation of lanreotide treatment, administration of higher lanreotide doses may achieve greater prolongation of survival, as used towards the end of the treatment cycle reported here.

Although spontaneous regression of metastatic lung lesions of HCC have been reported (14,15), these cases are extremely rare, and it is unlikely that such a phenomenon would explain the long duration of progression-free survival reported for the patient in our case report.

This case study, which reports the successful treatment of SSTR2-positive tumors with lanreotide, suggests that a subset of patients who have tumors expressing SSTR2 or 5 (on which the existing drugs act) could benefit from somatostatin analog therapy.

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