Pegylated Liposomal Doxorubicin in Combination With Hyperthermia in the Treatment of a Case of Advanced Hepatocellular Carcinoma

Josef Dvořák, M.D., Zdeněk Zoul, M.D., Bohuslav Melichar, M.D., Ph.D., Pavel Jandík, M.D., Ph.D., Jindřiška Mergancová, M.D., Ivana Motyčková, M.D., Dagmar Kalousová, M.D., and Jiří Petera, M.D., Ph.D.

Abstract

Background: Currently, there is no standard treatment of inoperable advanced hepatocellular carcinoma. Study: A patient with advanced hepatocellular carcinoma was treated with intravenous infusion of pegylated liposomal doxorubicin (PLD, Caelyx) in combination with ultrasound hyperthermia of the liver. Each cycle consisted of infusion of 60 mg of PLD followed by two fractions of hyperthermia 41°C to 43°C for 45 minutes 1 and 48 hours after infusion, respectively. Results: A substantial regression of the tumor was observed on computed tomography scans. No toxicity of combined treatment was noted. Conclusions: This may be the first report of the combination of PLD and hyperthermia in the treatment of advanced hepatocellular carcinoma. Our observation suggests that the combination of PLD with hyperthermia is technically feasible, well tolerated, and could have synergistic potential.

Key Words: Pegylated liposomal doxorubicin—Hyperthermia—Hepatocellular carcinoma.

Although less common in western countries, hepatocellular carcinoma represents a significant problem because of the associated high mortality rate. Among patients with advanced disease, there are few 1-year survivors. Liver cirrhosis is the major factor that limits aggressive intervention in patients with hepatocellular carcinoma. The current patient had no cirrhosis. Transcatheter arterial embolization, or percutaneous ethanol injection, has been widely used to treat inoperable hepatocellular carcinoma. Nevertheless, the outcome for more advanced cases remains poor, demonstrating the lack of effective treatment. Recent advances in the design of liposomes as cytotoxic drug carriers have resulted in a new formulation of doxorubicin with improved pharmacokinetic and tumor localization properties. Incorporation of doxorubicin into polyethylene glycol-coated (pegylated) liposomes has altered the pharmacokinetics of the drug. This new generation of liposomes is characterized by a long circulation time with stable retention of drug and enhanced tumor localization. Pegylated liposomal doxorubicin (PLD) has shown substantial antitumor activity, and it appears that hyperthermia induces the doxorubicin release from the liposomes, which results in enhanced antitumor efficacy. Hyperthermia has been shown to augment drug delivery and antitumor effects when used with drugs that contain liposomes, as compared with free (not encapsulated in liposomes) drug or liposome-encapsulated drug that is administered under normothermic conditions. The extravasation of liposomes from the vascular compartment is enhanced by a factor of 40 to 50 compared with normothermic treatment. The hyperthermic treatment can also potentiate the cytotoxic effects of doxorubicin. Therefore, encapsulating doxorubicin in thermosensitive liposomes (to associate two modes of treatment) could potentially enhance the activity of doxorubicin while reducing cardiotoxicity. We report a favorable effect of PLD and hyperthermia in a patient with advanced hepatocellular carcinoma.

MATERIALS AND METHODS

Drug and Administration

Pegylated liposomal doxorubicin (Caelyx; Schering-Plough, Central East AG, Lucerne, Switzerland) after dilution was administered intravenously in 250 mL of 5% glucose for 30 minutes. The dose of PLD in each cycle was 60 mg, and the interval between cycles was 21 days. The t1/2 of PLD is 5.2 ± 1.4 hours, and the t1/2 is 55 ± 4.8 hours.

