Lipiodol chemoembolization and additional tamoxifen and verapamil as chemosensitizers in unresectable hepatocellular carcinoma with immunohistochemically P-glycoprotein positive case

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This report describes the treatment of an advanced hepatocellular carcinoma case which has immunohistochemically proven P-glycoprotein positive cells, by chemoembolization and additional tamoxifen and verapamil as chemosensitizers. Chemotherapy resistance is a major problem in the treatment of patients with hepatocellular carcinoma and P-glycoprotein contributes to the resistance. Detection of P-glycoprotein positively by immunohistochemistry may affect therapy modalities in patients with hepatocellular carcinoma. [Turk J Cancer 2001;31(2):78-81]

Key words: Hepatocellular carcinoma, P-glycoprotein, chemotherapy resistance

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. When HCC is discovered staging is important in order to guide treatment. The treatment depends on both the patient's clinical condition related to liver function and other comorbid conditions and the number, size, and location of the tumor. The effectiveness of tumor resection, liver transplantation, percutaneous alcohol injection, transarterial chemoembolization, and systemic chemotherapy depend on staging (1).

Transarterial chemoembolization has been used as a palliative treatment for patients with unresectable HCC, but its prognostic usefulness has not been clarified. Advanced HCC still has an extremely poor prognosis, even after cancer chemotherapy and/or transarterial embolization (2,3).

Drug resistance is a major obstacle to successful chemotherapy of primary liver cancer, which is associated with high expression of the multidrug resistance (MDR) gene product, P-glycoprotein (P-gp), a multidrug efflux transporter. Although the most effective single agent in treatment of primary
liver carcinoma is the anthracycline family, the human hepatoma cells rich in P-gp is resistant to epirubicin (4).

Tamoxifen and verapamil are able to block transport of cytotoxic drugs out of tumor cells which has P-gp, so can re-sensitise resistant cells to cytotoxics (5,6).

In this article, we present the treatment of an advanced HCC case which has immunohistochemically proven P-gp positive cells, by chemoembolization and additional tamoxifen and verapamil as chemosensitizers.

Case Report

A 57 years old man was admitted to the hospital with abdominal pain. Multiple hepatic lesions in two lobes were seen in abdominal computed tomography. The patient’s basal serum alpha-fetoprotein level (AFP) was 800 ng/ml and additional tests did not reveal any metastasis, therefore the stage was considered as IV-A. HBs Ag was found as positive. Histopathologic diagnosis of liver biopsy was hepatocellular carcinoma and specimens were stained immunohistochemically by P-glycoprotein (JSB-1 monoclonal antibody) and found as positive. The patient received verapamil 120 mg/day bid, p.o. for 5 days and tamoxifen 150 mg bid, p.o. for 10 days for P-gp blockage in addition to hepatic artery chemoembolization with lipiodol-mediated injection of epirubicin (75 mg/m²). This procedure was administered 2 times for right and 1 time for left liver lobe in 6-week intervals. Pretreatment and posttreatment abdominal computed tomography imaging and AFP levels were obtained prospectively 1 month after treatment and then every 3 months. After 3 chemoembolization session the patient’s serum alpha-fetoprotein level decreased 75% and liver lesions regressed by imaging, so biologic and evaluable morphologic response were partial. The toxicities were tolerable and reversible and included transient elevation of serum transaminases after 1st and pulmonary thromboembolism after the 3rd session. The patient had good quality of life after the treatment and died 24 months after the diagnosis.

Discussion

Hepatocellular carcinoma is a common malignancy worldwide. Viral hepatitis B and C and cirrhosis are the most important risk factors (1). In the present case HbsAg was found as positive. Llado et al. (3) reported that in patients with unresectable hepatocellular carcinoma treated by transcatheter arterial chemoembolization; ascites, alpha-fetoprotein (>400 U/L), tumor size (>50%), Child-Pugh grade (Child C), pattern of iodized oil uptake, and portal vein thrombosis were independent bad prognostic factors in multivariate analysis.

In our case basal serum level of AFP was greater than 400 ng/ml and radiologically multiple lesions in two liver lobes were seen and these two conditions are bad prognostic factors. Rose et al. (7) reported that median survival was less than 3 months for 31 patients with late stage HCC who received supportive care only.
Percutaneous tumor ablation methods include percutaneous ethanol injection (PEI) and transarterial chemoembolization (TACE) (1,2). PEI is the treatment of choice for single HCCs smaller or equal to 3 cm in size. In the presence of multiple HCC nodules, TACE remains the treatment of choice (8). Inoperable patients with large or multiple HCCs are usually treated with transarterial chemoembolization (TACE) with lipiodol in combination with a chemotherapeutic drug. The most effective single agents in treatment of primary liver carcinoma are the anthracycline family (4).

In our case multiple liver lesions were present, so we administered transarterial chemoembolization with lipiodol-mediated injection of epirubicin. Drug resistance is responsible for unsuccessful chemotherapy results for primary liver cancer, which is associated with high expression of the multidrug resistance (MDR) gene product P-gp, a multidrug efflux transporter (4). Tamoxifen and verapamil are known as chemosensitizers for P-gp and so can re-sensitise resistant cells to cytotoxics (5,6). Immunohistochemical examination in the case revealed positive P-gp. In order to increase the cytotoxicity, we gave tamoxifen and verapamil as chemosensitizers to the patient.

Abdominal pain, transient elevation of serum creatinine, bilirubin, and transaminases, ototoxicity and peripheral neuropathy were toxicities in TACE administration for HCC (9). Serum transaminases elevation and pulmonary thromboemboli were seen after TACE administration in our case.

Advanced HCC still has an extremely poor prognosis, even after cancer chemotherapy and/or transarterial embolization (2,3).

A randomized study established that lipiodol chemoembolization (lipiodol, cisplatin (2 mg/kg)) did not improve the survival of patients with unresectable hepatocellular carcinoma compared to patients treated with tamoxifen only (10).

Another study including 67 unresectable hepatocellular carcinoma case, median overall survival was 36 weeks (range 3 days-4 years) after administration of chemoembolisation with doxorubicin (60 mg/m²) and lipiodol. The author’s conclusion is that large tumours show a poor response and significant incidence of side effects, suggesting that this treatment offers little benefit in advanced disease (11).

Chemotherapy resistance is a major problem in the treatment of patients with HCC and P-gp contributes to the resistance. Detection of P-gp positivity by immunohistochemistry may effect therapy modalities in chemotherapy resistant cases. The case lived two years with good quality of life after the diagnosis. Although the exact contribution of chemosensitizer treatment for survival time and quality of life should be shown by series, hepatic artery chemoembolization with epirubicin, lipiodol and additional tamoxifen and verapamil as chemosensitizers might be an effective treatment for irresectable advanced HCC with P-gp (+) status.

References


