Selective Internal Radiation Therapy of Hepatocellular Carcinoma: Potential Hepatopulmonary Shunt Reduction after Sorafenib Administration

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ABSTRACT

Sorafenib, a protein kinase inhibitor, is a systemic drug that has been licensed for the treatment of hepatocellular carcinoma (HCC). This retrospective study assessed whether the administration of sorafenib can result in a reduction of the hepatopulmonary shunt (HPS) before selective internal radiation therapy (SIRT). After exclusion from SIRT because of high HPS, computed tomography scan indicated a shunt reduction in seven patients with HCC receiving sorafenib. Repeated measurements revealed HPS reduction (from 26.5% to 7.5% on average), and subsequent SIRT became possible. In conclusion, sorafenib may reduce HPS in patients with advanced HCC in some cases.

ABBREVIATIONS

DSA = digital subtraction angiography, HCC = hepatocellular carcinoma, HPS = hepatopulmonary shunt, MAA = macroaggregated albumin, SIRT = selective internal radiation therapy, SPECT = single photon emission computed tomography

Selective internal radiation therapy (SIRT) using the beta emitter yttrium-90 is an emerging therapy option for unresectable liver malignancies. However, a high hepatopulmonary shunt (HPS) secondary to tumorous arteriovenous fistulas may be a contraindication for SIRT because of increased risk of radiation pneumonitis or lung fibrosis (1,2).

The kinase inhibitor sorafenib is an alternative systemic treatment option for advanced HCC in patients with contraindications for SIRT (3,4). The therapeutic effect of sorafenib is based on the interference with tumor cell proliferation and angiogenesis by inhibiting the serine-threonine kinases Raf-1 and B-Raf and the tyrosine kinase activity of vascular endothelial growth factor receptors (5,6). It can be assumed that not only tumor cells but also concomitant arteriovenous fistulas are affected by sorafenib. We performed a retrospective study to assess sorafenib treatment results in terms of a reduction of the HPS before SIRT and whether patients with excessive lung shunting may become eligible for SIRT after sorafenib administration.

MATERIALS AND METHODS

A waiver of institutional review board requirements was obtained because of the retrospective character of this study.

Patients

Between June 2009 and January 2011, seven patients (5 men and 2 women with a mean age 64.1 y) with advanced stage HCC were excluded from SIRT using TheraSphere (MDS Nordion, Ottawa, Canada) because of high HPS. Clinical follow-up computed tomography (CT) scans obtained after sorafenib (Nexavar; Bayer Schering Pharma, Berlin, Germany) therapy indicated a reduction of intrahe-

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Table. Patient and Hepatopulmonary Shunt Data before and after Sorafenib Administration

Patient	Gender	Age (y)	Tumor Load (% Right/Left Lobe)	Duration of Sorafenib Administration (d)	Estimated Lung Shunt/Exposure before Sorafenib (%/Gy)	Estimated Lung Shunt/Exposure after Sorafenib (%/Gy)	Decrease of Lung Shunt/ Exposure (%/%)	Treatment Dose (Gy)
1	F	50	60/0	109	28/29.0*	9/6.8	68/77	120
2	M	57	60/20	72	37/85.6	14/23.5	62/73	100
3	M	60	40/20	297	23/89.4	3/9.4	87/89	115
4	M	83	90/0	76	18/35.0	4/5.4	78/85	115
Mean		62.5		138.5	26.5/67.0	7.5/11.3	74/81	

F = female; M = male.
* Patient had concomitant lung disease.

patic shunts in these patients. HPS was measured by single photon emission computed tomography (SPECT) with CT after angiography and injection of macroaggregated albumin (MAA) (ROTOP Pharmaka AG, Radeberg, Germany).

Angiography

Hepatic arteriography was performed before treatment using a biplane digital subtraction angiography (DSA) system (Toshiba Infinix DP-i; Toshiba Medical Systems, Tokyo, Japan, or Philips Allura; Philips Healthcare, Best, Netherlands). After identifying the extent of tumor spread, a microcatheter (Rebar 0.27 in; EV3 Plymouth, Minnesota) was placed in the intended treatment position or positions encompassing the right or left hepatic artery or both. MAA was injected from these positions; 150 MBq of technetium 99m–MAA was used.

Single Photon Emission Computed Tomography/Computed Tomography

After administration of technetium 99m–MAA and subsequent catheter removal, all patients were referred to the Department of Nuclear Medicine. A SPECT/CT examination was performed on a Symbia SPECT/CT system (Siemens Healthcare, Erlangen, Germany) to facilitate better anatomic coregistration compared with SPECT alone. Fusion images were reconstructed from the coregistered low-dose CT images and SPECT using the e.soft 2007 application package (Siemens Healthcare). Regions of interest were drawn manually over the liver and the lungs. HPS was calculated from the geometric mean as shunt = lung / (lung + liver).

Management of Patients with Elevated HPS and Data Assessment

Patients with HPS resulting in a lung dose of > 30 Gy were not scheduled for subsequent SIRT. In patients with an estimated dose of 25–30 Gy, the decision was based on the clinical status of the patient and on concomitant lung disease. Patients who were initially excluded from SIRT because of high lung shunts received sorafenib in continuous oral dosing (maximum daily dose of 800 mg). Patients were clinically followed, and side effects with regard to sorafenib administration were noted. Inclusion criteria of this study were based on follow-up CT scans indicating a relevant intrahepatic shunt reduction. Patients were rescheduled for another angiogram followed by SPECT/CT and calculation of HPS. HPS values and calculated predicted lung doses before and after sorafenib administration were compared, and the differences in percentage between the two values were calculated.

RESULTS

Four of seven patients with high HPS as a contraindication for SIRT (three men, one woman; mean age, 62.5 y; age range, 50–83 y) received sorafenib for an average of 138 days (range, 72–297 d) before a repeat angiogram followed by lung shunt calculation. The remaining three patients were not rescheduled for SIRT because of progressive disease and increasingly reduced liver function. In three of the four patients who were reevaluated, the initial estimated lung dose was > 30 Gy. In one patient, the dose calculation was 25–30 Gy. However, this patient had concomitant lung disease and was not initially considered for SIRT.

Sorafenib administration was well tolerated by all patients. Only minor side effects were seen, including mild to moderate diarrhea, nausea, and fatigue. A decrease of HPS after sorafenib treatment could be found in all four patients. Reduction of HPS was from 26.5% (range, 18%–37%) to 7.5% (range, 3%–14%), or estimated exposure reduction was from 67 Gy (range, 29–89.4 Gy) to 11.3 Gy (range, 5.4–23.5 Gy). In all four patients, predicted lung exposure was < 25 Gy after sorafenib. These patients became eligible for SIRT and received a target dose of 100–120 Gy to the liver. All patient data are shown in the **Table**. Imaging findings of two patients before and after sorafenib treatment are shown in **Figures 1a–d** and **2a–d**.

DISCUSSION

The administration of sorafenib may lead to a reduction of HPS in patients with advanced stage HCC. We first considered the reevaluation of patients with increased HPS for