

A Long-Term Survival Case of Primary Angiosarcoma in Liver Treated with Weekly Docetaxel Chemotherapy

Sun Kyung Park, M.D., Jin Young Kim, M.D., Jung Min Lee, M.D., Gang Guk Lee, M.D.,
Young Rok Do, M.D., Keon Uk Park, M.D., Hong Suk Song, M.D.

*Division of Hematology-Oncology, Department of Internal Medicine,
Keimyung University School of Medicine, Daegu, Korea*

Abstract

Angiosarcoma is rare malignant endothelial cell tumor of vascular or lymphatic origin. It may occur in any region of the body, but more frequent in skin and soft tissue. Though hepatic angiosarcoma is rare primary tumor of the liver, it is the third most common primary malignant tumor of the liver. Treatment options for hepatic angiosarcoma are limited, and they depend mainly on the stage of the disease during diagnosis. We report a rare case of primary angiosarcoma of the liver. We treated our patient with weekly docetaxel chemotherapy regimen. She received a total of six cycles without disease progression or unendurable toxicity occurred, and had long-term survival fourteen months after the diagnosis. An effective treatment for hepatic angiosarcoma has not yet been established. Chemotherapy with docetaxel should be considered in the treatment of patients with primary angiosarcoma of the liver.

Key Words : Angiosarcoma, Docetaxel, Liver

Introduction

Angiosarcoma is a subtype of soft tissue sarcoma and a rare, aggressive malignant endothelial cell tumor of vascular or lymphatic origin [1]. About 2% of soft tissue sarcomas are angiosarcomas, and that may arise in any soft-tissue structure or viscera. Angiosarcoma

typically present later in life, in the 6th and 7th decades, and have a high rate of recurrence and are frequently disseminated at the time of diagnosis, thereby making them difficult to cure [2]. The liver is the fifth most common primary site of presentation in angiosarcoma, but it is the most common malignant mesenchymal tumor of the liver [3].

Corresponding Author: Hong Suk Song, M.D., Division of Hematology-Oncology, Department of Internal Medicine,
Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 700-712, Korea
Tel: +82-53-250-7436 E-mail: shs7436@dsmc.or.kr

Hepatic angiosarcoma has unusual presentation and difficulty in diagnosis, because of the unspecific symptoms and radiologic findings, and has a high rate of recurrence and distant metastasis. In metastatic case, there is no effective treatment and the prognosis is poor [4].

We report a case of primary hepatic angiosarcoma with spleen and multiple bone metastasis. Percutaneous liver biopsy showed a primary angiosarcoma of the liver. Our patient underwent treatment with docetaxel chemotherapy.

Case Report

A 61-year-old woman presented neck and both shoulders pain for six months which was aggravated on heavy material lifting. Two weeks prior to visit of her local neurosurgical clinic, she noticed both shoulders pain became worse. After being taken to the magnetic resonance scan of cervical spine, which showed multiple bone metastasis with fracture of C7 body, she was referred to our hospital for diagnosis and treatment. She did not have other medical histories. Physical examination on admission revealed no abdominal tenderness, masses, or organomegaly.

Laboratory data was as follows. Hb 13.3 g/dL, Hct 38.1%, platelets 93,000/ μ L, prothombin time 10.7 sec, albumin 4.3 g/dL, alkaline phosphatase 57 IU, AST 44 IU, ALT 41 IU, AFP 1.25 IU/mL, and CEA 1.1 ng/mL. hepatitis A, B, and C profiles were negative.

