Complete pathological response of hepatocellular carcinoma with systemic combination chemotherapy

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Prognosis of advanced hepatocellular carcinoma is dismal when locoregional treatments have failed. Systemic chemotherapy is seldom effective in inducing objective response and prolonging survival. We report a case of complete pathological remission of hepatocellular carcinoma after three cycles of systemic chemotherapy. A 64-year-old woman presented with histologically documented hepatocellular carcinoma without associated liver disease, relapsed after earlier locoregional therapy. Surgery was not performed as thoracic computerized tomography (CT) demonstrated pulmonary bilateral nodules. The patient was treated with chemotherapy consisting of three cycles of epirubicin, cisplatin, and infusional 5-fluorouracil (ECF regimen); stable lung disease and a good partial response in the liver were obtained as documented by CT scan. Hepatic segmentectomy was therefore performed and the histologic examination revealed necrosis without evidence of residual disease. Two more cycles of adjuvant chemotherapy were infused after surgery. At 1-year follow-up the patient is alive and free of disease according to a positron emission tomography/CT scan. It is suggested that an aggressive regimen like ECF should be considered in fit patients who are not affected by concomitant liver disease. ***Anti-Cancer Drugs*** **19:837–840 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Hepatocellular carcinoma (HCC) incidence and mortality are increasing worldwide. This trend has been mainly ascribed to the spread of hepatitis C virus from eastern Asia and southern Europe to the United States [1,2]. Currently, three to four million people are infected with hepatitis C virus; it is estimated that 30% of these patients will develop chronic liver disease and cirrhosis. The risk for cirrhotic patients of developing HCC is 1–2% per year [3].

Optimal treatments for early HCC are either surgical resection or liver transplantation. European and Japanese institutions have reported 5-year survival rates of 60–70% considering highly restrictive selection criteria for surgery [4–6]. In Western countries less than 5% of HCC patients meet these stringent criteria and are candidates for resection with acceptable risk [7]. Locoregional therapy has been shown to prolong patients' survival, and may even replace surgical resection in some cases; in the past 20 years, approaches such as percutaneous ethanol injection therapy and transcatheter hepatic arterial embolization have greatly improved the results of locoregional treatment [8–11].

Otherwise, patients unsuitable for surgical or locoregional approach or with metastatic disease have a dismal median survival of approximately 4 months [12,13]. Systemic chemotherapy has limited efficacy in HCC; and whereas stability of disease and partial response are frequently obtained, a complete clinical and pathological response is rarely achieved [13–16].

About 60% of patients affected by HCC have underlying cirrhosis. Nzeako *et al.* [17] reported that patients with cirrhosis are significantly older, have high-grade tumors, and local portal venous invasion significantly more often than patients without cirrhosis. Portal hypertension and other liver-related abnormalities such as thrombocytopenia make systemic chemotherapy difficult to deliver in patients with liver disease. Noncirrhotic patients or patients with a good liver function are therefore the best candidates for systemic therapy. The Cancer of the Liver Italian Program (CLIP) score is helpful in identifying patients who can afford aggressive treatment [18].

We present a case of complete pathological remission of HCC after three cycles of systemic chemotherapy with epirubicin, cisplatin, and infusional 5-fluorouracil

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(ECF regimen) [19], and we discuss the possibility to reach excellent results in a specific subset of patients with normal or slightly altered liver function tests.

Case report

A 64-year-old woman presented to our department with a sharp pain in the right flank. She had no history of viral chronic hepatitis or alcohol abuse. She suffered from hypertension well controlled by enalapril. A hard mass was palpable in the right hipocondrium 10 cm under the costal edge. An abdominal CT scan showed a mass of 15 cm in diameter involving the sixth segment of the liver without radiological signs of chronic liver disease or portal vein thrombosis.

The patient underwent a wide resection of the sixth segment and cholecystectomy. Postoperative course was uneventful. Histological examination showed a moderately differentiated mixed-type hepatocellular carcinoma, Edmonson grade III, with necrosis and multifocal vascular invasion, pT3 Nx according to TNM staging (Fig. 1).

Preoperatively serum α-fetoprotein (AFP) level was 3188 ng/ml (normal < 13.4 ng/ml). After surgery serum AFP level decreased to 36.1 ng/ml.

