

# Complete Pathological Response for Unresectable Hepatocellular Carcinoma with a Fluorouracil-Based Regimen after Sorafenib Failure

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## ABSTRACT

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**Background:** Hepatocellular carcinoma is the third most common cause of cancer death worldwide. Early stage hepatocellular carcinoma is typically silent, leading to diagnosis in advanced stages in up to 80% of patients. Therapeutic options available to these patients are limited and often have a poor prognosis. Sorafenib is the only systemic treatment that has shown increased overall survival in patients with advanced hepatocellular carcinoma. However, there is no actual consensus on a second-line systemic therapy in patients who are unresponsive to sorafenib. Evidence suggests that some patients may benefit from fluorouracil-based schemes after failure with sorafenib. We report on a histopathologic complete response likely induced by a fluorouracil-based regimen in a patient with advanced, sorafenib-refractory, unresectable hepatocellular carcinoma. **Case presentation:** A 51-year old Latin male with an unresectable stage IIIC hepatocellular carcinoma was initially treated with oral sorafenib therapy. Sorafenib was discontinued after disease progression was documented. Palliative systemic chemotherapy was started with oxaliplatin and 5-fluorouracil (Mayo scheme). A substantial reduction of the tumor size was achieved and allowed a complete surgical resection. Pathological examination revealed extensive necrosis. Twenty months after the resection, there is no evidence of tumor recurrence. **Conclusion:** A pathological complete remission was induced by a fluorouracil-based regimen in a patient with advanced sorafenib-refractory hepatocellular carcinoma. Since complete tumor resection is the only definite treatment, it is of major importance to promote treatment options that improve its resectability as in the case presented. (J CANCEROL. 2015;2:29-33)

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**Key words:** Hepatocellular carcinoma. Mayo scheme. 5-Fluorouracil. 5-FU. Oxaliplatin. Sorafenib. Complete response.

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## BACKGROUND

Hepatocellular carcinoma (HCC) is a public health problem that represents the third most common cause of cancer death worldwide, behind only lung and stomach cancers<sup>1</sup>.

Clinical presentation of HCC varies widely. Early stage HCC is typically silent, leading to diagnosis in advanced stages in up to 80% of patients<sup>2-4</sup>. Potential curative treatments such as orthotopic liver transplantation, complete surgical resection, and percutaneous ablation are only suitable for those patients without advanced disease or extensive comorbidities<sup>5-9</sup>. However, as already noted, most patients are diagnosed with advanced HCC and therapeutic options available to these patients include transarterial chemoembolization, transarterial embolization alone, intra-artery chemotherapy, radiation therapy, and systemic therapy<sup>4,5</sup>. Despite these treatments, the prognosis remains poor<sup>3</sup>.

At present, sorafenib, an inhibitor of proliferation and angiogenesis, is the only systemic treatment that has shown increased overall survival when used in patients with advanced HCC, based on two phase III randomized controlled trials<sup>4,8,10</sup>. However, there is no actual consensus on an effective second-line

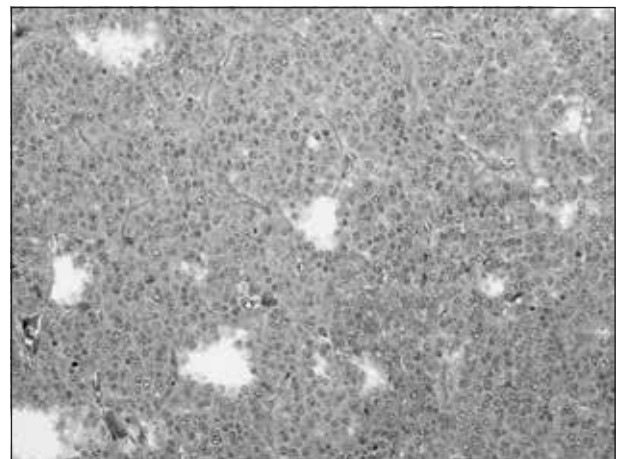
systemic therapy in patients who are unfit for or unresponsive to sorafenib therapy. Evidence suggests that some of these patients may benefit from systemic chemotherapies<sup>11</sup>, particularly using fluorouracil-based schemes<sup>12</sup>. We report on a histopathologic complete response induced by a fluorouracil-based regimen after sorafenib failure in a patient with an initially unresectable HCC.