A computerized tomographic scan of abdomen and pelvis showed numerous small hypo-attenuating masses scattered throughout the whole liver and spleen (Fig. 1). Whole

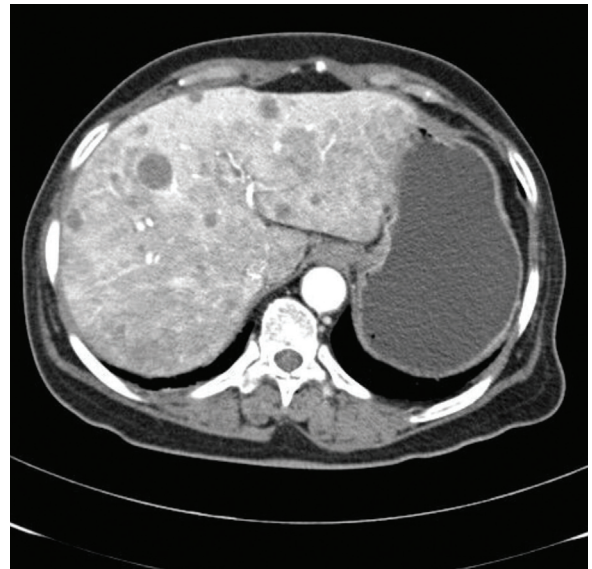


Fig. 1. At the time of presentation, a computerized tomographic scan of abdomen and pelvis showed numerous small hypo-attenuating masses scattered throughout the whole liver and spleen.

body bone scan demonstrated increased radioactivity at anterior ends of right first and third ribs, right humeral neck, right iliac bone, right ischium, and left femoral shaft, which suggested multiple bone metastasis (Fig. 2). On the fifth day of admission, the patient had a surgical C7 spine biopsy which revealed atypical spindle cell proliferation (Fig. 3A). It was not enough for diagnosis. So she underwent a CT-guided percutaneous liver biopsy to confirm histological diagnosis. Microscopically, neoplastic proliferation with sinusoid growth configuring cavernous spaces covered by atypical spindle cells indicated of angiosarcoma (Fig. 3B). Microscopic findings of spine were similar to hepatic mass lesion, and tumor cells were positive for CD31 (Fig. 3C) and factor VIII-related antigen (Fig. 3D). In conclusion, it seems compatible with hepatic angiosarcoma.

