



Neoadjuvant sorafenib combined with gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma

Nicolas Williet, Olivier Dubreuil, Tarek Boussaha, Isabelle Trouilloud, Bruno Landi, Martin Housset, Muriel Botti, Philippe Rougier, Jacques Belghiti, Julien Taieb

Nicolas Williet, Olivier Dubreuil, Tarek Boussaha, Isabelle Trouilloud, Bruno Landi, Philippe Rougier, Julien Taieb, Department of Gastroenterology, European Georges Pompidou Hospital, Medical University, 75908 Paris, France

Martin Housset, Muriel Botti, Department of Radiotherapy, European Georges Pompidou Hospital, Medical University, 75908 Paris, France

Jacques Belghiti, Beaujon Hôpital, Medical University, 100, boulevard du Général Leclerc, 92110 Clichy, France

Author contributions: All authors contributed equally to this work; Williet N wrote the paper.

Correspondence to: Nicolas Williet, MD, Department of Gastroenterology, European Georges Pompidou Hospital, Medical University, 20 rue Leblanc, 75908 Paris, France. nwilliet@yahoo.fr

Telephone: +33-1-56092822 Fax: +33-1-56093529

Received: November 2, 2010 Revised: January 18, 2011

Accepted: January 25, 2011

Published online: May 7, 2011

Abstract

This paper reports the first case of a patient with hepatocellular carcinoma with lymph node metastasis treated by sorafenib combined with gemcitabine plus oxaliplatin, with a partial response and normalization of α fetoprotein, which allowed curative surgery. The potential synergy between these three drugs needs to be confirmed, and is currently being investigated in a randomized phase II trial.

© 2011 Baishideng. All rights reserved.

Key words: Hepatocellular carcinoma; Gemcitabine; Oxaliplatin; Sorafenib; Neoadjuvant therapy

Peer reviewer: Fernando J Corrales, Associate Professor of Biochemistry, Division of Hepatology and Gene Therapy, Proteomics Laboratory, CIMA, University of Navarra, Avd. Pío XII, 55, Pamplona, 31008, Spain

Williet N, Dubreuil O, Boussaha T, Trouilloud I, Landi B, Housset M, Botti M, Rougier P, Belghiti J, Taieb J. Neoadjuvant sorafenib combined with gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma. *World J Gastroenterol* 2011; 17(17): 2255-2258 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i17/2255.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i17.2255>

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer mortality^[1]. Underlying cirrhosis is present in 90% of cases. Its prognosis remains poor with lots of advanced forms, and there is no curative therapeutic approach.

Since 2007, sorafenib has been the standard treatment for first-line therapy of advanced or metastatic disease that is not eligible for intra-arterial chemo-embolization. It has been shown to significantly improve progression-free and overall survival^[2]. However, sorafenib is not able to induce any objective response and tumor shrinkage that allows secondary surgery. Its role in neoadjuvant therapy has not been established either.

Although HCC has been documented as a chemoresistant tumor, some chemotherapeutic regimens, such as gemcitabine plus oxaliplatin, have shown some interesting efficacy results, with objective response rates around 20% and disease control rates > 50% in phase II trials^[3-5]. Here, we report what is believed to be the first case of a patient with advanced HCC who received sorafenib together with gemcitabine plus oxaliplatin, which allowed secondary curative surgery.