## CASE PRESENTATION

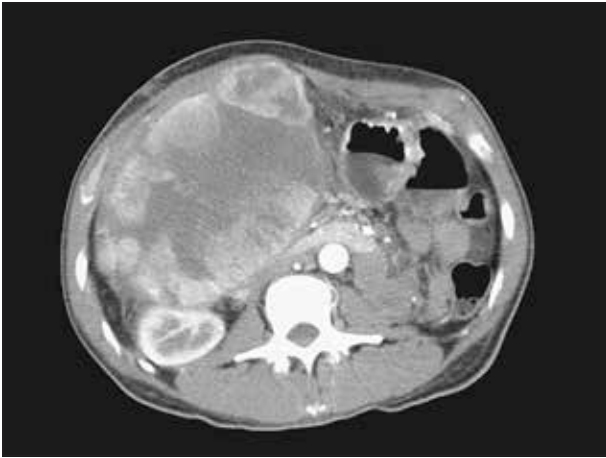
A 51-year-old man was initially evaluated in our hospital in April 2011 for right upper quadrant abdominal pain. A computed tomography (CT) scan demonstrated a 9.4 × 8.1 cm liver mass in segment V with findings typical of HCC (Fig. 1). There was no evidence of satellite nodules or distant metastases. Serum alpha-fetoprotein levels were 3,340 ng/ml. Serology against hepatitis B and C virus infection was negative. Liver function was preserved without clinical signs of liver impairment (Child-Pugh A6). The patient's Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0. The tumor was staged as IIIC. Complete tumoral resection was attempted, but duodenal infiltration was found and therefore tumor resection was not performed. Intraoperative biopsy reported HCC Edmondson grade II (Fig. 2). Oral sorafenib therapy was initiated with a



**Figure 1.** Baseline computed tomography of the abdomen. This scan carried out after the administration of contrast medium showed a mass in hepatic segment V that measured 9.4 × 8.1 cm.



**Figure 2.** Pathological specimen of the tumor. Neoplastic substitution of normal liver parenchyma. Large granular eosinophilic cytoplasm with subtle loss of the nucleus-cytoplasm relationship.



**Figure 3.** Computed tomography scan showing disease progression. This scan revealed a marked dimensional increase of the tumor corresponding to progression of disease according to RECIST.

dosage of 400 mg twice daily. Seven weeks after the onset of treatment, a CT scan revealed a marked dimensional increase of the tumor size, corresponding to progression of disease in agreement with RECIST (Fig. 3). Sorafenib was discontinued. The patient's ECOG PS was 0. Palliative systemic chemotherapy was started with Mayo scheme (oxaliplatin 85 mg/m<sup>2</sup> and 5-fluorouracil 425 mg/m<sup>2</sup>). Subsequent clinical and radiological evaluations confirmed a gradual and sustained decrease in tumor size. After 16 months of palliative chemotherapy, and having received 17 cycles of treatment, a CT scan of the abdomen showed a significant reduction in tumor size (5.2 × 3.8 cm; Fig. 4). The alpha-fetoprotein value accounted for 31.2 ng/ml. On the basis of size reduction, the patient underwent surgical treatment; pathology reported large areas of necrosis and fibrosis compatible with complete histologic response (Fig. 5). Postoperative CT scan showed no residual tumor and confirmed a complete response according to RECIST (Fig. 6). Twenty months after the resection, there is no clinical, radiological, or laboratory evidence of tumor recurrence.

