2005 Volume 8
Pages 9–13

Regulation of neutrophilia by granulocyte colony-stimulating factor: a new cancer therapy that reversed a case of terminal hepatocellular carcinoma

Journal of Clinical Research 2005; **8**: 9–13 JCR

Regulation of neutrophilia by granulocyte colony-stimulating factor: a new cancer therapy that reversed a case of terminal hepatocellular carcinoma

Antonio Brú[1], Sonia Albertos[2], Fernando García-Hoz[3], Isabel Brú[4]

Summary

This work reports the possible cure of a 56-year-old patient with advanced hepatocarcinoma. Intense peritumoral neutrophilia was achieved by administering granulocyte colony-stimulating factor (G-CSF), an experimental treatment based on the theory of universal tumour dynamics. After the first 8-week cycle of treatment, the patient's α-fetoprotein (AFP) levels were reduced to normal and his general condition improved sufficiently to allow him to return to work. Following a second cycle of treatment, administered because of doubt regarding the tumoral or inflammatory nature of the now smaller liver mass, the patient's AFP levels remained normal and he continued to enjoy good general health.

Key words: hepatocellular carcinoma, liver, granulocyte colony-stimulating factor (G-CSF), α-fetoprotein, tumour dynamics, peritumoral neutrophilia

Accepted for publication: 10th May 2005

[1] Departamento de Matemática Aplicada, Universidad Complutense de Madrid, Spain
[2] Servicio de Aparato Digestivo, Hospital Clínico San Carlos, Madrid, Spain
[3] Servicio de Aparato Digestivo, Hospital Ramón y Cajal, Madrid, Spain
[4] Centro La Estación, Talavera de la Reina, Toledo, Spain

Address for correspondence: Dr Antonio Brú, Departamento de Matemática Aplicada, Facultad de Ciencias Matemáticas, Universidad Complutense de Madrid, Avenida Complutense s/n, 28040 Madrid, Spain. Tel: +34 91 294 4725, fax: +34 91 3946413, e-mail: antonio.bru@mat.ucm.es

Introduction

Hepatocellular carcinoma (HCC) is a major cause of death worldwide. Only approximately 30% of cases are treatable, and then only by surgery or liver transplant. Most patients are not candidates for this treatment because they are usually diagnosed when the disease is advanced, or because of liver failure due to underlying cirrhosis. Even after surgical resection, the tumour recurs in approximately 70% of patients within 3 years[1–3]. New therapies are therefore urgently required.

This paper reports the treatment of a patient with HCC via generation of intense neutrophilia. According to recent publications, all solid tumours grow by the same mechanism, namely 'diffusion' of tumour cells at the tumour border[4,5]. Via this mechanism, new tumour cells aid their future proliferation by relocating themselves in cavities at the tumour surface. Even though these cavities provide them less oxygen and nutrients and are altogether more acidic environments[5], the evidence suggests that space is the major limiting factor of tumour growth, and it is in these cavities at the tumour/host tissue interface where space is most available[5]. Here, these new tumour cells can continue to divide and to degrade the extracellular matrix.

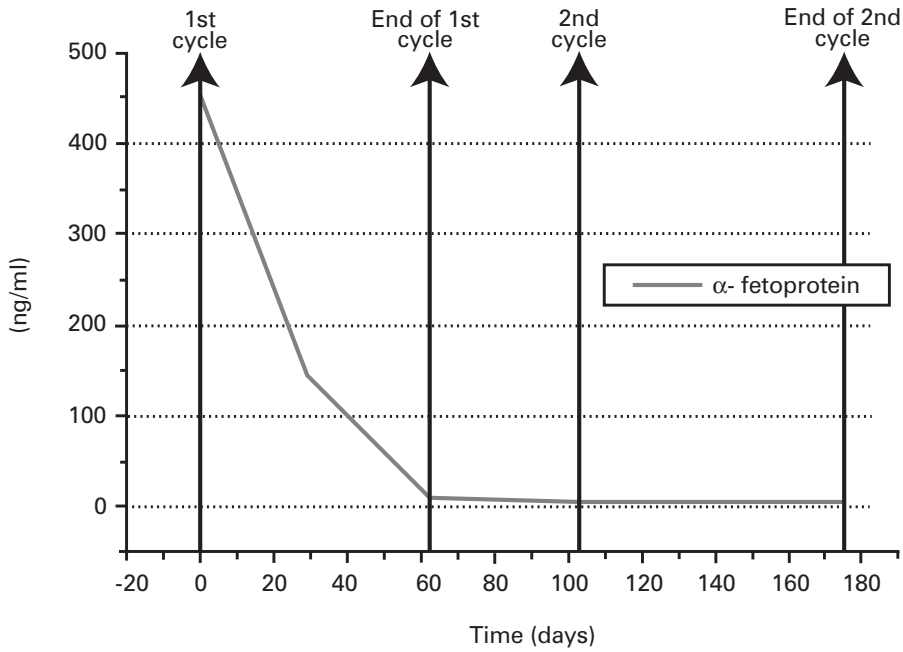
It has been shown in mice that neutrophils come into intimate contact with the tumour/host interface, and that when their numbers are large enough they can generate sufficient pressure to prevent this host growth mechanism[6]. In fibroehrlicht tumours, 80–90% regression was seen in 8 out of 10 rats after only 8 weeks following the induction of intense neutrophilia. The tumours of the remaining two animals completely disappeared. This paper reports similar results in a human patient with terminal hepatocarcinoma.