CASE REPORT

A 61-year-old man, working as a radiologist, was admitted

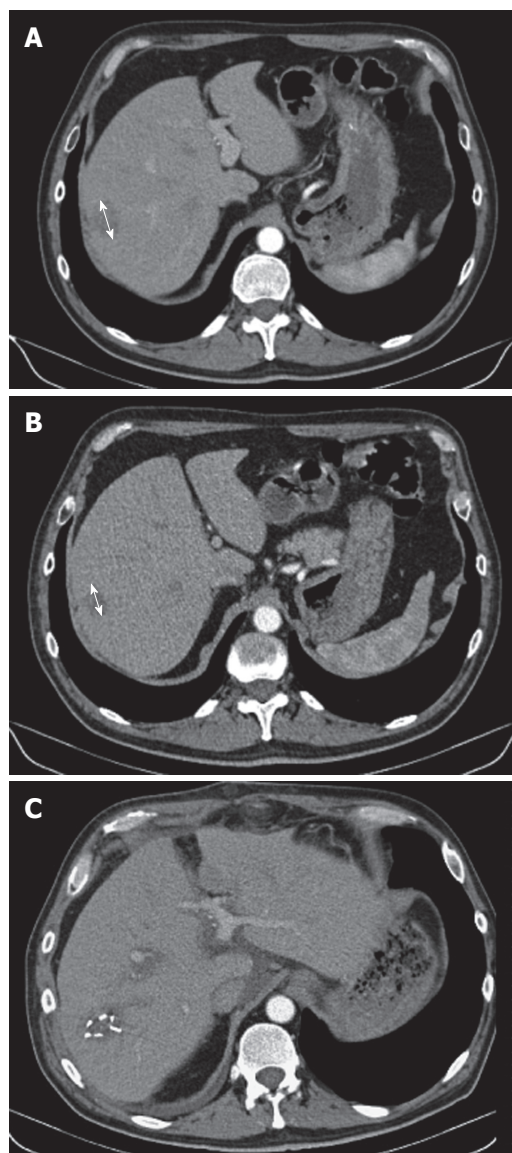


Figure 1 Computed tomography scan. A: A 4.5-cm hypervascular hepatic tumor (arrow) that occupied the sixth hepatic segment, without signs of underlying cirrhosis; B: After eight cycles of gemcitabine and oxaliplatin combined with sorafenib, we observed tumor shrinkage of > 40% (arrow), as compared to baseline assessment; C: Secondary surgery was performed: hemostatic clips were still visible on this postoperative CT scan.

for a liver mass that was detected by ultrasonography that was performed for abdominal pain, in December 2009. He had a history of cholecystectomy and post-transfusion hepatitis C, which was treated effectively by interferon and ribavirin therapy in 1998. Clinically, the ECOG performance status was 0, the patient weighed 94 kg, his height was 188 cm, and he had no symptoms except for moderate abdominal pain that was controlled with class II analgesics. In January 2010, Abdominal computed tomography (CT) showed a 4.5-cm hypervascular hepatic tumor that occupied the sixth hepatic segment, without signs of underlying cirrhosis (Figure 1A). There were also two metastatic lymph nodes (MLNs): one celiac measuring 4 cm, and one measuring 3 cm located in the liver hilum (Figure 2A). Laboratory data showed normal blood

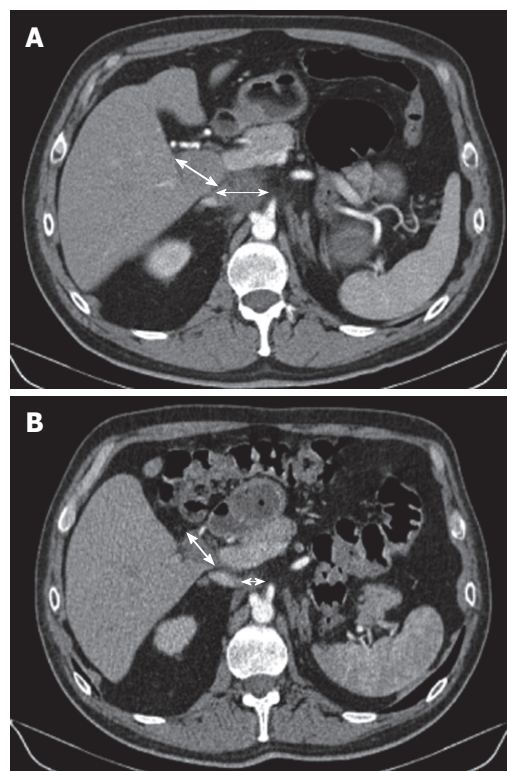


Figure 2 Computed tomography scan. A: Initially, there were two metastatic lymph nodes (MLNs): one celiac (thin arrow) measuring 4 cm and one measuring 3 cm located in the liver hilum (thick arrow); B: Computed tomography scan taken after the end of the eight cycles of gemcitabine plus oxaliplatin combined with sorafenib, showed that the MLNs (thin arrow for celiac node and thick arrow for hilar node) decreased in size dramatically with a more necrotic aspect, which allowed secondary surgery followed by radiotherapy.

cell and platelet counts, liver enzymes, bilirubin and albumin levels. α -fetoprotein (AFP) was markedly increased at 2572 ng/mL (upper limit of normal = 8). Esophago-gastroduodenoscopy did not show gastroesophageal varices or other upper gastrointestinal tract abnormalities.

