

Concomitant Interferon-alpha and Chemotherapy in Hepatitis C and Colorectal Cancer: A Case Report

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Abstract. *Hepatitis C virus (HCV) infection is one of the main causes of liver disease worldwide. Patients undergoing surgery are at risk of acquiring acute HCV infection and those undergoing surgical eradication of a neoplasia may be indicated for adjuvant treatment. Therefore, unlike chronic infection, these patients may simultaneously need antiviral therapy with interferon for acute hepatitis C and cytotoxic chemotherapy. To date, no data are available regarding the efficacy and tolerability of concomitant interferon treatment and antineoplastic chemotherapy in the setting of acute hepatitis C treatment. Here, we report the case of a 60-year-old man who developed acute hepatitis C after left hemicolectomy for an adenocarcinoma. He received concomitant antiviral treatment with interferon- α and adjuvant chemotherapy with capecitabine and oxaliplatin. Both treatments were well-tolerated and the patient completed the scheduled therapies. HCV infection was eradicated and the patient is free of neoplastic disease two years and 6 months after surgery.*

Hepatitis C virus (HCV) infection is one of the main causes of liver disease; in fact, it affects approximately 3% of the world's population (1). After penetration in the host, HCV gives rise to acute hepatitis, which is diagnosed based on seroconversion of antibodies to HCV (*i.e.* detection of antibodies to HCV in a patient previously anti-HCV-negative) in the presence of the viral genome (HCV RNA). If left untreated, about 70% of patients with acute hepatitis C do not recover and develop chronic hepatitis (2). Overall, 25% of patients with chronic HCV hepatitis will ultimately develop cirrhosis in two to three

decades (3). Annually, about 1.6% of patients with cirrhosis develop hepatocellular carcinoma (1).

Patients undergoing surgery are at risk of acquiring acute HCV infection (4-8). It is well-established that if administered within the first 12 weeks of infection, interferon results in clearance of the virus in about 90% of patients with acute hepatitis C (9).

Colorectal cancer is the second leading cause of death from cancer in Europe, and 40% of patients undergoing potentially curative surgery ultimately die from metastatic disease (10). Adjuvant chemotherapy can improve disease-free survival, mostly in patients with high-risk stage II or stage III disease (11). According to international guidelines, combined treatment with fluoropyrimidines and oxaliplatin is indicated in patients with stage III colonic cancer (12). Fluoropyrimidines, administered by infusion (5-fluorouracil) or orally (capecitabine) are associated with gastrointestinal, renal and hepatic toxicity, whereas oxaliplatin is often associated with peripheral neurotoxicity. After surgical treatment of colonic cancer, no more than 60 days should elapse between the date of surgery and the beginning of chemotherapy. In fact in cases of delay, treatment failure can occur (11, 12). Therefore, differently from patients with chronic hepatitis C, those with co-existing acute hepatitis C and malignancy may need concomitant treatment for several reasons: i) elevated aminotransferase levels are often a contraindication for antineoplastic chemotherapy; ii) treatment of acute hepatitis C must be administered within 12 weeks of surgery because the success rate drops dramatically after this time; iii) in some cases, antineoplastic chemotherapy (adjuvant or neoadjuvant) cannot be delayed (12), and iv) both therapies are standardized and must be administered over a relatively long period in order to be effective.

Despite this scenario, to our knowledge, no study or clinical report has been published regarding the efficacy and tolerability of concomitant interferon- α and antineoplastic chemotherapy in the setting of acute hepatitis C. Here we report the case of a patient who received concomitant adjuvant chemotherapy for stage III colonic adenocarcinoma and standard interferon- α therapy for acute hepatitis C.

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Case Report

A 60-year-old man, affected by arterial hypertension and benign prostatic hyperplasia, was admitted to the Department of Oncology and Endocrinology of our Institute in June 2010. He reported an episode of diarrhea with blood and mucorrea in January 2010. For this reason, his family doctor referred him for a colonoscopy, which the patient underwent in February 2010. Colonoscopy showed a large polypoid formation (diameter: 3 cm) at 10 cm from the anal margin. This polyp had a wide base, an eroded surface, and easily bled to the touch. Multiple biopsies of the polyp revealed the presence of adenocarcinoma.

