Prometheus' spirit: quality survival in advanced hepatocellular carcinoma after gemcitabine and cisplatin-based chemotherapy

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ABSTRACT

In advanced virus-induced hepatocellular carcinoma (HCC) associated with cirrhosis, the average survival is four months. We report a 56-year-old man with a large-volume advanced HCC, in whom gemcitabine and cisplatin-based chemotherapy resulted in near-complete regression, and quality survival of 24 months.

Keywords: alpha foetoprotein, cisplatin, gemcitabine, hepatocellular carcinoma, liver cancer, liver cirrhosis

Singapore Med J 2008; 49(10): e293-e295

INTRODUCTION

Survival in hepatocellular carcinoma (HCC) is very poor, due to the advanced stage of the disease at presentation, lack of infrastructure and expertise for liver transplantation, especially in the developing and underdeveloped economies, and unavailability of effective chemotherapeutic agents. HCC is one of the leading causes of death from malignancies worldwide.[1] More than 50% of the patients present with locally-advanced or extra-hepatic tumour.[2] Surgical resection is the most definitive and rewarding treatment, but a very low percentage of patients are suitable for surgical resection. HCC is a major challenge to the medical oncologist as it is classified as one of the highly chemoresistant tumours.

CASE REPORT

A 56-year-old man, a brigadier from an African country, was investigated elsewhere and was found to have deranged liver function tests (LFTs) three months prior to his presentation to us in June 2003 with constitutional symptoms, prostration, listlessness and weight loss. He was seen by us in the first clinical encounter in performance status (PS) two on the Zubrod scale. Clinical examination disclosed mild hepatomegaly without splenomegaly, with no free fluid in the peritoneal cavity. Icterus and peripheral lymphadenopathy were absent. Magnetic resonance (MR) imaging of the abdomen revealed multiple round enhancing lesions of various sizes in both lobes of the liver. The right adrenal gland was infiltrated by the largest tumour in the right liver lobe. Portal vein invasion was absent. Serum alpha-foetoprotein (AFP) was 16,300 ng/mL. Serum albumin level was 3.2 g/dL, bilirubin was 1.1 mg/dL, and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and alkaline phosphatase levels were 77, 80 and 259 U/L, respectively. Core-needle biopsy confirmed the diagnosis of HCC in the backdrop of cirrhosis. Enzyme-linked immunosorbent assay (ELISA) for HBsAg was positive; however, HBeAg was absent. He was seronegative for hepatitis C virus on ELISA.

He was in Child-Pugh class A, and had Stage IIIB with unresectable T4 disease (American Joint Committee on Cancer Staging) and Okuda Stage 2 disease. A discussion was held with the family about the options of chemotherapy, as he was not a candidate for resection or transplant as curative treatment. He was started on palliative chemotherapy based on gemcitabine (1.2 g/m^2 on days 1 and 8) and cisplatin (75 mg/m^2 in divided doses on days 1 and 2, every three weeks) in June 2003. On the advice of the gastroenterologist, throughout the period of first-line chemotherapy (and even in subsequent nontreatment and treatment periods), he was on oral lamivudine 100 mg once a day.

A partial response (PR) was witnessed after three cycles of chemotherapy. After the completion of six cycles of chemotherapy, a very good PR with 90% regression was documented on imaging in November 2003; AFP was 26 ng/ml. Maximum toxicities recorded were grade 3 anaemia, neutropenia and thrombocytopenia. The quality of life (in terms of lack of prostration and sense of wellbeing) improved dramatically at the conclusion of the chemotherapy programme, no particular scale of quality-of-life assessment was, however, used. He was on close follow-up thereafter.

