

Clinical features and treatment outcomes of advanced stage primary hepatic angiosarcoma

H. R. Kim¹, S. Y. Rha^{1,2}, S. H. Cheon^{1,3}, J. K. Roh^{1,2}, Y. N. Park^{2,4} & N. C. Yoo^{1,2*}

¹Department of Internal Medicine, Yonsei Cancer Center; ²Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine; ³East-West Neo Medical Center, Kyunghee University; ⁴Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

Received 11 June 2008; revised 5 October 2008; accepted 6 October 2008

Background: Primary hepatic angiosarcoma is a very rare malignancy with a poor prognosis. While surgical resection has been validated as curative choice, most cases are diagnosed too late for resection. Nonetheless, treatment protocols have not been established and also there are very few reports on the clinical features and treatment outcomes.

Patients and methods: Among 11 939 patients diagnosed with primary hepatic tumors from January 1985 to December 2007 at two centers, five patients were diagnosed with primary hepatic angiosarcoma. We analyzed patients' demographics, tumor characteristics, treatment modality, and outcomes using imaging, serology, and pathology.

Results: All five patients were diagnosed at advanced stage with distant metastases. The most common symptom was abdominal pain. The levels of the tumor markers were within the normal range and serological tests were negative for hepatitis B and C viruses. Two of four patients who received chemotherapy died <3 months after diagnosis, but the other two patients survived >6 months.

Conclusions: A combination of chemotherapy resulted in an improved outcome for two of four patients, suggesting the potential usefulness of palliative chemotherapy to improve survival. This case study may aid in planning chemotherapy for patients with advanced hepatic angiosarcoma.

Key words: chemotherapy, primary hepatic angiosarcoma, treatment outcomes

Introduction

Primary hepatic angiosarcoma is a rare malignancy accounting for only 0.1%–2% of all malignant primary liver tumors [1, 2]. This is a highly malignant and rapidly progressing vascular tumor of endothelial cell origin. It has been reported that the median survival with this cancer is <6 months without treatment, and most patients die within a year of diagnosis. While environmental carcinogens, such as vinyl chloride, thorium dioxide, and arsenic, are known to cause primary hepatic angiosarcoma [1, 3–5], exposure to these chemicals is very rare and the major causes remain unknown. Pathological examination has proven to be the best approach for confirming primary hepatic angiosarcoma [6–8], while imaging such as computed tomography and magnetic resonance is not conclusive, but can be helpful. The most frequent symptoms are abdominal pain, weakness, fever, and weight loss, but these are also found with other types of tumors [1, 9]. Due to the absence of early specific

symptoms and signs, diagnosis and treatment are often delayed. Collectively, delayed diagnosis and the highly malignant characteristics of the tumor, including chemoresistance, result in a poor prognosis. The unusual presentation of the tumor and the diagnostic difficulties combined with high mortality make early recognition very important.

When the lesion is confined to one lobe of the liver without any metastases, hepatic resection has proven to be beneficial and there have been reports of occasional long-term survivors after resection [10–12]. However, the majority of hepatic angiosarcoma is unresectable at diagnosis. Palliative chemotherapy is indicated for patients with unresectable angiosarcoma, but an effective chemotherapeutic agent has not been established. In addition, due to the rareness of this cancer, optimal management for patients is poorly characterized. In Korea, five primary hepatic angiosarcomas were reported [13–17], but the clinical outcomes after treatment were not described in detail. Here, we present the clinical manifestations of advanced primary hepatic angiosarcoma with distant metastases and the treatment outcomes from various combinations of

*Correspondence to: Dr N. C. Yoo, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-Ku, Seoul 120-752, Korea. Tel: +82-2-2228-8133; Fax: +82-2-393-3652; E-mail: ync0011@yuhs.ac

chemotherapeutic agents including ifosfamide, doxorubicin, and paclitaxel [18–20].

patients and methods

patients

We conducted retrospective case reviews of patients diagnosed with primary hepatic angiosarcoma at two centers in Korea. At the Yonsei University Health System (YUHS), there were four cases (0.04%) of advanced stage primary hepatic angiosarcoma out of 11 415 primary hepatic carcinoma patients from January 1985 to December 2007. At the Kyunghee University East-West Neo Medical Center (KHNMC), there was one case of advanced stage primary hepatic angiosarcoma (0.19%) out of 524 primary hepatic carcinoma patients from June 2006 to December 2007.

clinical evaluation of tumor

Demographic and clinicopathological information was obtained from the patients' medical records and included the following parameters: age, gender, environmental history, presenting symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, characteristics of primary hepatic angiosarcoma, laboratory profiles including complete blood count, liver function tests, carcinoembryonic antigen (CEA), CA 19-9 and α -fetoprotein (AFP), hepatitis B and C profile, and treatment modality. Characteristics of the primary hepatic angiosarcoma included pathologic type, tumor number, existence of tumor rupture, and metastatic sites. The pathological staging was determined according to the AJCC criteria (sixth edition, 2002).

follow-up and assessments

Overall survival (OS) was defined as the period of time from the initial diagnosis of primary hepatic angiosarcoma to death from any cause or last follow-up. An evaluation of the response to chemotherapy was carried out during the entire course of the chemotherapy using Response Evaluation Criteria in Solid Tumors [21].

results

clinical characteristics

The baseline characteristics of the patients are presented in Table 1. All five patients were men with a median age of 45 years (range 41–69 years). Three patients (patients 1–3) had a grade 2 or 3 ECOG performance status and the other two patients (patients 4 and 5) had a grade 1 ECOG performance status. None of the patients had a significant history of exposure to specific carcinogens that were related to primary hepatic angiosarcoma. Right upper quadrant abdominal pain was the most common presenting symptom and in patients with lung metastases, the initial symptom was hemoptysis. All patients had multiple hepatic lesions with bilobar distribution and extrahepatic distant metastases. Extrahepatic metastatic lesions were found in the spleen, lung, and bone. One patient had hemoperitoneum due to the rupture of angiosarcoma [17].