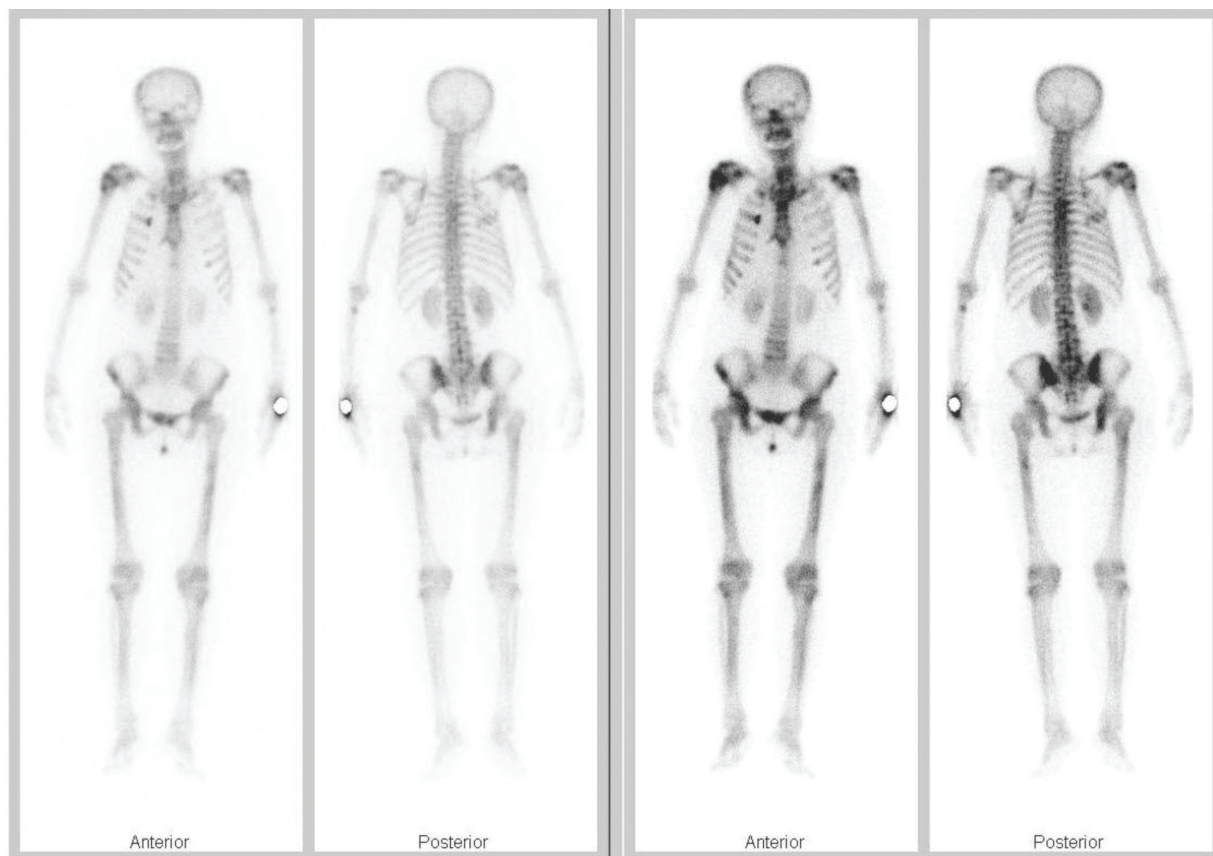


Fig. 2. At the time of presentation, whole body bone scan demonstrated intense increased radioactivity at anterior ends of right first and third ribs, right humeral neck, right iliac bone, right ischium, and left femoral shaft, that suggested multiple bone metastasis.

The patient underwent subtotal corpectomy and mesh insertion on C7, then cervical plate fixation on C6, C7 and T1. She was referred to oncologic department for systemic chemotherapy, as the primary angiosarcoma of liver was already extensive at the time of diagnosis. She was treated with two cycles of adriamycin 60 mg/m^2 on day 1 and ifosfamide 2 g/m^2 on days 1 through 3 with mesna, which are the current main chemotherapy drugs of metastatic or unresectable angiosarcoma. Though she tolerated well, follow-up abdomen and pelvic CT scan after chemotherapy showed increased size and number of the

multiple hepatic and splenic masses (Fig. 4). So we decided to change her regimen to docetaxel mono-therapy, because taxanes which may provide some objective responses remain the second-line treatment after adriamycin-based chemotherapy failure. She was treated with docetaxel 30 mg/m^2 on days 1, 8 and 15. Follow-up abdomen and pelvic CT revealed partial response, after second and fourth cycles of docetaxel mono-therapy (Fig. 5). She tolerated well, so that there was no toxicity of grade II or above. Therefore it was not necessary to reduce dose or to delay chemotherapy. Her symptoms of both

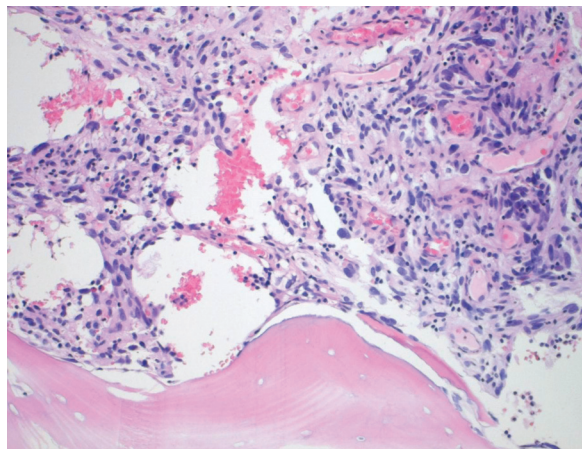


Fig. 3A. C7 spine biopsy showing an atypical spindle cell proliferation (H&E stain).