Fine needle echoendoscopic aspiration from celiac lymph nodes was performed and showed a typical trabecular liver carcinoma. Evaluation by a multidisciplinary team concluded that the primary tumor was theoretically resectable in this patient, who had an excellent performance status, without underlying cirrhosis, and who wished an aggressive therapeutic approach. However, because there were MLNs, initial surgery was rejected and intensive systemic therapy with sorafenib combined with gemcitabine plus oxaliplatin was initiated. He received four cycles of the GEMOX regimen (gemcitabine 1 g/m² on day 1 and oxaliplatin 100 mg/m² on day 2), as previously described^[3]. This treatment was repeated every 2 wk and sorafenib was taken every day (400 mg twice daily). No grade 3/4 toxicities were observed. Grade 1 diarrhea, thrombopenia and neurotoxicity were reported, together with grade 2 asthenia after the fourth cycle. Efficacy assessment showed a decrease of AFP from 2572 to 97 ng/mL. CT scan showed tumor shrinkage of 25% in the liver (Figure 1B), and a slight decrease in MLN size, which were more necrotic (Figure 2B). A new multidisciplinary

evaluation was performed and it was decided to continue the same therapeutic schedule for more cycles. Second efficacy evaluation showed normalization of AFP levels (2.7 ng/mL) and tumor volume reduction of around 40% (Figure 2A), as compared to baseline assessment.

Surgery was then decided upon, which consisted of removing the primary tumor, together with satellite adenopathies. The sites were marked by surgical clips (Figure 1C) to allow for postoperative radiotherapy (RT).

Pathological examination of the specimens showed a well-differentiated HCC that measured 2.5 cm, without underlying cirrhosis (METAVIR score A1F2). All resection margins were negative, and only one lymph node of five removed was metastatic, which was located in the liver hilum and measured 2 cm, with a necrotic center. There were no postoperative complications except for exacerbation of oxaliplatin-induced neurosensory toxicity, as previously described^[6,7]. Global status of the patient improved and postoperative RT of MLNs was performed, by delivering 46 Gy over 5 wk, without any side effects. Complementary adjuvant chemotherapy, with combined sorafenib and gemcitabine for 3 wk in four, was started for 3 mo, and is currently ongoing. Oxaliplatin was not reintroduced because of persistent grade 2 neurosensory toxicity.

DISCUSSION

The role of chemotherapy in HCC patients is still a matter of debate. There is no clear evidence for efficacy of any tested schedule in the adjuvant (or neoadjuvant) setting, as reviewed by a recent Cochrane study^[8]. However, many oncologists are using systemic chemotherapy for their HCC patients in a palliative setting. Doxorubicin, which was considered as potential standard chemotherapy 20 years ago, seems to be toxic and does not convincingly improve survival over that with supportive care^[9]. Recent studies have suggested that oxaliplatin and gemcitabine could be interesting agents, alone or in combination, even if there has been no phase III trial to confirm their efficacy. The choice of gemcitabine-oxaliplatin combinations in this disease is based on: (1) synergy between the two drugs and their sequence dependency (gemcitabine followed by oxaliplatin is most active in preclinical models)^[10]; (2) clinical activity of gemcitabine alone and of 5-fluorouracil/oxaliplatin combination in patients with HCC in phase II trials^[11,12]; and (3) lack of renal and hepatic oxaliplatin toxicity in cirrhotic patients, unlike doxorubicin. The GEMOX combination has thus been evaluated in many phase II studies with promising results in term of response rate and survival^[3-5,13]. Patients with complete response have been described by ourselves and others^[14].

In the pivotal SHARP trial, response rate with sorafenib was particularly low (2.3%) and not significantly different from placebo^[2]. To the best of our knowledge, only one patient receiving sorafenib and eligible for secondary surgery has been reported in the literature^[15]. Sorafenib does

not seem to be a candidate drug for tumor downstaging that allows secondary surgery. However, the antiangiogenic effect of sorafenib seems to modify HCC vascularization, by normalizing tumor vessels^[16]. This vascular normalization has been described as potentially favoring chemotherapy efficacy through better delivery of the drugs to the tumor site^[17]. Combination of sorafenib and GEMOX could thus lead to synergistic antitumor activity.

