



Complete response of hepatocellular carcinoma with sorafenib and ^{90}Y radioembolization

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ABSTRACT

Advanced hepatocellular carcinoma has a dismal prognosis, with a median overall survival of 7.9 months if untreated and of 10.7 months if treated with sorafenib. We present a case of advanced previously unresectable hepatocellular carcinoma in a 49-year-old man that achieved a pathologic complete response and was made amenable to surgery with sorafenib in combination with ^{90}Y radioembolization. The patient's survival was more than double the median for patients treated with sorafenib alone.

KEY WORDS

Cancer, oncology, surgery, gastrointestinal

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide¹. Treatments for HCC have conventionally been divided into curative and palliative. The curative treatments, which include transplantation and liver resection, achieve the best outcomes (5-year survivals are 60%–70%), but these procedures can be performed in only about 30% of patients. For patients with inoperable or advanced disease, the prognosis is dismal, mainly because of a lack of effective treatment options². Recently, sorafenib, an anti-angiogenic and anti-proliferative agent, was shown in a phase III trial to improve overall survival; sorafenib has since become the only approved targeted therapy for advanced HCC in patients with Child–Pugh grade A cirrhosis^{3,4}. Promising results have also been achieved using radioembolization with ^{90}Y ^{5,6}.

Anti-angiogenic agents have been shown to create a “vasculature normalization window” associated with increased sensitivity to radiation and enhanced radiation-induced tumour regression⁷. This window

provides a further rationale for combining sorafenib with radioembolization.

2. CASE DESCRIPTION

In April 2007, a 49-year-old man with hepatitis C and Child–Pugh grade A cirrhosis was also diagnosed with a 4.7-cm HCC in the left lobe of the liver. An exploratory laparotomy performed at an outside institution on April 2, 2007, found disease that was unresectable because of local tumour extension into the left and main portal veins, with biopsy-proven positive portal lymph node metastasis. The pathology report for the liver lesion revealed a poorly differentiated HCC, trabeculated type, with vascular invasion. It also confirmed the presence of metastases in the portal lymph nodes. At the time, the patient was offered no further treatment.

When this man consulted our team for a second opinion in May 2007, he was re-evaluated. The patient was asymptomatic at the time and had an excellent performance status. His α -fetoprotein was 155.9 $\mu\text{g/L}$, and no evidence of portal hypertension was present. Computed tomography (CT) and positron-emission tomography (PET) imaging were ordered. The CT image showed a 4.7-cm hypervascular lesion with left portal vein involvement. It also showed 3 other lesions: 1 adjacent to the main lesion, 1 in segment II, and 1 measuring 1.7 cm in size in segment IV. The PET image showed a 6-cm conglomerate of several confluent foci in the left lobe of the liver with a maximum standard uptake value (SUV) greater than 25, a 1.0-cm focus in segment IV with a SUV of 6.8, a 3.0-cm focus in the left adrenal gland with a maximum SUV greater than 16, 2 foci near the porta hepatis with a SUV of 6.6, and 1 very small focus in the aortocaval region with a SUV of 5.1.

Imaging by CT performed in July 2007 also revealed an increase in the size of the main lesion to 5.7 cm from 4.7 cm and of the left adrenal lesion to 2.1 cm from 1.8 cm (Figure 1). The case was presented

and discussed at our hepatopancreatobiliary and gastrointestinal tract tumour board. The board found the patient to be eligible for a newly instituted phase II chemoradiation therapy trial consisting of sorafenib and hepatic radioembolization.

