European Journal of Radiology 84 (2015) 424–430

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Transarterial chemoembolization in soft-tissue sarcoma metastases to the liver – The use of imaging biomarkers as predictors of patient survival

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ARTICLE INFO

Article history:
Received 30 April 2014
Received in revised form
14 November 2014
Accepted 28 November 2014

Keywords:
Liver cancer
Sarcoma
Transarterial chemoembolization
Volumetry
MRI
RECIST
mRECIST
EASL

ABSTRACT

Background: The clinical management of patients with metastatic soft-tissue sarcoma of the liver is complicated by the paucity of reliable clinical data. This study evaluated the safety profile, survival outcome as well as the role of imaging biomarkers of tumor response in metastatic soft-tissue sarcoma (mSTS) of the liver treated with conventional transarterial chemoembolization (cTACE).
Materials/methods: This retrospective analysis included 30 patients with mSTS of the liver treated with cTACE. The safety profile, overall survival (OS) and progression-free survival (PFS) after the procedure were evaluated. Tumor response in each patient was assessed using RECIST, modified (m) RECIST and EASL guidelines. In addition, a 3D quantification of the enhancing tumor volume (quantitative [q] EASL) was performed. For each method, patients were classified as responders (R) and non-responders (NR), and evaluated using Kaplan-Meier and multivariate Cox proportional hazard ratio (HR) analysis.
Results: No Grade III or IV toxicities were reported in a total of 77 procedures (mean, 2.6/patient). Median OS was 21.2 months (95% CI, 13.4–28.9) and PFS was 6.3 months (95% CI, 4.4–8.2). The enhancement-based techniques identified 11 (44%), 12 (48%) and 12 (48%) patients as R according to EASL, mRECIST and qEASL, respectively. No stratification was achieved with RECIST. Multivariate analysis identified tumor response according to mRECIST and qEASL as reliable predictors of improved patient survival ($P = 0.019$; HR 0.3 [0.1–0.8] and $P = 0.006$; HR 0.2 [0.1–0.6], respectively).
Conclusion: This study confirmed the role of cTACE as a safe salvage therapy option in patients with mSTS of the liver. The demonstrated advantages of enhancement-based tumor response assessment techniques over size-based criteria validate mRECIST and qEASL as preferable methods after intraarterial therapy.

1. Introduction

Soft-tissue sarcomas (STS) represent about 1% of all diagnosed adult malignancies in the United States [1,2]. With fewer than 12.000 new cases every year, the clinical management of STS is complicated by their relative rarity, histopathological heterogeneity and the paucity of clinical data with high levels of evidence [3]. Surgical resection as the mainstay for treatment of STS was reported to provide some survival benefits. However, not all patients are eligible for resection and more than 50% of these patients will eventually die from subsequent metastases to the liver and lungs [4,5]. Metastases to the liver occur in up to 60% of patients and represent a pattern of recurrence primarily in tumors of visceral and retroperitoneal origin [2,6]. Once metastasized, the prognosis becomes dismal with reported overall survival rates of no more than 15 months [2]. For most patients with liver metastases, systemic

Abbreviations: mSTS, metastatic soft-tissue sarcoma; qEASL, quantitative European Association for the Study of the Liver; RECIST, Response Evaluation Criteria in Solid Tumors.

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http://dx.doi.org/10.1016/j.ejrad.2014.11.034
0720-048X/

chemotherapy continues to be the first-line treatment; however, response rates are extremely low (10–25%) and survival benefits are minimal primarily because of the pronounced chemoresistance of most histological sarcoma types [7–9]. The marked ability of sarcoma cells to limit intracellular accumulation of most systemically applicable anti-neoplastic agents by active drug extrusion requires higher doses in order to achieve tumor response, which in return tips the balance between efficacy and toxicity towards the latter. This circumstance provides the opportunity for intraarterial therapies, such as transarterial chemoembolization (TACE), to fill the gap by delivering high doses of cytotoxic agents to the tumor while reducing systemic toxicity [10].

Because of the relative rarity of STS, only very few studies with small cohorts of patients are available to confirm the role of TACE as a reliable salvage option for this aggressive disease [10–12]. A particular lack of clinical data exists with regard to the post-procedural assessment of local tumor response on cross-sectional imaging. Most STS metastases to the liver present as large hypervascular lesions on arterial phase MRI. However, the assessment of these lesions is technically challenging as most patients present after several lines of systemic chemotherapy with tumors that typically demonstrate central necrosis as well as rim and segmental enhancement with scattered foci of remaining viable tumor tissue [13]. In addition, most intraarterial therapies involve the element of embolization of the tumor-feeding arteries, thus causing tissue necrosis without immediate effects on the overall lesions size. These characteristics constitute a significant obstacle for conventional assessment techniques, such as the anatomic Response Evaluation Criteria in Solid Tumors (RECIST), to quantify tumor response and to properly identify non-responders which have been meanwhile identified as a challenge not only for local, but also for new systemic chemotherapies [14].