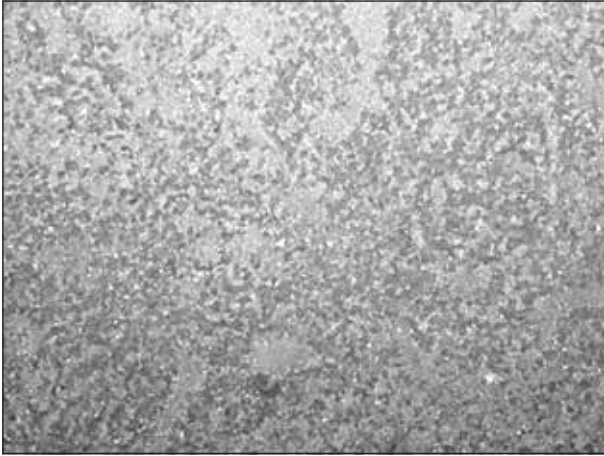
## REVIEW OF THE LITERATURE

Sorafenib is to date the only FDA-approved systemic treatment for advanced HCC with preserved



**Figure 4.** Computed tomography scan demonstrating partial response. A decrease in tumor size greater than 30% corresponding to partial response in agreement with RECIST was observed.

liver function. Systemic chemotherapy has long been regarded as ineffective in HCC because of toxicity and poor response<sup>3</sup>. However, there is evidence that with appropriate patient selection, chemotherapy may have a role<sup>11</sup>. In 1975, a small phase II trial reported high response rates among those patients receiving doxorubicin for HCC<sup>13</sup>. Nevertheless, subsequent studies did not confirm this finding<sup>14</sup>. In 1999, a phase II trial<sup>15</sup> of 50 patients using the PIAF regimen (cisplatin, interferon, doxorubicin, fluorouracil) demonstrated chemosensitivity; nine patients (18%) had at least partial response by imaging, of these four out of nine patients (45%) had complete pathological response. Unfortunately, this regimen was associated with high toxicity, including two treatment-related deaths, and use could not be recommended. In a phase III study<sup>16</sup>, 371 patients with advanced HCC were randomly assigned to open-label FOLFOX (fluorouracil-based regimen) versus systemic doxorubicin. Response rate was 8.15% for FOLFOX-4 and 2.67% for doxorubicin ( $p = 0.02$ ). The median survival for the doxorubicin arm was 4.9 months and 6.4 for FOLFOX-X. However, this trend was non-significant ( $p = 0.0695$ ). Another study<sup>17</sup> using FOLFOX-4 in 37 patients not candidates for sorafenib showed that 33% of patients with Child-Pugh A and 20% with Child Pugh B achieved radiological response and/or alpha-fetoprotein decrease.



**Figure 5.** Pathologic examination of the resected specimen. Large areas of necrosis and fibrosis compatible with complete pathological response.



**Figure 6.** Postoperative abdominal computed tomography. There is no evidence of residual tumor. According to RECIST, the disappearance of all lesions classifies a complete response.

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## CONCLUSION

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A pathologic complete remission was demonstrated in a patient with an initially unresectable HCC and this was likely induced by a fluorouracil-based regimen after radiological progression with sorafenib. This finding is consistent with previous studies that have suggested fluorouracil-based regimen efficacy as systemic treatment for advanced HCC. Current available therapies for unresectable HCC are very limited and since complete tumor resection is the only definite treatment, it is of major importance to promote treatment options that improve its resectability. Further investigation is required to identify any clinical or molecular markers that can be used to select patients that may benefit from fluorouracil-based regimens, especially those who are unfit, progress, or do not have access to sorafenib.

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## CONSENT

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Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written

consent is available for review by the Editor of this journal.

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## COMPETING INTERESTS

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Xóchitl Gómez Roel works as disease area head oncology and immunology for BMS Mexico.

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## AUTHORS' CONTRIBUTION

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GVJI, LCYA, GCGA, GVJL reviewed the literature, prepared the data, drafted and revised the manuscript. VBFE, GRX, BQO, BQA, CMLC and GGJF revised and helped to draft the manuscript. HBD and SFA contributed in drafting and patient care. All authors read and approved the final manuscript.

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