Table 2 shows the laboratory profiles of the patients enrolled in this study. Thrombocytopenia was observed in three patients, 83 000, 52 000, and 80 000. There was anemia in two patients, one of whom had hepatic rupture. Serologic tests for hepatitis B and C were carried out in four patients and all were negative. All patients were in Child-Pugh class A by liver function test. Two patients developed mild jaundice in which a total bilirubin level was <3 mg/dl. Aspartate transaminase (AST) and alanine transaminase (ALT) were <100 IU/l except in one patient who experienced rapid deterioration from multiorgan failure. Tumor markers, such as CEA, CA 19-9, and AFP, were all within normal ranges.

pathology

All tumors were microscopically evaluated to analyze the pathologic characteristics as well as to confirm diagnosis. Figure 1

Table 1. Characteristics of patients with primary hepatic angiosarcoma

Patient	Sex/age	ECOG	Carcinogen exposure	Presenting symptoms	No. of hepatic mass	Metastases	Hepatic rupture	OS (days)	Cause of death
1	Male/44	3	No	RUQ pain; leg edema	Multiple	Spleen	Yes	8	Hepatic rupture
2	Male/69	2	No	Hemoptysis	Multiple	Lung	No	49	PD
3	Male/49	2	No	RUQ pain; ascites; DOE	Multiple	Spleen	No	86	PD
4	Male/41	1	No	Chest discomfort	Multiple	Pericardium	No	474	PD
5	Male/45	1	No	RUQ pain	Multiple	Bone	No	222	PD

ECOG, Eastern Cooperative Oncology Group; OS, overall survival; RUQ, right upper quadrant; PD, disease progression; DOE, dyspnea on exertion.

Table 2. Initial laboratory profile of patients enrolled

Patient	WBC (/ μ l)	Hb (g/dl)	Platelet ($\times 10^3$ / μ l)	Total bilirubin (mg/dl)	Albumin (g/dl)	AST/ALT (IU/l)	Prothrombin time (INR/s)	AFP/CEA/CA19-9 (IU/ml)/(ng/ml)/(U/ml)	Hepatitis B and C
1	9900	9.2	83 000	1.4	3.6	212/140	1.87/20.1	<3/ND/ND	Negative
2	7950	11.5	123 000	1.0	3.7	35/50	1.02/12.5	2.83/1.52/33.2	ND
3	7170	8.0	52 000	2.5	3.0	97/35	1.39/15.7	3.81/ND/12	Negative
4	7540	11.7	191 000	2.4	3.8	25/35	1.15/13.2	0.9/1.46/4.2	Negative
5	6900	12.5	80 000	1.1	4.2	40/29	1.24/14.9	2.6/<1.5/10.16	Negative

WBC, white blood cell; Hb, hemoglobin; AST, aspartate transaminase; ALT, alanine transaminase; AFP, α -fetoprotein; CEA, carcinoembryonic antigen; ND indicates not done.