The patient was a 56-year-old man who had been diagnosed with hepatitis non-A non-B (designated hepatitis C 10 years ago) some 25 years earlier. He consumed approximately 80 g ethanol per day. The patient had undergone no surgery and had not received any transfusions, and had always been asymptomatic with respect to hepatitis C virus (HCV) infection. Indeed, he had received no treatment in this respect. He was admitted to hospital for the first time in February 2004 because of moderate ascites. A physical examination revealed signs of chronic hepatitis (palmar erythema, vascular spiders on the chest). Cardiopulmonary auscultation was normal. The abdomen showed moderate ascites without peritoneal irritation.

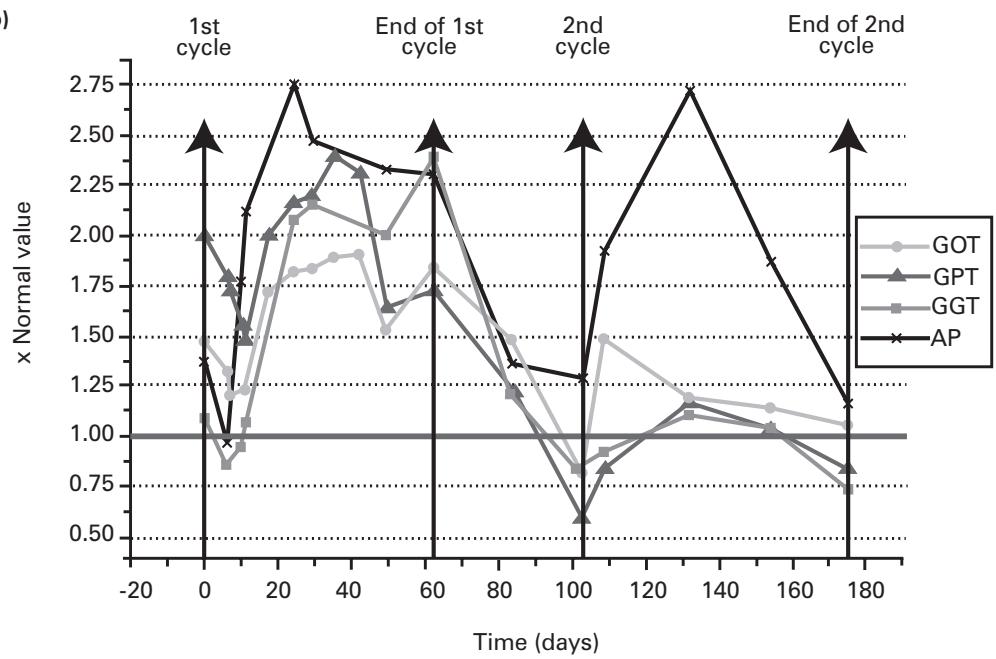
The results of blood analysis were: platelets 98,000 cells/µl; creatinine 1.6 mg/dl; total bilirubin 2 mg/dl; aspartate aminotransferase (AST) 162 U/l; alanine aminotransferase (ALT) 136 U/l; gamma glutamyltransferase 468 U/l; alkaline phosphatase 213 U/l; lactate dehydrogenase 574 U/l; prothrombin activity 68%; albumin 3.3 g/dl; and α-fetoprotein (AFP) 216 ng/ml. Cytology of the ascitic fluid revealed no malignant cells.

Figure 1. Changes in (a) α-fetoprotein and (b) transaminase levels. GOT (=AST), aspartate aminotransferase; GPT (=ALT), alanine aminotransferase; GGT, gamma glutamyltransferase; AP, alkaline phosphatase.

a)



b)



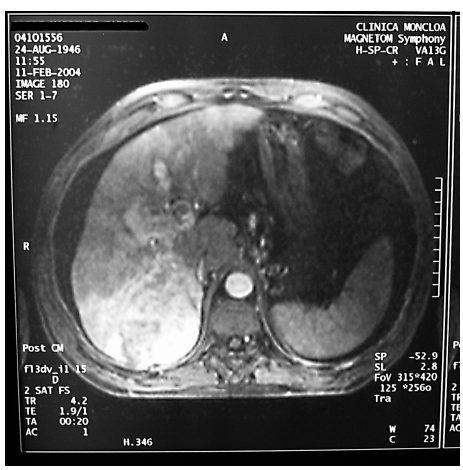
At the time of diagnosis of HCC in February 2004, a CT scan of the pelvic–abdominal area revealed a heterogeneous liver, especially noticeable in the right lobe. Ascites was present. Non-specific alteration of the mesenteric fat was also observed, along with an effusion of the left pleura and cholelitiasis. Nuclear magnetic resonance (NMR) revealed findings compatible with a diffuse hepatocarcinoma of the right hepatic lobe approximately 95 mm in diameter (in a background of liver cirrhosis), accompanied by thrombosis of the common portal vein and its two main branches. Ascites was confirmed.
A non-specific nodule was found in the spleen. Cholelitiasis was again observed. Fine needle aspiration under radiological control revealed a poorly differentiated hepatocarcinoma.