This study evaluated the safety profile, survival outcome as well as the role of imaging biomarkers of tumor response in soft-tissue sarcoma (STS) metastases to the liver treated with conventional transarterial chemoembolization (cTACE).

2. Materials and methods

2.1. Patients

This single-institution study was conducted in compliance with the Health Insurance Portability and Accountability Act and approved by the Institutional Review Board, which waived the need for informed consent in this retrospective analysis. Between December 2000 and December 2013, a total of 32 patients with liver-only or liver-dominant STS metastases underwent their first session of conventional TACE within our institution. Patients with secondary ongoing malignancies ($N = 2$) were excluded. The remaining 30 patients were included into the outcome analysis. An additional five patients lacked contrast-enhanced baseline imaging and were excluded from the tumor response analysis. A total of 25 patients (83%) had received contrast-enhanced CT (N = 5, on baseline only) or MR imaging ($N = 20$ on baseline, $N = 25$ on follow-up) within 6 weeks before and after the initial TACE session and were included into the imaging analysis. Table 1 summarizes the baseline characteristics of the selected patient cohort. Median patient age was 54.9 years (range, 18.9–70.6) and the majority of patients were female (63%). Median lesion size was 6.4 cm (mean, 6.9 cm; range, 1.2–16.9 cm). Periprocedural adverse events were recorded and reported for all treatment sessions in each patient according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03.

Table 1
Baseline patient characteristics.

Parameter		*N* (%)
Demographics		
Age, years	<65	24 (80)
	≥65	6 (20)
Sex	Male	11 (37)
	Female	19 (63)
Race	White	26 (86)
	African American	2 (7)
	Other	2 (7)
ECOG performance status	0	9 (30)
	≥1	21 (70)
Bilirubin, mg/dL	Median	0.5
	Range	0.2–1.0
Albumin, g/dL	Median	4.1
	Range	2.9–4.7
Prothrombin time (INR)	Median	1.0
	Range	0.9–1.2
Child-pugh class	A	30 (100%)
Tumor characteristics		
Tumor burden, %	<50	22 (73)
	≥50	8 (27)
Synchronous disease	Yes	9 (30)
	No	21 (70)
Extra-hepatic metastases	Yes	19 (63)
	No	11 (37)
Tumor location	Bilobar	24 (80)
	Unilobar	6 (20)
Tumor multiplicity	Single Lesion	3 (10)
	2–5 Lesions	8 (27)
	>5 Lesions	19 (63)
Primary site	Retroperitoneum	9 (30)
	Uterus	8 (27)
	GI tract	4 (13)
	Other:	9 (30)
Histological type	Leiomyosarcoma	
	Angiosarcoma	25 (84)
	Fibrosarcoma	3 (10)
	Chondrosarcoma	1 (3)
		1 (3)

ECOG, Eastern Cooperative Oncology Group.

2.2. Intraarterial therapy, CT and MR imaging technique

All procedures were performed by one experienced interventional radiologist (XX with 16 years of experience in hepatic interventions). A consistent approach according to our standard institutional cTACE and Yttrium90-radioembolization protocols was used. A total of 5 patients received native and contrast-enhanced multi-detector CT on baseline using a multi-slice CT scanner (Sensation 64; Siemens Medical Solutions, Erlangen, Germany). The remaining scans were acquired using a standardized MRI protocol before and after the initial cTACE. MRI was performed on a 1.5 Tesla scanner (Siemens Magnetom Avanto, Erlangen, Germany). The details of the procedure protocols and image acquisition techniques can be found within the appendix.

2.3. Imaging data evaluation

Tumor assessment was performed by two independent readers (a radiologist with 9 years of experience in abdominal imaging and a radiology resident with 2 years of experience). Any ambiguity was resolved by consensus. A target lesion was defined as the largest, dominant lesion treated during the first session of cTACE. A single targeted lesion per patient was selected for analysis. The analysis of multiple target lesions was omitted as other studies did not confirm the benefit of this methodology [15].

The selected target lesions were assessed using RECIST, modified (m) RECIST as well as using the European Association for the Study of the Liver (EASL) guidelines [16]. All measurements made