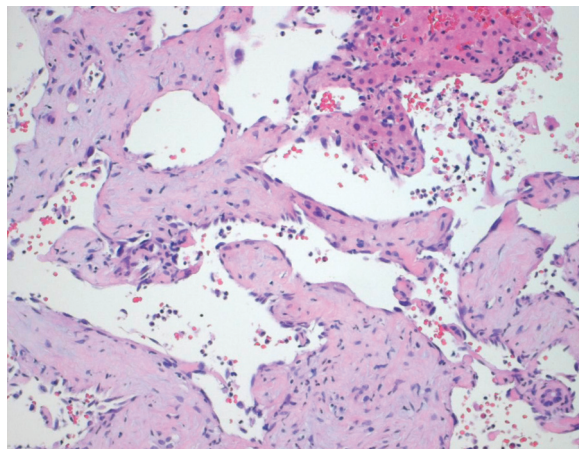


Fig. 3B. Liver biopsy showing neoplastic proliferation with sinusoid growth configuring cavernous spaces covered by atypical spindle cells indicative of angiosarcoma. Both microscopic findings of spine and liver were similar.

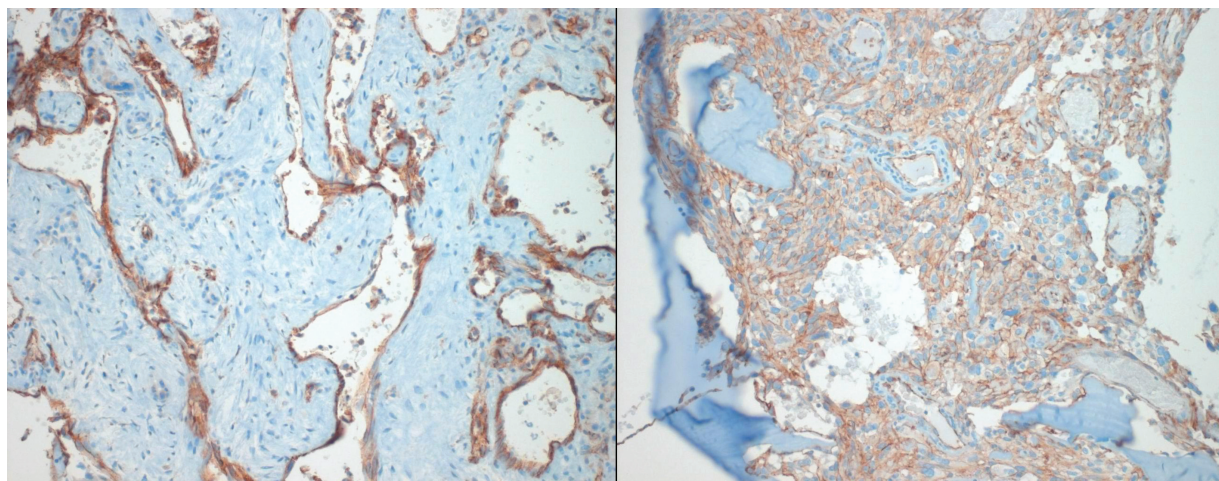


Fig. 3C, D. In both spine and liver biopsy, spindle cells are strongly immunoreactive for the vascular endothelial marker CD31 (C) and factor VIII RA (D).

shoulders pain and abdominal discomfort were improved and were controlled well with additional analgesics including opioids. However, after sixth cycles of docetaxel mono-therapy, follow-up abdomen and pelvic CT showed stable disease. Then, we decided

that her docetaxel mono-therapy shall be completed with a total of six cycles. After all, she lived well without progressive disease for eleven months, and died fourteen months after the diagnosis from hepatic failure.