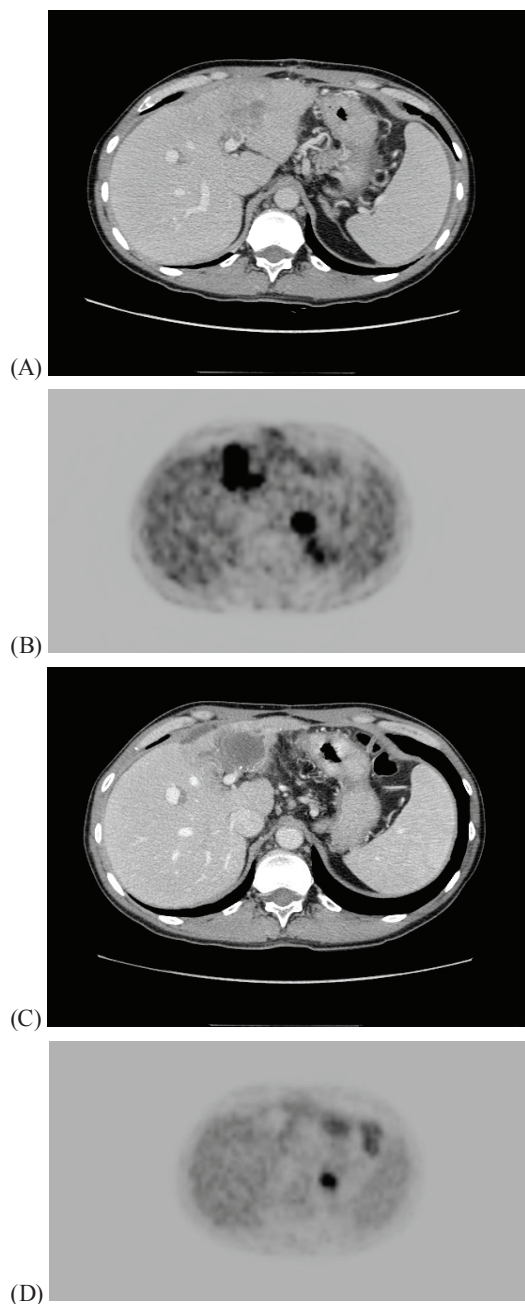


FIGURE 1 Typical images from fused computed tomography (CT) and positron-emission tomography (PET) imaging (PET-CT) before and after ^{90}Y treatment. (A) Pre-treatment axial CT shows hepatocellular carcinoma (HCC) and vascular invasion (arrow). (B) Pre-treatment PET-CT shows uptake in HCC (arrow). (C) Imaging by CT 6 months after treatment. Note necrosis and lesser enhancement of the lesion. (D) Imaging by PET-CT 6 months after treatment.

The patient started sorafenib in mid-July 2007 at the usual dose of 400 mg twice daily. At the end of July, he had a severe episode of nausea and vomiting, and the sorafenib dose was lowered to 200 mg twice daily. On August 2, 2007, the patient underwent a ^{90}Y (TheraSphere: MDS Nordion, Ottawa, ON) radioembolization of the left lobe of the liver. The infused dose of ^{90}Y was calculated to be 0.59 GBq, yielding an estimated dose of 119 Gy. The patient continued taking sorafenib 200 mg twice daily.

Post-radioembolization CT imaging performed on August 23, 2007, showed a decrease in the size of the main liver lesion to 4.4 cm from 5.7 cm. The lesion also demonstrated fewer septations than previously. The remaining lesions were unchanged. On follow-up CT imaging, the dominant lesion continued to decline in size to 3.7 cm, and it appeared avascular, with re-canalization of the left portal vein. The remaining lesions were unchanged. Those findings were confirmed by PET imaging, which showed marked improvement in the overall appearance of the hepatic hypermetabolic findings: only 1 hypermetabolic lesion, in segment IV, was observed (SUV 5.6). Few changes were observed in the other lesions. Based on those results, the patient was re-presented at the our hepatopancreatobiliary and gastrointestinal tract tumour board, and another international cancer centre was consulted. A decision was made to offer the patient a left hepatectomy and left adrenalectomy outside of the treatment protocol.

The patient underwent a formal left hepatectomy (segments II, III, and IV), with extrahepatic vascular ligation and a left adrenalectomy, on January 29, 2008. The pathology report showed presence of necrosis, but no viable tumour in the left liver resection specimen. The left adrenal gland showed undifferentiated carcinoma consistent with metastasis from HCC. After surgery, the patient did not resume treatment with sorafenib because of a severe episode of hand-and-foot syndrome.

On follow-up CT imaging performed at the end of April 2008, no evidence of hepatic recurrence was observed, but necrotic lymph nodes were seen at the level of the superior mesenteric artery and in the retroperitoneum. A CT-PET image revealed progressive extrahepatic disease in the abdomen and in the cervical, tracheal, and pulmonary regions. Because the patient could no longer tolerate sorafenib, the tumour board referred him for cytotoxic chemotherapy. Patient received oxaliplatin and gemcitabine from July 2008 until January 2009. Patient died in early February 2009 from general deterioration as a result of extensive extrahepatic metastases (pulmonary, mediastinal, retroperitoneal, bony).

3. DISCUSSION AND CONCLUSIONS

In this case, a previously unresectable patient was made amenable to surgery using a combination of

targeted therapy: sorafenib and ^{90}Y radioembolization. This patient had large lesions, macrovascular invasion, poor differentiation, and extrahepatic disease. The postoperative pathology report confirmed that 100% tumour response had been achieved and that the patient's liver was free of viable tumour. Those findings are further supported by follow-up imaging, which showed no recurrence in the liver. This treatment may also have improved the patient's survival, given that he lived 23 months after diagnosis (average survival for patients with metastatic HCC is less than 6 months)⁴.

Results of a phase II trial of sorafenib in combination with local hepatic radiation treatment are soon to be reported. Further investigation of this combination therapy is warranted.

4. CONFLICT OF INTEREST DISCLOSURES

All authors declare that no financial conflicts of interest exist.

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