In June 2004, no conventional treatment was indicated given the stage of the carcinoma (lesion larger than 6 cm with portal thrombosis). The patient was therefore treated compassionately with granulocyte colony-stimulating factor (G-CSF) (Neupogen, 10 µg/kg/day for 8 weeks; Amgen Labs, Thousand Oaks, CA), modifying the dose to maintain a leukocyte count of no greater than 60,000 cells/ml. Blood analysis showed: haemoglobin 11.2 g/dl; leukocytes 4,760 cells/µl; platelets 115,000 cells/µl; creatinine 1.33 mg/dl; AST 86 U/l; ALT 124 U/l; and AFP 453 ng/ml.

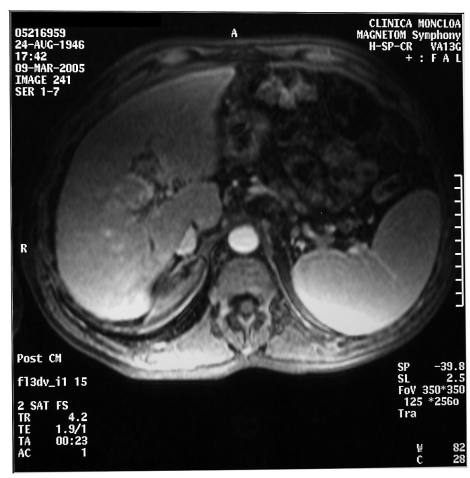
During treatment, which was very well tolerated, the patient showed only sporadic episodes of mild fever. The leukocyte count was successfully maintained below 60,000 cells/ml at all times. On only one occasion did it reach 58,900 cells/µl, on day 17 of treatment, which required an adjustment to half the normal dosage (5 µg/kg/day) for 1 day. The following day the initial dose was restored since the increase in the number of leukocytes in the blood had been controlled. Haemoglobin, platelet

Figure 2. Nuclear magnetic resonance images (a) at the time of diagnosis, and (b) at the end of treatment

a)



b)



and creatinine levels underwent no significant changes.
A significant reduction was seen in the AFP level, from 453 ng/ml to 8.2 ng/ml over the 8 weeks of treatment. Two weeks after the end of treatment it had fallen to 4.74 ng/ml (normal values <10 ng/ml) (Figure 1a). In addition, the leukocyte count normalised. No other significant changes were observed.

After finishing this first cycle of treatment, NMR continued to show a mass smaller than on the initial images (Figure 2). Despite the fall in AFP levels and the patient's general state of good health, it was unclear whether this mass was tumoral or inflammatory in nature. Given its inaccessibility to biopsy (owing to the reduction in size of the lesion) and owing to the good tolerance shown to the G-CSF treatment, a second cycle of treatment was begun in September 2004 (same dose and duration). This second cycle was equally well tolerated and the patient remained in good general condition. At the end of this cycle, no differences were noticed with respect to the previous NMR images (Figure 2). Ascites was still present (although less than when treatment was begun), possibly attributable to the cirrhosis suffered by the patient.

Four months after the second cycle of treatment, the patient underwent fine needle aspiration again. The cytological results were compatible with small cell dysplasia, but not malignancy. In addition, radiological images were unchanged and AFP levels remained normal.
The patient remained asymptomatic and continued to work; the hepatocarcinoma may therefore have been cured.

This is the first report of maintained G-CSF-induced neutrophilia leading to a likely cure of multicentric hepatocarcinoma accompanied by portal hypertension. The use of G-CSF in the treatment of HCC should be studied further.

References

1. Lin TY, Lee CS, Chen KM *et al*. Role of surgery in the treatment of primary carcinoma of the liver: a 31-year experience. *British Journal of Surgery* 1987; **74**: 839–842.
2. Chen MF, Hwang TL, Jeng LB *et al*. Postoperative recurrence of hepatocellular carcinoma. Two hundred five consecutive patients who underwent hepatic resection in 15 years. *Archives of Surgery* 1994; **129**: 738–742.
3. Nagasue N, Uchida M, Makino Y *et al*. Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. *Gastroenterology* 1993; **105**: 488–494.
4. Brú A, Pastor JM, Fernaud I *et al*. Super-rough dynamics of tumor growth. *Physical Review Letters* 1998; **81**: 4008–4011.
5. Brú A, Albertos S, Subiza JL *et al*. The universal dynamics of tumor growth. *Biophysical Journal* 2003; **85**: 2948–2961.
6. Brú A, Albertos S, López García-Asenjo JA *et al*. Pinning of tumoral growth by enhancement of immunological response. *Physical Review Letters* 2004; **92**: 238101.