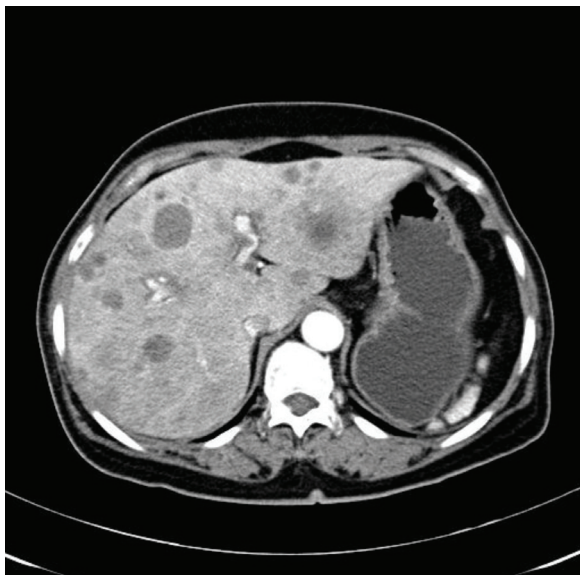


Fig. 4. Follow-up computerized tomographic scan of abdomen and pelvis after initial adriamycin and ifosfamide chemotherapy showed increase size and number of the multiple hepatic and splenic masses.

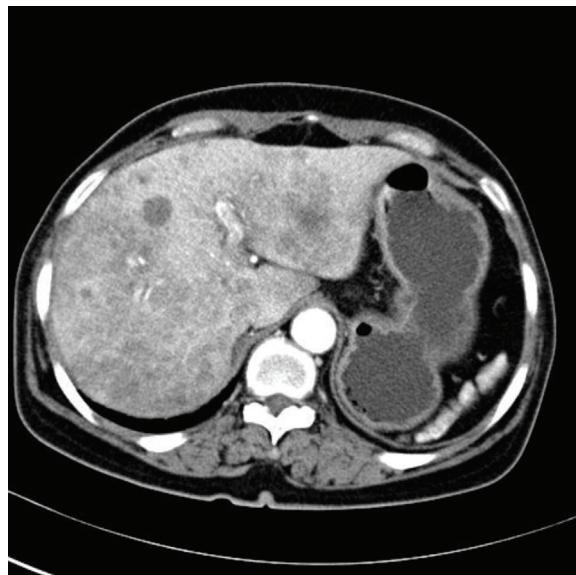


Fig. 5. Follow-up computerized tomographic scan of abdomen and pelvis after second-line docetaxel mono-therapy showed partial response.

Discussion

Hepatic angiosarcoma is a malignant tumor of mesenchymal origin consisting of spindle or pleomorphic cells that are vasoformative and form poorly organized vessels or a line that grow into preformed vascular spaces, such as sinusoids and small veins [5]. It is an uncommon malignancy which is 0.5–2% of all primary neoplasms of the liver [3].

In these patients clinical findings will not help for diagnosis. Symptoms and signs are nonspecific, includes abdominal pain, hepatosplenomegaly, jaundice, ascites, intraperitoneal hemorrhage and hepatic failure [4,6]. Laboratory data in cases of hepatic angiosarcoma are not specific. It is usual to find altered hepatic enzymes with predominating cholestasis, and iron deficiency anemia, which in some cases

have been described accompanied by micro-angiopathic hemolysis and mild thrombocytopenia. Tumor markers are negative [6].

Hepatic angiosarcoma is difficult to differentiate from other vascular tumors of the liver using radiographic techniques. On ultrasound, single or multiple masses are demonstrated with differing echo texture due to amount of necrosis and hemorrhage [4]. Primary angiosarcoma of the liver presents with solitary or multiple hypervascular lesions showing heterogeneous enhancement on early-phase images and continuing progressive enhancement on delayed-phase CT and angiography images [7,8]. These findings are similar to hemangiomas. Other CT findings that will help in the diagnosis are the findings of residual Thorotrast in a reticular pattern and intraperitoneal hemorrhage. Arterioportal

shunting is not seen in hemangiomas, and if present, it favors the diagnosis of angiosarcoma [8,9]. T1-weighted magnetic resonance imaging shows low intensity lesions with focal areas of high intensity which suggest hemorrhage, but utility is still limited [7].