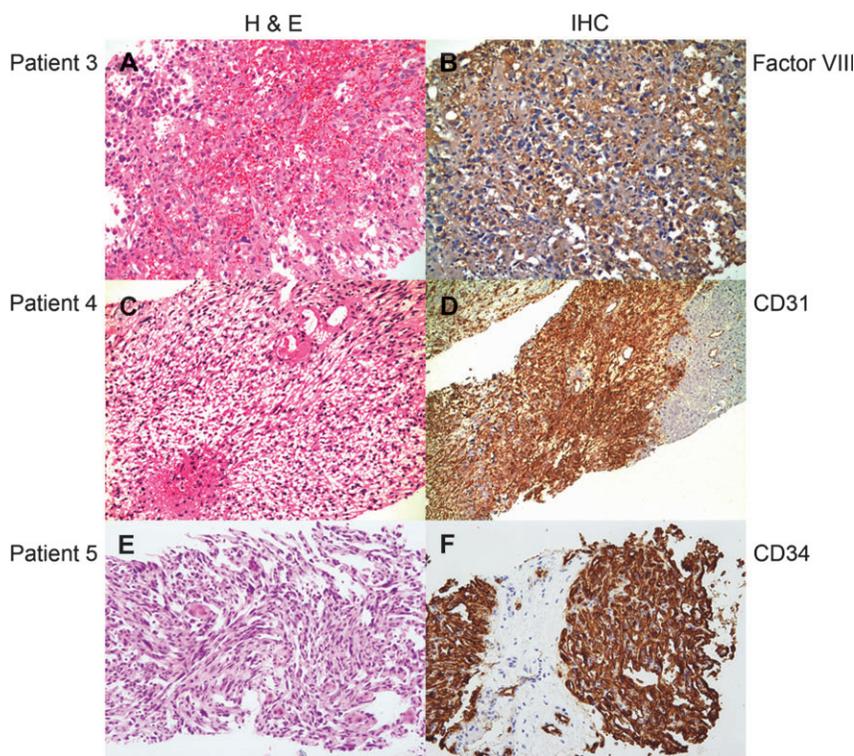


Figure 1. Pathologic findings in patients 3, 4, and 5. Pathology findings in patient 3 [A, hematoxylin and eosin (H&E) stain, $\times 200$; B, immunohistochemical stain of factor VIII, $\times 200$] show malignant pleomorphic tumor forming vessel-like structures, suggestive of angiosarcoma and factor VIII positive. Pathology findings in patient 4 (C, H&E stain $\times 200$; D, immunohistochemical stain of CD31, $\times 100$) show malignant spindle cell tumor, favoring angiosarcoma and CD31 positive. Pathology findings in patient 5 (E, H&E stain $\times 200$; F, immunohistochemical stain of CD34, $\times 200$) show malignant spindle cell tumor, favoring angiosarcoma and CD34 positive. Among other immunohistochemical stains, both cytokeratine and carcinoembryonic antigen, marker for carcinoma, were negative (data not shown, see Table 3).

showed the representative pathologic findings from patients 3, 4, and 5. Hematoxylin and eosin stain of all patients showed malignant pleomorphic tumor forming vessel-like structures, suggesting angiosarcoma. Compared with patient 3, patients 4 and 5 showed relatively well-differentiated findings. Positive immunohistochemical staining for CD31, favoring angiosarcoma, was observed in patients 3, 4, and 5. In addition, the immunohistochemical staining for factor VIII was positive in patients 3 and 5. These results confirm that tumors from all three patients are angiosarcoma (Table 3).

treatment outcomes

All cases were surgically unresectable at diagnosis due to multiple hepatic tumor masses and metastases to other organs. Radiotherapy was not conducted for any of the patients because angiosarcoma is known to be radioresistant [22]. Therefore, palliative chemotherapy is the only available treatment option. Figure 2 shows the treatment outcomes as well as chemotherapy regimens for the individual patients. Patient 1 died of multiple organ failure caused by initial hemoperitoneum with rapid progression without any chance to receive chemotherapy. This previously reported case was diagnosed after death via autopsy [17]. The other four patients received palliative chemotherapy as summarized in Figure 2.

The initial first-line chemotherapy for the three patients (patients 2, 3, and 4) at YUHS was a doxorubicin/carboplatin/

Table 3. Immunohistochemical staining results in patients 3, 4, and 5

Patient no.	Immunohistochemical stain	
	Positive	Negative
3	CD31, factor VIII, reticulin	cytokeratin, CD34
4	CD31, CD34	CEA, c-Kit, demin
5	CD31, factor VIII, Ki-67	c-Kit, elastin fiber, masson trichrome, reticulin

5-fluorouracil regimen, which is composed of 5-fluorouracil (5-FU) and carboplatin in combination with transhepatic artery infusion of doxorubicin. These patients had progressive disease (PD) after one to two cycles and two patients (patients 2 and 3) died of PD. Meanwhile, patient 4 received a second palliative ifosfamide/doxorubicin (IA) regimen chemotherapy composed of ifosfamide infusion (i.v.) every 3 weeks, accompanied by doxorubicin infusion via hepatic artery every 5 weeks. After five cycles, patient 4 received six more cycles of chemotherapy with both ifosfamide and doxorubicin by i.v. due to inaccessibility to the hepatic artery. The best response for patient 4 was stable disease (SD) (less than a 30% reduction and less than a 20% increase in the sum of the long diameter of target lesions and the appearance of no new lesions) and survival was observed for 16 months after diagnosis (Figure 2 and Figure 3A–E).

Downloaded from <http://annonc.oxfordjournals.org/> at YONSEI UNIVERSITY MEDICAL LIBRARY on January 14, 2014