Four months after the completion of chemotherapy, an FDG-PET scan in February 2004 revealed three hypermetabolic foci in segment eight of the liver, right adrenal gland, and the seventh and tenth dorsal

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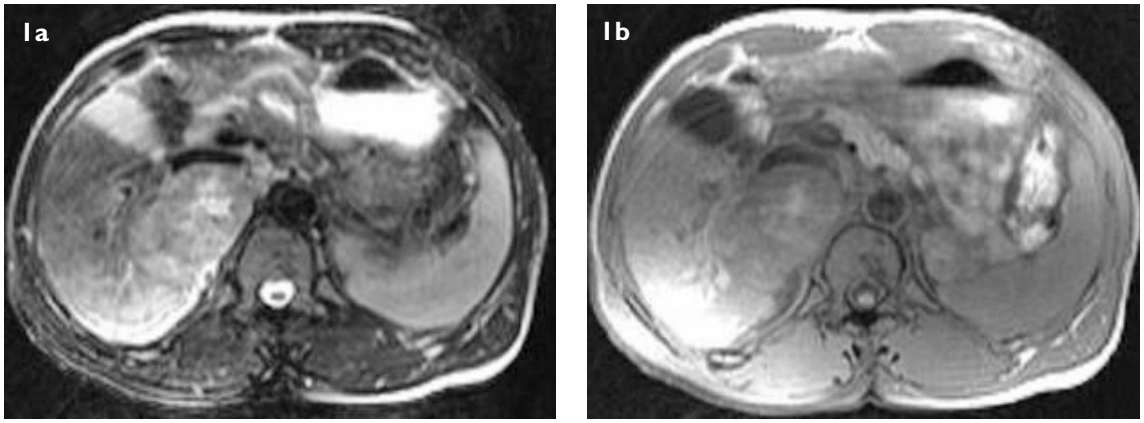

Fig. 1 Axial (a) fat-suppressed T2-W, and (b) fat-suppressed T1-W MR images show a heterogeneous exophytic mass (arrow) in relation to segment VII of the liver.

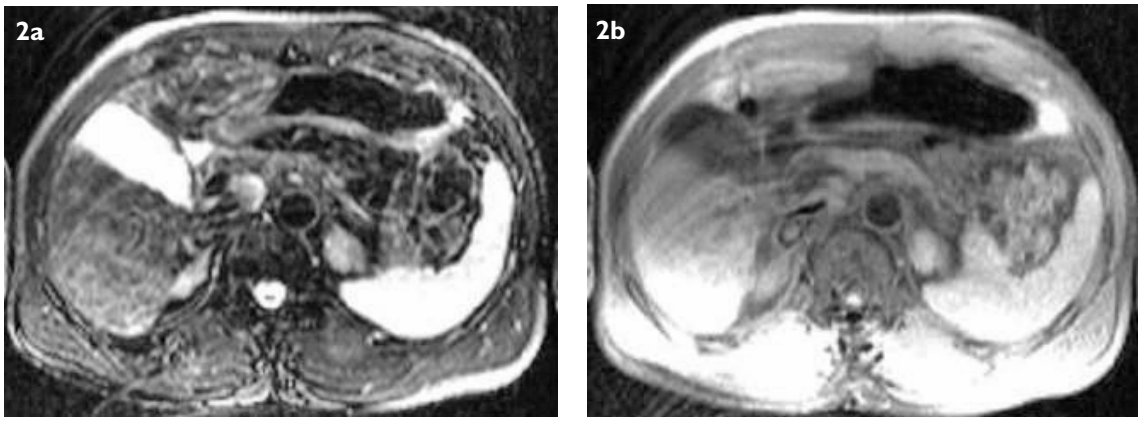

Fig. 2 Axial (a) fat-suppressed T2-W, and (b) fat-suppressed T1-W MR images taken at the same level after six cycles of chemotherapy show near-complete regression of the hepatic mass.

vertebrae. He was asymptomatic, and remained so for the subsequent four months. At another centre, he underwent cytoreductive surgery in the form of right adrenalectomy and right extended hepatectomy in July 2004.

Three months later, in October 2004, he presented back to us for the progressive disease. He was in PS 2 on the Zubrod scale. Liver functions were only marginally deranged: bilirubin was 1.2 mg/dL, AST and ALT were close to 2 × ULN. After a thorough discussion with the family and the patient, we started him on chemotherapy with FOLFOX regimen (oxaliplatin [85 mg/m^2, day 1], leukovorin [400 mg/m^2, day 1] and 5-FU [bolus 400 mg/m^2, days 1 and 2; and 22-hour CIVI 600 mg/m^2, days 1 and 2]). Grade 3 thrombocytopenia was the only toxicity of higher grade encountered. Evaluation after six cycles of FOLFOX showed progressive disease. He succumbed to the inexorably progressive disease in May 2005. He survived, from the recognition of disease, for 24 months overall.