The diagnosis of hepatic angiosarcoma is often performed too late due to nonspecific symptoms, laboratory tests and radiologic findings. As the vascular nature and tendency for hemorrhage makes percutaneous biopsy dangerous, the definitive diagnosis is nevertheless always given by pathology techniques. Histology reveals the presence of endothelial neoplastic cells with epithelioid appearance, pleomorphic and hyperchromatic nuclei and prominent nucleoli, and formation of cytoplasmic vascular spaces with cavernous morphology [10]. Immunohistochemistry shows tissues to be positive for endothelial markers, specially factor VIII-related antigen and CD31 [11].

Hepatic angiosarcoma has very limited treatment options. The clinical treatment of localized angiosarcoma includes wide resection following by adjuvant radiation therapy as possible [12]. Surgery is the definitive treatment and may improve survival in some cases. However, it is technically complex, a great number of cases are nonresectable because of size and extension. Even with complete tumor resection to treat primary hepatic angiosarcoma, recurrence is common and patient died within 11 months [8]. These patients are rarely considered for liver transplantation, as patients who have been transplanted have not shown any survival benefit, and who had a median survival of only 7 months [13].

Cytotoxic chemotherapy is the primary treatment option for metastatic angiosarcoma,

although the evidence for this is limited [1]. In soft-tissue sarcomas, doxorubicin and ifosfamide as single drug show response rates of 16–36%. Combination chemotherapy is associated with increased toxicity but not necessarily with better outcomes [14]. Adriamycin-based chemotherapy remains the standard treatment of metastatic or unresectable angiosarcoma, which provides a median progression-free survival and a median overall survival of about 4 and 8 months, respectively [12,15]. Dannaher et al reported that chemotherapy showed an objective improvement in three of four patients. The regimen consisted of intravenous adriamycin 60 mg/m² every 3–4 weeks, and in three of the four cytoxan and methotrexate were added [16]. There is no recommended second-line regimen, clearly. Taxanes (paclitaxel and docetaxel) are considered as a non-effective treatment for soft tissue sarcoma, but an effective treatment for angiosarcomas because of which have antiangiogenic activity [1,12]. Some case reports and retrospective studies have suggested some kind of clinical benefit with paclitaxel [17] or docetaxel [18] in patients with unresectable or metastatic angiosarcoma. The French Sarcoma Group has conducted a phase II clinical trial, which states the efficacy of weekly paclitaxel as a treatment for unresectable or metastatic angiosarcoma [19]. No data comparing the efficacy of anthracycline and taxane chemotherapy are available, but retrospective data suggest similar response rates and survival with both [20].

Generally, the prognosis of hepatic angiosarcoma is poor. At the time of presentation often affects all the parenchyma and has

spread to other organs in quite a number of cases. Early metastasis mainly in lung, pleura, spleen, lymph nodes and bone contribute to its poor prognosis [2]. Disease progression is fast after becoming clinically apparent, and survival is 6 months at most after diagnosis without treatment, with only 3% living longer than 3 years [6].

In our report, the patient had primary hepatic angiosarcoma with spleen and multiple bone metastasis at the time of presentation. She had received systemic chemotherapy with adriamycin and ifosfamide initially, and had a progressive disease. Then, she had changed regimen with docetaxel mono-therapy. She received a total of six cycles without disease progression or unendurable toxicity occurred, and died fourteen months after the diagnosis. Our report has suggested the efficacy of docetaxel in the treatment of primary angiosarcoma of the liver. It is necessary to carry out more studies to develop more effective and well-tolerated treatment options for unresectable hepatic angiosarcoma.