In April 2010, the patient underwent sigmoid-rectal resection for a well-differentiated colon adenocarcinoma. Pathology staging was pT3G1N1, stage III. No metastasis was found by whole-body contrast-enhanced computerized tomographic scan. At the time of surgery, antibodies to HCV were negative and laboratory examinations showed normal aminotransferase levels: aspartate aminotransferase (AST)=20 IU/l (normal value <40 IU/l); alanine aminotransferase (ALT)=20 IU/l (normal value <40 IU/l).

According to international guidelines (11, 12), a course of adjuvant treatment with fluoropyrimidines and oxaliplatin was planned. However, elevated transaminase levels (AST=238 U/l; ALT= 457 U/l) were identified at the patient's baseline oncology visit (20 May 2010). Consequently, he underwent screening for liver disease, and was found positive for antibodies to HCV, antibodies to Hepatitis A Virus IgG, antibodies to Hepatitis B surface antigen, antibodies to Hepatitis B core antigen IgG, and negative for Hepatitis B surface antigen, antibodies to Hepatitis B core antigen IgM, antibodies to Hepatitis A Virus IgM. Laboratory tests revealed AST= 238 U/l, ALT= 457 U/l, alkaline phosphatase= 130 U/l, γ -glutamyl transferase= 85 U/l, total bilirubin= 1.12 mg/dl; HCV RNA 1,750,000 IU/ml, genotype 1a. Therefore, based on anti-HCV seroconversion and positivity for HCV RNA, acute hepatitis C was diagnosed.

In June 2010 the patient started therapy with interferon- α 2a at a dose of 6,000,000 IU/day for the first four weeks, and then 6,000,000 IU three-times per week for 20 weeks. Baseline AST and ALT levels were 207 U/l and 337 U/l, respectively. HCV RNA, re-evaluated after four weeks of treatment, was negative. AST and ALT levels were normal at the same time point. HCV RNA remained negative throughout treatment and for six months after treatment withdrawal; aminotransferases continued to be normal during and after antiviral therapy. Then, while on treatment with interferon, the patient began adjuvant chemotherapy according to the XELOX regimen (capecitabine 1000 mg/m² *bid* days 1 to 14; oxaliplatin 130 mg/m² day 1, each 21 days). The patient completed all the antineoplastic cycles scheduled without any worsening or alteration of hepatic function parameters, and

had a good compliance and tolerability to the concomitant treatments. The only side-effects related to chemotherapy were grade 1 diarrhea (due to capecitabine) and grade 1 peripheral sensory neuropathy (due to oxaliplatin). The patient experienced slight anemia, leukopenia and thrombocytopenia. The nadir points for hemoglobin, white blood cells and platelet count were 10.5 g/dl, 2,380/ μ l, 81,000/ μ l respectively. No other toxicity was reported. Screening at 2 years and 6 months after surgery showed no signs of relapse for either HCV infection or malignancy.

Discussion

Our case shows that concomitant use of interferon- α and antineoplastic chemotherapy is feasible. This combined treatment is rarely necessary in the setting of chronic hepatitis C. Indeed, very little is known about the long-term evolution of patients with chronic hepatitis C and malignancies treated with chemotherapy (2). Antineoplastic drugs can induce immunosuppression and hepatotoxicity and therefore can, potentially, cause liver damage in HCV-positive patients. In fact, a more rapidly progressive liver disease was found in long-term leukemia survivors with chronic HCV than in age-matched controls (13). However, in cases of concomitant chronic hepatitis C and malignancy, due to the slow evolution of chronic hepatitis and to the urgent need for antineoplastic treatment, priority is usually given to antineoplastic therapy and treatment for chronic hepatitis C is usually delayed until completion of the antineoplastic chemotherapy. Nevertheless, two case reports described the administration of interferon (14) and of interferon and ribavirin combined (15) for treatment of chronic hepatitis C in patients who received concomitant chemotherapy for hematological diseases. It is noteworthy that our case represents, to our knowledge, the first case of concomitant interferon- α administration and antineoplastic chemotherapy in the setting of acute hepatitis C and a solid tumor.

Our patient, who was a candidate for early antineoplastic therapy to avoid metastasis, had high levels of ALT due to acute hepatitis C. Since elevated ALT levels are a contraindication for chemotherapy, we administered interferon first in order to clear the virus and, upon normalization of ALT values, we started chemotherapy. Because each of the two therapies are well-standardized and lengthy, their administration largely overlapped in our patient.