Hyperthermia

Hyperthermia was performed using the Sonotherm 1000 Ultrasound Therapy System (Labthermics Technologies Inc., Champaign, IL, U.S.A.). After intravenous application of PLD, two fractions of hyperthermia were applied to the liver tumor. Because the t1/2 of PLD is 55 ± 4.8 hours and because of the thermodotolerance of the tumor cells, we delivered hyperthermia twice during each cycle of the combined treatment, with the first application of hyperthermia 1 hour after infusion of PLD and the second application 48 hours after infusion of PLD. The temperature in the target volume was 41°C to 43°C for 45 minutes. The tissue up to

From the Departments of Oncology and Radiotherapy (J.D., Z.Z., B.M., J.P.), Surgery (P.J., J.M.), and Radiology (I.M., D.K.), Charles University Medical School & Teaching Hospital, Hradec Králové, Czech Republic.
Address correspondence and reprint requests to Dr. Josef Dvořák, Department of Oncology and Radiotherapy, Charles University Medical School and Teaching Hospital, Hradec Králove, 50005, Czech Republic. E-mail: dvorakj@fnhd.cz

the depth of 10 cm was heated by an ultrasound frequency of 1 MHz. Temperature was measured by two thermometry probes.

RESULTS

The 66-year-old man was examined in February 1999 for weight loss. The performance status of the patient was WHO 1, and he had no cirrhosis. A computed tomography scan of the abdomen on February 10, 1999, revealed inoperable tumor in the right lobe of the liver; the diameter of the tumor was 14 × 11 cm and there were multiple lymphadenopathies of up to 5 cm (Fig. 1). The biopsy confirmed hepatocellular carcinoma. The level of alfa-1-fetoprotein was 3,643 IU/mL. From May to November 1999 the patient was treated with six cycles of intravenous infusion of doxorubicin (30 mg in short infusion every 28 days). A computed tomography scan of the abdomen on November 11, 1999, documented partial response of the tumor in the right lobe of the liver; the diameter of the tumor was 7 × 6 cm and the multiple lymphadenopathies measured up to 4 cm (Fig. 2). The level of alfa-1-fetoprotein was 101.15 IU/mL.

Because of concerns about the cardiotoxicity of further doxorubicin administration, the patient received three cycles of PLD in combination with hyperthermia from February to April 2000. Each cycle consisted of intravenous infusion of PLD followed by two applications of hyperthermia 1 hour and 48 hours after infusion of PLD. The interval between cycles was 21 days. A computed tomography scan of the abdomen on June 19, 2000, documented partial response of the tumor in the right lobe of the liver; the diameter was 5 × 3.5 cm and the multiple lymphadenopathies measured up to 4 cm (Fig. 3). The alfa-1-fetoprotein level was 51.61 IU/mL. At the last control on June 29, 2000, was patient alive, with a performance status of 1. The treatment was well tolerated without notable toxicity.
DISCUSSION

To our best knowledge, this is the first reported case of the combination of PLD and hyperthermia in the treatment of advanced hepatocellular carcinoma. Pegylated liposomal doxorubicin was used successfully in the treatment of advanced hepatocellular carcinoma without hyperthermia.\[9\] Pegylated liposomal doxorubicin monotherapy in patients with acquired immunodeficiency syndrome–related Kaposi sarcoma produced overall response rates of 43% and 59% in comparative studies, which are better than those seen with combination chemotherapy.\[11\] Pegylated liposomal doxorubicin monotherapy also has remarkable activity in breast and ovarian cancers, some of which are refractory to standard therapy.\[12,13\] Local hyperthermia treatment is able to accelerate doxorubicin release from long-circulating liposomes, increase tumor uptake, and enhance antitumor efficacy of the drug.\[4\] Liposomal contents leak into the vicinity of the tumor when the temperature in the tumor region is elevated by an external source. The cytotoxic effect is thus enhanced.\[14\] The first thermosensitive formulation of liposomes was proposed by Yatvin et al. in 1978.\[15\] In vitro studies demonstrated that the combination of hyperthermia and thermosensitive liposomes increases drug concentration in heated tumors.\[16\] The current case suggests that the combination of the PLD and hyperthermia may be a safe, technically feasible, and well-tolerated method and that the administration of PLD with hyperthermia in advanced hepatocellular carcinoma could have a synergistic effect. The combination of PLD and local hyperthermia should be studied in phase II trials in hepatocellular carcinoma.

REFERENCES