References

1. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. *Lancet Oncol* 2010;**11**:983-91.
2. Wilson R, Glaros S, Brown RK, Michael C, Reisman D. Complete radiographic response of primary pulmonary angiosarcomas following gemcitabine and taxotere. *Lung Cancer* 2008;**61**:131-6.
3. Zocchetti C. Liver angiosarcoma in humans: epidemiologic considerations. *Med Lav* 2001;**92**:39-53.
4. Molina E, Hernandez A. Clinical manifestations of primary hepatic angiosarcoma. *Dig Dis Sci* 2003;**48**:677-82.
5. Lee YS, Hwang JY, Park KS, Cho KB, Hwang JS, Ahn SH, *et al*. A case of primary hepatic angiosarcoma: Report of a case and review of previous Korean cases. *Korean J Med* 2004;**66**(2):224-9.
6. Locker GY, Doroshow JH, Zwelling LA, Chabner BA. The clinical features of hepatic angiosarcoma; a report of four cases and a review of the English literature. *Medicine* 1979;**58**:48-64.
7. Koyama T, Fletcher JG, Johnson CD, Kuo MS, Notohara K, Burgart LJ. Primary hepatic angiosarcoma: findings at CT and MR imaging. *Radiology* 2002;**222**:667-73.
8. Park YS, Kim JH, Kim KW, Lee IS, Yoon HK, Ko GY, *et al*. Primary hepatic angiosarcoma; imaging findings and palliative treatment with transcatheter arterial chemoembolization or embolization. *Clinical Radiology* 2009;**64**:779-85.
9. Ohmoto K, Hirokawa M, Takesue M, Yamamoto S. Hepatic angiosarcoma with early central enhancement and arerioportal shunt on dynamic CT. *Hepatogastroenterol* 2000;**47**:1717-8.
10. Kojiro M, Nakashima T, Ito Y, Ikezaki H, Mori T, Kido C, *et al*. Thorium dioxide-related angiosarcoma of the liver. Pathomorphologic study of 29 autopsy cases. *Arch Pathol Lab Med* 1985;**109**:853-7.
11. Saleh HA, Tao LC. Hepatic angiosarcoma: aspiration biopsy cytology and immunocytochemical contribution. *Diagn Cytopathol* 1998;**18**:208-11.
12. Penel N, Lansiaux A, Adenis A. Angiosarcomas and taxanes. *Curr Treat Options Oncol* 2007;**8**:428-34.
13. Husted TL, Neff G, Thomas MJ, Gross TG, Woodle ES, Buell JF. Liver transplantation for primary or metastatic sarcoma to the liver. *Am J Transplant* 2006;**6**:392-7.
14. Mocellin S, Rossi CR, Brandes A, Nitti D. Adult soft tissue sarcomas: conventional therapies and molecularly targeted approaches. *Cancer Treat Rev* 2006;**32**:9-27.
15. Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic

- factors, and treatment outcomes with surgery and chemotherapy. *Cancer J* 2005;**11**:241-7.
16. Dannaher C, Tamburro CH, Yam LT. Chemotherapy of vinyl chloride-associated hepatic angiosarcoma. *Cancer* 1981;**47**:466-9.
17. Pestoni C, Paredes-Suarez C, Peteiro C, Toribio J. Early detection of cutaneous angiosarcoma of the face and scalp and treatment with paclitaxel. *J Eur Acad Dermatol Venereol* 2005;**19**:357-9.
18. Veliz M, Chang V, Kasimis B, Choe JK. Durable response of angiosarcoma of the face and scalp to docetaxel. *Clin Oncol* 2007;**19**:210.
19. Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, *et al*. Phase II trial of weekly paclitaxel ofr unresectable angiosarcoma: The ANGIOTAX study. *J Clin Oncol* 2008;**25**:5269-74.
20. Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. *Cancer J* 2005;**11**:241-7.
-