This simultaneous treatment was both effective and safe. In fact, the patient was able to complete the adjuvant treatment for the pathological stage of cancer and a complete clearance of HCV was achieved. A potential concern of this simultaneous therapy is the increased risk of myelosuppression due to the direct effect of interferon and chemotherapy on bone marrow progenitor cells. However, in our patient, hematological side-effects were not severe and he did not require the administration of hematological growth factors.

It is noteworthy that in the setting of patients who undergo surgery, the diagnosis of acute hepatitis C can be easier due to the frequent availability of a previous (usually pre-surgery) anti-HCV test and hence it is possible to identify seroconversion.

In conclusion, in this first report, the concomitant use of interferon- α for acute hepatitis C and antineoplastic adjuvant chemotherapy with capecitabine and oxaliplatin for colorectal cancer was both effective and safe.

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References

- Lavanchy D: The global burden of hepatitis C. *Liver Int* 29(Suppl 1): 74-81, 2009.
- The Global Burden of Hepatitis C Working Group: Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 44: 20-29, 2004.
- Hoofnagle JH: Hepatitis C: The clinical spectrum of disease. *Hepatology* 26(Suppl 1): 15S-20S, 1997.
- Hung CH, Lu SN, Wang JH, Hung SF, Chen CH, Hu TH, Lee CM and Changchien CS: Identified cases of acute hepatitis C from computerized laboratory database: A hospital-based epidemiological and clinical study. *J Infect* 56: 274-280, 2008.
- Martínez-Bauer E, Fornis X, Armelles M, Planas R, Solà R, Vergara M, Fàbregas S, Vega R, Salmerón J, Diago M, Sánchez-Tapias JM, Bruguera M and Spanish Acute HCV Study Group: Hospital admission is a relevant source of hepatitis C virus acquisition in Spain. *J Hepatol* 48: 20-27, 2008.
- Brouard C, Pradat P, Delarocque-Astagneau E and Silvain C: Epidemiological characteristics and medical follow-up of 61 patients with acute hepatitis C identified through the hepatitis C surveillance system in France. *Epidemiol Infect* 136: 988-996, 2008.
- Mele A, Spada E, Sagliocca L, Ragni P, Tosti ME, Gallo G, Moiraghi A, Balocchini E, Sangalli M, Lopalco PL and Stroffolini T: Risk of parenterally transmitted hepatitis following exposure to surgery or other invasive procedures: results from the hepatitis surveillance system in Italy. *J Hepatol* 35: 284-289, 2001.
- Gallo C, Gaeta GB, Galanti B and Giusti G: The role of surgery in transmitting "post-transfusion hepatitis". *Eur J Epidemiol* 2: 95-98, 1986.
- European Association for the Study of the Liver EASL: Clinical Practice Guidelines: Management of hepatitis C virus infection. *J Hepatol* 55: 245-264, 2011.
- Ferlay J, Parkin DM and Steliarova-Foucher E: Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 46: 765-781, 2010.
- André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F and de Gramont A: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 27: 3109-3116, 2009.
- Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Köhne CH, Labianca R, Price T, Scheithauer W, Sobrero A, Tabernero J, Aderka D, Barroso S, Bodoky G, Douillard JY, El Ghazaly H, Gallardo J, Garin A, Glynne-Jones R, Jordan K, Meshcheryakov A, Papamichail D, Pfeiffer P, Souglakos I, Turhal S and Cervantes A: ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. *Ann Oncol* 23: 2479-2516, 2012.
- Paul IM, Sanders J, Ruggiero F, Andrews T, Ungar D and Eyster ME: Chronic hepatitis C virus infections in leukemia survivors: Prevalence, viral load, and severity of liver disease. *Blood* 93: 3672-3677, 1999.
- Waldron P: Interferon treatment of chronic active hepatitis C during therapy of acute lymphoblastic leukemia. *Am J Hematol* 61: 130-134, 1999.
- Ayyub M, El-Moursy SA, and Al-Abbas F: Outcome of combination antiviral therapy in chronic hepatitis C virus infection during therapy of acute lymphoblastic leukemia. *Saudi J Gastroenterol* 17: 283-286, 2011.

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