DISCUSSION

The age-adjusted incidence rate of HCC in India ranges in regional cancer registries from 1.9 to 3.4 cases per 100,000 population.[3] The incidence rates in the United States among men and women are, respectively, 9.3 and 3.3 per 100,000 population.[4] HCC continues to be a disease with very abysmal prognosis. The survival rate in untreated HCC varies greatly: a median survival of less than one month from diagnosis in sub-Saharan African patients is contrasted by an average survival of four months in virus-induced HCC associated with cirrhosis.[5] A minority of patients (T1, T2, N0, M0) are the candidates for the surgical resection as that is the only curative treatment available at this point in time. Patients whose tumours are localised but unresectable (T1–4, N0, M0) due to location in the liver, concomitant medical considerations (such as cirrhosis), or even limited bilateral tumours, may be candidates for chemoembolisation, cryosurgery, percutaneous ethanol injection, or radiofrequency ablation for cancers smaller than 5 cm in size. The present case had unresectable HCC by virtue of multicentricity of high volume and involvement of the right adrenal gland. He did not meet the United Network for Organ Sharing (UNOS) criteria for liver transplantation.

HCC is classified as a highly chemoresistant disease. Systemic chemotherapy yields response rates of 0%–20%. The agents that have been shown to have good potency are: doxorubicin, 5-FU, interferon, and cisplatin. Gemcitabine, a pyrimidine anti-metabolite that exhibits a broad range of activity against a variety of tumours, has been shown to have only minimal

activity in HCC in phase II studies.[6-9] High-dose gemcitabine was shown to be no better.[10] Gemcitabine was shown to have a modest activity in combination with Doxorubicin;[11] with cisplatin, it showed a PR rate of 20% and stable disease in 43% patients,[12] and with oxaliplatin, it was shown to yield a response rate of 19%.[13] In a most recent phase II study, a triplet of gemcitabine, oxaliplatin and bevacizumab was found to have an objective response rate of 20%, along with a proportion of stable disease of an additional 27%.[14] Other agents demonstrated to have some activity in HCC in anecdotes, small retrospective and prospective studies are: thalidomide, arsenic trioxide and docetaxel.

Sorafenib, a multikinase inhibitor, was not available when this patient was treated in 2003. It has been shown to have a good activity in HCC and has come to the forefront of choices in the palliative treatment of HCC patients in Child-Pugh status A and B.[15] Sorafenib, however, has a prohibitive cost of therapy. Doxorubicin, although effective as a single agent, may be a poor choice in hepatic function. Our institutional experience of safety and efficacy of gemcitabine and cisplatin combination in HCC led us to treat the unresectable disease in the index case with these agents. Because of the Hesketh level I propensity for emesis with the gemcitabine-cisplatin combination, dexamethasone could not be avoided in the anti-emetics. After six cycles, an excellent response was obtained (Figs. 1–4).

Cytoreduction in the form of right adrenalectomy and right extended hepatectomy, was performed at another centre after four months. The necessity of such a surgery could not be justified. However, during the course of the chemotherapy, the postchemotherapy period and the postoperative period until the terminal six months of progressive disease, his quality of life had been excellent. Sequential systemic chemotherapy every fortnight with oxaliplatin, 5-FU and leukovorin for six cycles on progression did not yield any response.

Our patient's case is an apt example of stretching quality survival in the devastating disease of the liver, reminiscent of the same spirit as Prometheus. The present anecdote of the gemcitabine and cisplatin combination in the index case might offer a paradigm in HCC: if the molecular determinants of a good response of this degree to the combination become known, an unresectable-but-potentially-resectable disease may be made resectable in the favourable subset of patients by the combination of these agents; a large resectable tumour may be shrunken with these agents and surgery may be made less invasive and less radical; good palliation may be achieved in the metastatic setting. Finally, a word of caution is in order: overzealous extrapolation of anecdotal reports cannot be upheld for the routine decision-making by the clinician. In conclusion, the gemcitabine and cisplatin combination yielded a very good PR, and consequent good progression-free survival in the present case of unresectable HCC. The molecular determinants of such a good response to this combination of agents in HCC need to be further investigated.

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