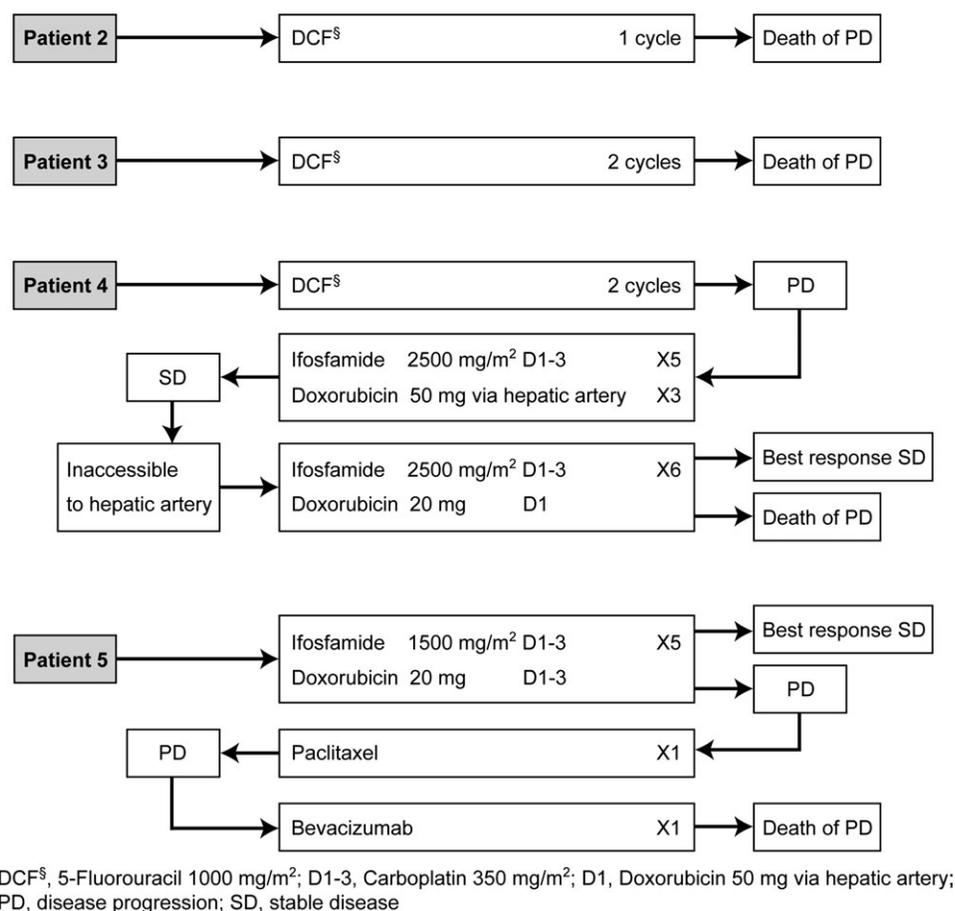


Figure 2. Chemotherapy regimen and treatment outcomes for the individual patients.

Patient 5 at KHNMC was treated with an IA regimen as the first-line chemotherapy and had SD lasting 4 months. After five cycles of the IA regimen, the patient developed PD and was changed to paclitaxel. After the first cycle of paclitaxel chemotherapy, the chemotherapy regimen was replaced with bevacizumab due to PD. Finally, the patient died of PD after the first cycle of bevacizumab, with an OS period of 9 months (Figure 2 and Figure 3F–J).

The median OS in these patients was 86 days (range 8–439 days). Even though three patients died <3 months after diagnosis, the remaining two patients (patients 4 and 5) received second or third lines of chemotherapy regimens and survived for 16 and 9 months, respectively.

discussion

Primary hepatic angiosarcoma progresses rapidly and therefore, most cases are diagnosed at an advanced stage. Less than 20% of patients can receive surgery [23, 24], which has been proven to be beneficial, and occasional long-term survivors after resection have been reported [12, 25]. However, the majority of hepatic angiosarcomas are not resectable at diagnosis. All patients enrolled in our study were unresectable due to advanced stage cancer with multiple and systemic metastases.

Primary hepatic angiosarcoma shows a strong male predominance with a male to female ratio of 3 : 1 [9], which may be due to a direct link between angiosarcoma and exposure to industrial chemicals. While the patients in our study were all male, none of them had a prior history of exposure to known carcinogenic agents. The chemicals that have been shown to be clear and definitive causative factors are thorotrast, polyvinyl chloride, and arsenic powder [3, 4]. However, the chance of being exposed to these carcinogens has decreased in recent years and the majority of hepatic angiosarcomas are not related to the above etiologic causes. Hepatitis is endemic to Asia and might induce or stimulate liver fibrosis, so we analyzed the potential relationship between hepatitis and hepatic angiosarcoma. However, none of the patients in our study were positive for a hepatitis B or C marker.

Initial laboratory findings in our cases are not specific as shown in previous reports. Some reports showed that liver function tests were not largely abnormal except mild hyperbilirubinemia, mild elevated AST/ALT [2, 9, 15, 25–27]. We think our liver function test profile is relatively similar with that of previously reported. Thrombocytopenia, which was shown in 50%, and anemia are relatively common characteristic of hepatic angiosarcoma and may be related