No adjuvant therapy was performed. Five months later an intrahepatic recurrence was diagnosed by magnetic resonance demonstrating the presence of a mass 7 cm in diameter in the S5 region. At the time of recurrence the patient was asymptomatic with good performance status. On physical examination a moderate hepatomegaly was found. Liver function tests were: total bilirubin 0.85 mg/dl (0.1–1.0), aspartate aminotransferase 25 U/l (3–31), alanine transaminase 50 U/l (3–31), alkaline phospatase 255 UI/l (40–150), albumin 4.55 g/dl, international normalized ratio 1.06. CLIP score was 1. Serum AFP level was increased to 854.8 ng/ml.

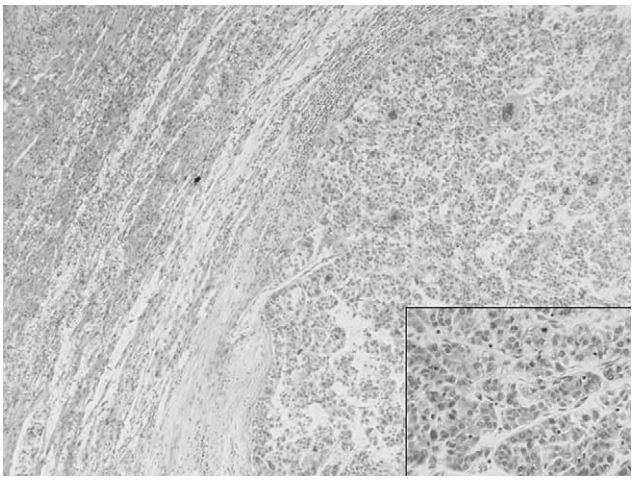
A new liver resection was excluded because of multiple lung nodules suspected to be metastases, although fluorodeoxyglucose-PET negative. Therefore, also on the basis of the absence of a underlying liver disease the patient was treated with chemotherapy, according to the ECF regimen, every 3 weeks: epirubicin 50 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, and 5-fluorouracil 200 mg/m^2/day administered as a continuous infusion from day 1 to day 21.

Owing to grade 2 nausea, vomiting and diarrhea requiring antiemethics, loperamide and mineral replacement after the second ECF cycle, the third cycle was administered at a reduced dose of cisplatin (80%). Hematological toxicity was irrelevant.

After three cycles of chemotherapy, at the CT scan lung nodules were unchanged both in number and size, whereas the hepatic lesion was reduced from 7 to 3.2 cm with loss of the earlier present ringed enhancement in the hepatic arterial phase.

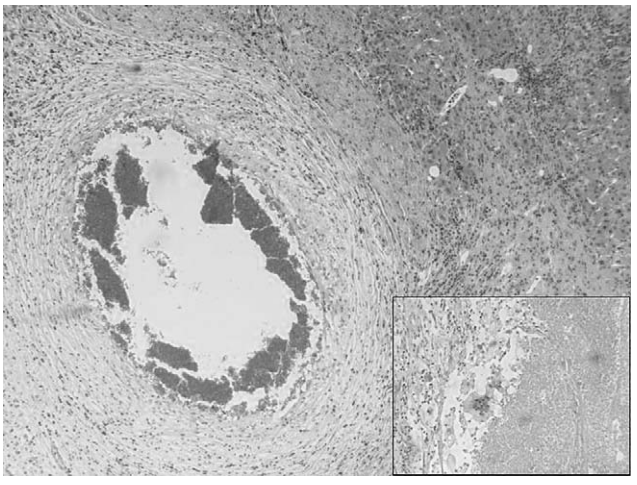
Questioning the metastatic nature of the lung nodules based on their stability, on the basis of the good liver response, the patient was referred to surgeons and underwent 4th to 5th segment hepatic resection. The histological examination showed necrotic nodules, calci-

Fig. 1



Hepatocellular carcinoma (right) separated by a thin incomplete capsule from the non-neoplastic compressed parenchyma (left). At higher magnification (inset) neoplastic cells show a trabecular structure (hematoxylin–eosin, × 40, inset × 400).