The toxicity of the GEMOX regimen has been well described over the past 10 years through 31 phase II and two phase III trials, mainly in pancreatic and biliary tract cancers. Grade 3 neutropenia, thrombocytopenia and neurotoxicity have been reported in 22%, 11% and 10%, respectively, and severe nausea has occurred in 16% of the cases^[18]. These results are similar to those described in the phase II trials that have evaluated this combination in HCC patients with underlying cirrhosis. The elevated liver enzymes and anaphylactic reactions (due to gemcitabine and oxaliplatin, respectively) did not seem more frequent in this population.

In the SHARP trial, diarrhea (grade 2 in 50%, grade 3 in 10%), weight loss, fatigue, hand-foot skin reaction (grade 2 in 30%, grade 3 in 8%), and hypophosphatemia were the most frequent toxicities associated with sorafenib. To date, no trial has assessed GEMOX plus sorafenib combination therapy.

Adjuvant RT after resection of MLNs from HCC is not common. To the best of our knowledge, only two Asian cases have been described in the literature^[19,20]. However, three retrospective studies have demonstrated its role in local control of MLNs from HCC that is not eligible for surgery, but is present in patients with good performance status. RT doses range from 40 to 60 Gy, and could prolong overall survival^[21-23]. For example, in Zeng's retrospective study on 125 patients, partial and complete responses were observed in 37.1% and 59.7% of patients, respectively. The median survival was 9.4 mo^[23]. However, these results need to be confirmed. To avoid unnecessary toxicity, the RT dose chosen in the present case did not exceed 50 Gy^[21].

In conclusion, this case is an example of successful multimodal aggressive treatment for advanced HCC, which combined for the first time, GEMOX and sorafenib followed by surgery and adjuvant radiotherapy and chemotherapy. GEMOX + sorafenib combination therapy was well tolerated with only grade 1/2 toxicity that was easily manageable, and gave an objective response, together with a dramatic decrease in AFP levels. These promising results need to be confirmed and GEMOX/sorafenib combination therapy is currently being evaluated in an ongoing randomized phase II trial and compared to sorafenib alone.

REFERENCES

- 1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917
- 2 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc

- JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390
- 3 **Taïeb J**, Bonyhay L, Golli L, Ducreux M, Boleslawski E, Tigaud JM, de Baere T, Mansoubakht T, Delgado MA, Hannoun L, Poynard T, Boige V. Gemcitabine plus oxaliplatin for patients with advanced hepatocellular carcinoma using two different schedules. *Cancer* 2003; **98**: 2664-2670
- 4 **Asnacios A**, Fartoux L, Romano O, Tesmoingt C, Louafi S S, Mansoubakht T, Artru P, Poynard T, Rosmorduc O, Hebbat M, Taïeb J. Gemcitabine plus oxaliplatin (GEMOX) combined with cetuximab in patients with progressive advanced stage hepatocellular carcinoma: results of a multicenter phase 2 study. *Cancer* 2008; **112**: 2733-2739
- 5 **Louafi S**, Boige V, Ducreux M, Bonyhay L, Mansoubakht T, de Baere T, Asnacios A, Hannoun L, Poynard T, Taïeb J. Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC): results of a phase II study. *Cancer* 2007; **109**: 1384-1390
- 6 **Gornet JM**, Savier E, Lokiec F, Cvitkovic E, Misset JL, Goldwasser F. Exacerbation of oxaliplatin neurosensory toxicity following surgery. *Ann Oncol* 2002; **13**: 1315-1318
- 7 **Cournede A**, Ries P, Richard K, Guillaïn A, Dahan L, Grandval P, Pourroy B, Moutardier V, Hardwigsen J, Braguer D, Seitz JF. [Oxaliplatin neurotoxicity: a report of three cases with post-operative exacerbation]. *Gastroenterol Clin Biol* 2005; **29**: 461-464
- 8 **Samuel M**, Chow PK, Chan Shih-Yen E, Machin D, Soo KC. Neoadjuvant and adjuvant therapy for surgical resection of hepatocellular carcinoma. *Cochrane Database Syst Rev* 2009; CD001199
- 9 **Burroughs A**, Hochhauser D, Meyer T. Systemic treatment and liver transplantation for hepatocellular carcinoma: two ends of the therapeutic spectrum. *Lancet Oncol* 2004; **5**: 409-418
- 10 **Faivre S**, Raymond E, Woynarowski JM, Cvitkovic E. Supra-additive effect of 2',2'-difluorodeoxycytidine (gemcitabine) in combination with oxaliplatin in human cancer cell lines. *Cancer Chemother Pharmacol* 1999; **44**: 117-123
- 11 **Yang TS**, Lin YC, Chen JS, Wang HM, Wang CH. Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer* 2000; **89**: 750-756
- 12 **Berretta M**, Lleshi A, Di Benedetto F, Bearz A, Spina M, Tirelli U. Oxaliplatin and capecitabine (Xelox) in association with highly active antiretroviral therapy in advanced hepatocarcinoma HIV/HCV-infected patients. *Ann Oncol* 2006; **17**: 1176-1177
- 13 **Zhu AX**, Blaszkowsky LS, Ryan DP, Clark JW, Muzikansky A, Horgan K, Sheehan S, Hale KE, Enzinger PC, Bhargava P, Stuart K. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 1898-1903
- 14 **Boschetti G**, Walter T, Hervieu V, Cassier P, Lombard-Bohas C, Adham M, Scoazec JY, Dumortier J. Complete response of hepatocellular carcinoma with systemic combination chemotherapy: not to get out the chemotherapy? *Eur J Gastroenterol Hepatol* 2010; **22**: 1015-1018
- 15 **Bathaïx F**, Marion D, Cuinet M, Maillard E, Zoulim F, Mornex F, Merle P. Markedly effective local control of hepatocellular carcinoma with a poor prognosis by combined multimodal therapy with sorafenib as a neoadjuvant approach. *Gastroenterol Clin Biol* 2010; **34**: 314-318
- 16 **Jain RK**. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005; **307**: 58-62
- 17 **Kerbel RS**. Antiangiogenic therapy: a universal chemosensitization strategy for cancer? *Science* 2006; **312**: 1171-1175
- 18 **Poplin E**, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, Alberts S, O'Dwyer P, Haller D, Catalano P, Cella D, Benson AB 3rd. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; **27**: 3778-3785
- 19 **Mima K**, Masuda T, Beppu T, Horino K, Komori H, Imsung C, Hayashi H, Okabe H, Takamori H, Baba H. [A long-term survival case of hepatocellular carcinoma with lymph node metastases treated with surgery and radiotherapy]. *Gan To Kagaku Ryoho* 2008; **35**: 2096-2098
- 20 **Lim JH**, Lee JW, Kim EJ, Lee JI, Jeong S, Lee DH, Shin YW, Kim JM. [A case of recurrent small hepatocellular carcinoma as a solitary lymph node metastasis after hepatic resection]. *Korean J Gastroenterol* 2007; **50**: 66-69
- 21 **Park YJ**, Lim do H, Paik SW, Koh KC, Lee JH, Choi MS, Yoo BC, Nam HR, Oh DR, Park W, Ahn YC, Huh SJ. Radiation therapy for abdominal lymph node metastasis from hepatocellular carcinoma. *J Gastroenterol* 2006; **41**: 1099-1106
- 22 **Yamashita H**, Nakagawa K, Shiraishi K, Tago M, Igaki H, Nakamura N, Sasano N, Siina S, Omata M, Ohtomo K. Radiotherapy for lymph node metastases in patients with hepatocellular carcinoma: retrospective study. *J Gastroenterol Hepatol* 2007; **22**: 523-527
- 23 **Zeng ZC**, Tang ZY, Fan J, Qin LX, Ye SL, Zhou J, Sun HC, Wang BL, Wang JH. Consideration of role of radiotherapy for lymph node metastases in patients with HCC: retrospective analysis for prognostic factors from 125 patients. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1067-1076

S- Editor Tian L L- Editor Kerr C E- Editor Zheng XM