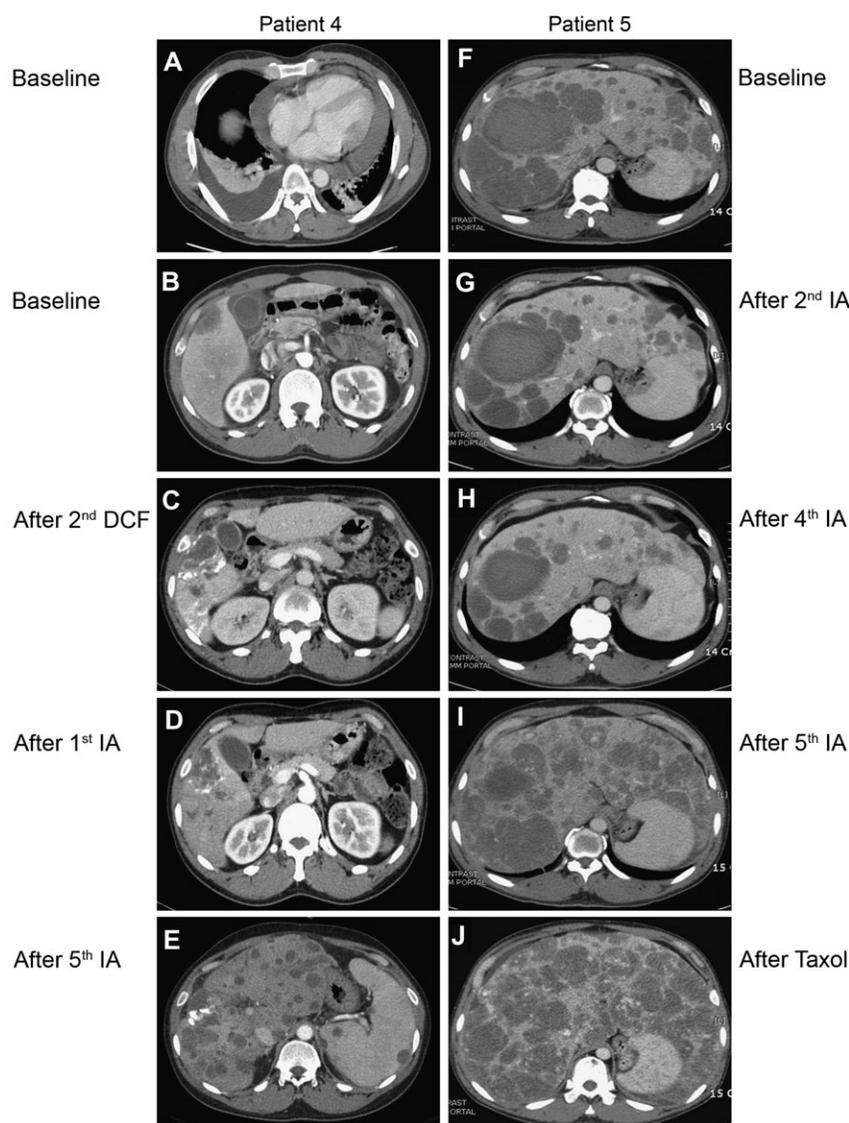


Figure 3. Computed tomography images of patient 4 (A–E) and patient 5 (F–J). (A, B) Initial finding before chemotherapy. (A) Malignant pericardial effusion due to pericardial metastasis is observed. (C) Progressive disease (PD) finding after second doxorubicin, carboplatin, 5-fluorouracil chemotherapy. Newly developed multiple intrahepatic metastatic nodules are observed in both lobes of the liver. (D) Stable disease (SD) finding after first ifosfamide, doxorubicin (IA). Peribiliary and liver parenchymal necrosis are progressed in both lobes of liver. In contrast, there is no newly developed lesion or progression evidence. (E) Marked progression of liver nodules in size and number. Newly developed multiple nodules of spleen are observed compatible with metastasis. (F) Initial finding before chemotherapy. (G, H) SD finding after second, fourth IA chemotherapy, respectively. (I) PD finding after fifth IA chemotherapy. (J) PD finding after paclitaxel treatment.

to consumption of clotting factors [2, 14, 15, 27]. It seems that these clotting abnormalities and the vascular nature of the primary hepatic angiosarcoma lead to catastrophic rupture of hepatic angiosarcoma and induce the intraabdominal bleeding in about one-fourth of all cases. Our case has relatively large portion of thrombocytopenia (~80%). Anemia is commonly related to the rupture of tumor and intraabdominal bleeding.

To improve the survival of hepatic angiosarcoma, early detection and resection are supposed to be factors leading to the good prognosis. Therefore, it is important to be suspicious of hepatic angiosarcoma when it is combined with nonspecific symptoms such as right upper quadrant pain and mild fever. It should also be noted that the liver function test

and tumor markers such as CEA, AFP, and CA 19-9 are not specific as mentioned previously. Therefore, liver biopsy could be necessary to confirm the tumor, although imaging studies are helpful.

There are only a few reports showing the median survival for patients without treatment which is <6 months [2, 9, 15, 17]. Even though there is little evidence that chemotherapy is efficacious for primary hepatic angiosarcoma in unresectable hepatic angiosarcoma, palliative chemotherapy could be an option. Moreover, there are few reports about treatment regimens and clinical outcomes for patients with an advanced stage of primary hepatic angiosarcoma. Table 4 shows the summary of treatment modality and clinical outcomes of primary hepatic angiosarcoma. There are various

Table 4. Summary of treatment modality and clinical outcomes of primary hepatic angiosarcoma including previous reports and current study

Author	Period	PHA	Stage	Treatment modalities	Clinical outcomes
Dannaher et al.	1974–1976	PHA (<i>n</i> = 4)	NA	ADR, cyclophosphamide, MTX	MS: 14 months
Molina et al.	1979–1997	PHA (<i>n</i> = 5)	Resectable (<i>n</i> = 2); unresectable (diffuse) (<i>n</i> = 3)	Resection followed by adjuvant chemotherapy (etoposide/ifosfamide) (<i>n</i> = 1); IA ADR/DTIC (<i>n</i> = 1); no treatment (<i>n</i> = 2); resection (<i>n</i> = 1)	MS: 6 months
Fayette et al.	1980–2004	PHA (<i>n</i> = 7)/AS (<i>n</i> = 204)	NA	NA	5-Year survival rate: 0%
Weitz et al.	1981–2004	PHA (<i>n</i> = 5)/LS (<i>n</i> = 30)	Resectable (<i>n</i> = 3); unresectable (<i>n</i> = 2)	Resection (2 R0, 1 R1/2) (<i>n</i> = 3); NA (<i>n</i> = 2)	R0 (<i>n</i> = 2): die within 11 months
Abraham et al.	1980–2006	PHA (<i>n</i> = 1)/AS (<i>n</i> = 82)	Unresectable (diffuse) (<i>n</i> = 1)	NA	NA
Penel et al.	2005–2006	PHA (<i>n</i> = 3)/AS (<i>n</i> = 30)	Unresectable (metastatic) (<i>n</i> = 3)	Weekly paclitaxel	NA
Kim et al. (current study)	1985–2007	PHA (<i>n</i> = 5)	Unresectable (metastatic) (<i>n</i> = 5)	Variable chemotherapy	MS: 5 months