Fig. 2



Non-neoplastic inflamed liver (upper right) and necrotic nodule surrounded by fibrosis (left). At higher magnification (inset) the nodule shows coagulative necrosis with giant cell reaction (hematoxylin–eosin, × 40, inset × 400).

fied and sclerojalin tissue associated with diffuse giant cell granulomatous reaction and no evidence of residual tumor (Fig. 2).

Postoperatively two more cycles of ECF with 'adjuvant' purpose were administered, based on the earlier chemosensitivity. A follow-up was performed with physical examination, serum AFP, and chest–abdominal CT scan every 4 months. One year after the end of chemotherapy the patient is asymptomatic without any clinical sign of recurrence, the serum AFP level is 20.1 ng/ml, and a CT-PET scan showed the absence of lung nodules and no evidence of disease.

Discussion

HCC is moderately responsive to systemically administered chemotherapy, likely due to multidrug resistance gene overexpression, frequently observed in this tumor (52%) [20]; moreover cirrhosis, modifying the metabolism and the excretion of various drugs, may reduce the therapeutic index of chemotherapy though increasing toxicity. Two other clinical features may affect chemotherapy administration: thrombocytopenia, caused by hypersplenism, and reactivation of hepatitis viruses. Several drugs have been assessed in single-agent regimens with unsatisfactory results (response rates ranging from 0 to 20%) and no clear impact on survival was observed [21–26]. Among these agents, anthracyclines such as doxorubicin have been the most effective, yielding response rates of up to 20% and median survival of 4 months. Epidoxorubicin and cisplatin administered as transcatheter arterial infusion have been evaluated alone or in combination with systemic 5-fluorouracil [27]. In Jang's trial the median survival time was 13.5 months for the ECF group and 10.5 months for the adriamycin group ($P = 0.026$). Recently, third generation compounds such as CPT-11, gemcitabine, and oxaliplatin have been studied alone or in association with antiangiogenetic agents with similar discouraging results [23–26].

In the literature few cases of complete pathological remission to systemic chemotherapy in advanced HCC are reported [15,16,19,28,29]. Regimens producing the highest response in HCC are the combination of cisplatin, interferon, doxorubicin, and 5-fluorouracil (PIAF) and the ECF regimen [15,19,28]. In a phase II trial, Leung *et al.* treated 50 patients with either inoperable or metastatic HCC. Although there were no complete responses, in four of the nine patients undergone surgery because of a partial response [obtained in a total of 13 patients (26%)], histological examination of multiple sections through the resected specimens only showed a necrotic tissue without any viable tumor cells. All patients had normalization of serum AFP level after treatment [28]. In phase III trial by Yeo *et al.* [15], the same result was achieved in two out of 188 patients (one per each arm).

The regimen we used is the same as the one proposed by Boucher *et al.* [19] who treated 21 patients in a phase II trial. A partial response was achieved in three patients (14.5%). One of them underwent surgical resection after five courses of chemotherapy. Initially, the patient had a multinodular 10-cm tumor of the right lobe. Histological examination identified three nodules of 0.5, 3, and 4.5 cm without viable tumor cells defining a histological complete response.

In the PIAF trial significant independent predictors associated with an objective response were absence of cirrhosis ($P = 0.006$), low bilirubin level ($P = 0.006$), and positive hepatitis C serology ($P = 0.025$) [21]. According to Ihde *et al.* [22] factors associated with improved survival in HCC patients receiving chemotherapy are: fully ambulatory performance status, lack of jaundice, response to chemotherapy, the fibrolamellar carcinoma pathologic variant, absence of cirrhosis, and normal serum AFP levels.

Our patient fulfilled all these characteristics except for AFP levels that were higher than normal but declined rapidly after surgery and adjuvant chemotherapy. CLIP score was favorable and both these factors can explain the excellent result obtained by the treatment.

Conclusion

The ECF regimen, or similar regimens such as PIAF, cannot be recommended as a standard therapy for advanced HCC because in prospective trials they failed to demonstrate a survival advantage over doxorubicin.

However, in a well-defined setting of patients characterized by absence of cirrhosis, low bilirubin level and good performance status, combination chemotherapy may convert unresectable to resectable disease, potentially producing a good shrinkage of the tumor (even up to a complete pathological response), therefore improving overall survival.

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