PHA, primary hepatic angiosarcoma; AS, angiosarcoma; LS, liver sarcoma; ADR, adriamycin; MTX, methotrexate; DTIC, dacarbazine; MS, median survival; diffuse, diffuse liver involvement; NA, not available.

chemotherapeutic regimens, which implied no established and efficacious regimens. (Table 4) Even if these data are not sufficient for providing detail clinical information including stage, median survival, the kinds of chemotherapeutic regimens, these may be helpful to recognize status of treatment modality, poor prognosis, rarity, and clinical manifestation [18, 28, 29]. In some reports with survival data, the median survival of primary hepatic angiosarcoma range from 5 to 14 months. Especially, Dannaher et al. have reported the favorable outcomes after chemotherapy for four patients. The chemotherapy regimen consisted of i.v. doxorubicin 60 mg/m² every 3–4 weeks, with cyclophosphamide and methotrexate added in three patients [26]. This previous study reported an objective improvement in three of four patients and SD in the other patient. Survival in the four patients from the time of diagnosis was 11, 13, 15, and 53 months. The reason for the differences between the report and our study might be the fact that their study included asymptomatic patients of good performance status diagnosed by screening examinations for industrial employees. However, there was no information about distant metastases, extension of liver involvement, and stage in this study compared with our study. In the other hand, all patients in our study were diagnosed with metastatic primary hepatic angiosarcoma ineligible for surgery, which stresses the aggressive behavior of this tumor.

Until now, there has been little information on treatment, no established chemotherapy regimen, and few reports about clinical outcomes of chemotherapy for advanced primary hepatic angiosarcoma. As there is no standard regimen, we selected chemotherapeutic agents that have been used for various sarcomas. Based on previous studies, we used a variety of chemotherapeutic agents such as 5-FU, carboplatin, doxorubicin, ifosfamide, paclitaxel, and bevacizumab [18–20, 29]. In our study, patients 2, 3, and 4 received 5-FU and carboplatin in combination with transhepatic artery infusion of doxorubicin. In addition, based on previous experience in treating hepatocellular

carcinoma, we combined transhepatic artery infusion of doxorubicin for local control. Two patients failed the treatment, but one patient received the salvage chemotherapy for a significant period of time. In patient 5, paclitaxel and bevacizumab were used in the second and third salvage chemotherapy after five cycles of IA regimen failure. The rationale behind the use of paclitaxel is that it appears to be useful for unresectable or metastatic angiosarcoma [20, 30–34]. Paclitaxel has antiangiogenic and apoptotic effects. Because the origin of angiosarcoma is the endothelial cell, it is conceivable that the antiangiogenic activity of paclitaxel is efficacious in angiosarcoma. Recently, phase II trial of weekly paclitaxel for metastatic and unresectable angiosarcoma presented that the efficacy and tolerable toxicity showing that median time to progression was 4 months and median OS was 8 months [29]. A novel biology-based approach will be needed to improve the current systemic chemotherapy for patients with unresectable angiosarcoma [35–38]. Bevacizumab, which is known to have an antiangiogenic effect, was used as an alternative chemotherapy in angiosarcoma because angiosarcoma is rich in vascularity due to its endothelial cell origin and showed high expression for vascular endothelial growth factor. However, this chemotherapeutic approach in our study was not efficacious because the patient was in an advanced stage with being refractory to several treatments. Some newer biologic therapies including antiangiogenic therapies such as bevacizumab or sorafenib may be effective theoretically against sarcoma or angiosarcomas [36, 37]. However, the majority of these results are those for patients with scalp and face angiosarcoma and limited in numbers [20, 30, 32–34, 39].

As we mentioned previously, conventional chemotherapy and external radiotherapy for primary hepatic angiosarcoma had limitation due to low efficacy, the intrinsic radioresistance of this tumor, and the relative sensitivity of nontumorous liver tissue [40, 41]. Therefore, we need to consider the alternative

approaches such as selective internal radiation therapy (SIRT) using intrahepatic arterial infusion of ^{90}Y trium microspheres [42, 43]. In SIRT, the pure beta-emitting isotope ^{90}Y trium is composed of millions of microspheres that are injected into the hepatic artery or one of its branches. The radioactive microspheres deposit in the feeding vasculature of the tumor, resulting in the delivery of intense local radiation to tumor but relative sparing of normal liver parenchyma [44, 45]. There are abundant data of SIRT for liver metastases arising from colorectal cancer, neuroendocrine tumor, and primary hepatocellular carcinoma and so on, and the reports represented promising survival [46]. These factors can be rationale that SIRT using intrahepatic arterial ^{90}Y trium apply to primary hepatic angiosarcoma. So we think SIRT has potential role in treatment primary hepatic angiosarcoma and can apply to this tumor carefully.

Little is mentioned about prognostic factors for primary hepatic angiosarcoma. As shown in previous reports, unresectable, advanced stage of primary hepatic angiosarcoma had especially poor prognosis. In addition, poor survival was noted in cases of hemoperitoneum by tumor rupture [2, 17, 47]. In cases of resectable hepatic angiosarcoma, it has been suggested that positive resection margins, but not tumor size, were associated with early recurrence and poor survival [22]. Based on our study, we suggest that it is worthwhile to consider the major determinants of prognosis or survival after chemotherapy of unresectable primary hepatic angiosarcoma. From the pathologic findings, patients 4 and 5 showed well-differentiated patterns compared with patient 3, indicating that pathologic differentiation might be related to survival. ECOG could also be another determinant associated with OS. In our study, the OS of patients 3, 4, and 5 was 86, 474, and 222 days, respectively, and their functional classes were ECOG 2, ECOG1, and ECOG1, respectively, which suggests that a relatively better ECOG leads to an increased long-term survival. Therefore, both pathologic differentiation and ECOG status could be used as prognostic factors to predict the treatment outcome from hepatic angiosarcoma.

Until now, there is no established chemotherapy regimen for primary hepatic angiosarcoma. Here, we suggest that the use of 5-FU–carboplatin accompanied with doxorubicin or ifosfamide–doxorubicin could be an efficient regimen. Furthermore, it might be reasonable to prevent hepatic angiosarcoma rupture during treatment [47, 48] because hemoperitoneum requires urgent diagnosis and management. In our chemotherapy regimen, doxorubicin infusion via hepatic artery appeared to be helpful in preventing hepatic angiosarcoma rupture and bleeding, although hepatic artery chemoinfusion still needs to be studied in more detail. Lastly, favorable pathology and ECOG with tolerable to palliative chemotherapy appears to be prognostic factors for this tumor. We anticipate that our study will be a useful reference for developing a treatment for patients with advanced primary hepatic angiosarcoma.

funding

Korea Science and Engineering Foundation grant funded by the Korean government (MOST) (R11-2000-082-03006-0).

acknowledgements

We appreciate Dr Ha for his comments on this manuscript.

references

- Mani H, Van Thiel DH. Mesenchymal tumors of the liver. *Clin Liver Dis* 2001; 5: 219–257, viii.
- Molina E, Hernandez A. Clinical manifestations of primary hepatic angiosarcoma. *Dig Dis Sci* 2003; 48: 677–682.
- Bolt HM. Vinyl chloride—a classical industrial toxicant of new interest. *Crit Rev Toxicol* 2005; 35: 307–323.
- Lee FI, Smith PM, Bennett B, Williams DM. Occupationally related angiosarcoma of the liver in the United Kingdom 1972–1994. *Gut* 1996; 39: 312–318.
- Thomas LB, Popper H, Berk PD et al. Vinyl-chloride-induced liver disease. From idiopathic portal hypertension (Banti's syndrome) to Angiosarcomas. *N Engl J Med* 1975; 292: 17–22.
- Lyburn ID, Torreggiani WC, Harris AC et al. Hepatic epithelioid hemangioendothelioma: sonographic, CT, and MR imaging appearances. *AJR Am J Roentgenol* 2003; 180: 1359–1364.
- Tateishi U, Hasegawa T, Muramatsu Y, Moriyama N. Hepatic metastases of soft tissue angiosarcoma: CT and MR imaging findings. *Abdom Imaging* 2003; 28: 660–664.
- Yu R, Zhang S, Hua J. Hepatic angiosarcoma: CT findings. *Chin Med J (Engl)* 2003; 116: 318–320.
- 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 (Baltimore)* 1979; 58: 48–64.
- Cady B, Bonneval M, Fender HR Jr. Elective hepatic resection. *Am J Surg* 1979; 137: 514–521.
- Rui J, Wang S, Chen S. Hepatic trisegmentectomy for 29 patients with huge neoplasms of liver. *Zhonghua Wai Ke Za Zhi* 2001; 39: 759–763.
- Weitz J, Klimstra DS, Cymes K et al. Management of primary liver sarcomas. *Cancer* 2007; 109: 1391–1396.
- Kang H, Lee J, Kim M et al. A case of hepatic angiosarcoma presenting as submucosal tumor resulting from gastric invasion. *Korean J Gastrointest Endosc* 2005; 31: 257–262.
- Lee W, Kim J, Kim Y et al. A case of primary angiosarcoma of the liver. *Korean J Hepatol* 1999; 5: 246–252.
- Lee Y, Hwang J, Park K et al. A case of primary hepatic angiosarcoma: report of a case and review of previous Korean cases. *Korean J Med* 2004; 66: 224–229.
- Park B, Park W, Kim B et al. Angiosarcoma of the liver: a case report. *J Korean Radiol Soc* 1997; 36: 1033–1036.
- Park S, Chon C, Shin H et al. A case of primary hepatic angiosarcoma. *Korean J Med* 1993; 45: 818–822.
- Abraham JA, Hornicek FJ, Kaufman AM et al. Treatment and outcome of 82 patients with angiosarcoma. *Ann Surg Oncol* 2007; 14: 1953–1967.
- Mathew P, Vakar-Lopez F, Troncso P. Protracted remission of metastatic epithelioid angiosarcoma with weekly infusion of doxorubicin, paclitaxel, and cisplatin. *Lancet Oncol* 2006; 7: 92–93.
- Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer* 2005; 104: 361–366.
- Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92: 205–216.
- Almogly G, Lieberman S, Gips M et al. Clinical outcomes of surgical resections for primary liver sarcoma in adults: results from a single centre. *Eur J Surg Oncol* 2004; 30: 421–427.
- Arima-Iwasa S, Chijiwa K, Makino I et al. A case of hepatic angiosarcoma surviving for more than 16 months after hepatic resection. *Hepatogastroenterology* 2007; 54: 533–535.
- Timaran CH, Grandas OH, Bell JL. Hepatic angiosarcoma: long-term survival after complete surgical removal. *Am Surg* 2000; 66: 1153–1157.

25. Ozden I, Bilge O, Erkan M et al. Five years and 4 months of recurrence-free survival in hepatic angiosarcoma. *J Hepatobiliary Pancreat Surg* 2003; 10: 250–252.
26. Dannaher CL, Tamburro CH, Yam LT. Chemotherapy of vinyl chloride-associated hepatic angiosarcoma. *Cancer* 1981; 47: 466–469.
27. Ikeda K, Maehara M, Ohmura N et al. Spontaneous rupture of a necrotic hepatic angiosarcoma: findings on dual-phase computed tomography and angiography. *Radiat Med* 2006; 24: 369–372.
28. Fayette J, Martin E, Piperno-Neumann S et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. *Ann Oncol* 2007; 18: 2030–2036.
29. Penel N, Bui BN, Bay JO et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX study. *J Clin Oncol* 2008 Sep 22. [Epub ahead of print].
30. Fata F, O'Reilly E, Ilson D et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. *Cancer* 1999; 86: 2034–2037.
31. Mano MS, Fraser G, Kerr J et al. Radiation-induced angiosarcoma of the breast shows major response to docetaxel after failure of anthracycline-based chemotherapy. *Breast* 2006; 15: 117–118.
32. 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: 357–359.
33. Tomasello L, Gardin G, Boccardo F. Secondary breast angiosarcoma: lethal response to anti-angiogenic therapy with paclitaxel chemotherapy. A case report. *Anticancer Res* 2006; 26: 4775–4777.
34. Yamada M, Hatta N, Mizuno M et al. Weekly low-dose docetaxel in the treatment of lung metastases from angiosarcoma of the head. *Br J Dermatol* 2005; 152: 811–812.
35. Budd GT. Management of angiosarcoma. *Curr Oncol Rep* 2002; 4: 515–519.
36. D'Adamo DR, Anderson SE, Albritton K et al. Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. *J Clin Oncol* 2005; 23: 7135–7142.
37. D'Adamo DR, Keohan M, Schuetz S et al. Clinical results of a phase II study of sorafenib in patients (pts) with non-GIST sarcomas (CTEP study #7060). *J Clin Oncol* 2007; 25: 18S (Abstr 10001).
38. Penel N, Lansiaux A, Adenis A. Angiosarcomas and taxanes. *Curr Treat Options Oncol* 2007; 8: 428–434.
39. Nagano T, Yamada Y, Ikeda T et al. Docetaxel: a therapeutic option in the treatment of cutaneous angiosarcoma: report of 9 patients. *Cancer* 2007; 110: 648–651.
40. Ho S, Lau WY, Leung TW, Johnson PJ. Internal radiation therapy for patients with primary or metastatic hepatic cancer: a review. *Cancer* 1998; 83: 1894–1907.
41. Jakobs TF, Hoffmann RT, Poeppel G et al. Mid-term results in otherwise treatment refractory primary or secondary liver confined tumours treated with selective internal radiation therapy (SIRT) using (90)Yttrium resin-microspheres. *Eur Radiol* 2007; 17: 1320–1330.
42. Kennedy A, Nag S, Salem R et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys* 2007; 68: 13–23.
43. Neff R, Abdel-Misih R, Khatri J et al. The toxicity of liver directed yttrium-90 microspheres in primary and metastatic liver tumors. *Cancer Invest* 2008; 26: 173–177.
44. King J, Quinn R, Glenn DM et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer* 2008; 113: 921–929.
45. Gulec SA, Fong Y. Yttrium 90 microsphere selective internal radiation treatment of hepatic colorectal metastases. *Arch Surg* 2007; 142: 675–682.
46. Sato KT, Lewandowski RJ, Mulcahy MF et al. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres—safety, efficacy, and survival. *Radiology* 2008; 247: 507–515.
47. Tordjman R, Eugene C, Clouet O et al. [Hepatosplenic angiosarcoma complicated by hemoperitoneum and disseminated intravascular coagulation. Treatment by arterial embolization and chemotherapy]. *Gastroenterol Clin Biol* 1995; 19: 625–628.
48. Mahony B, Jeffrey RB, Federle MP. Spontaneous rupture of hepatic and splenic angiosarcoma demonstrated by CT. *AJR Am J Roentgenol* 1982; 138: 965–966.