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CT imaging findings in patients with advanced hepatocellular carcinoma treated with sorafenib: Alternative response criteria (Choi, European Association for the Study of the Liver, and modified Response Evaluation Criteria in Solid Tumor (mRECIST)) versus RECIST 1.1

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ABSTRACT

Purpose: The first aim was to compare Response Evaluation Criteria in Solid Tumor (RECIST) 1.1, modified Response Evaluation Criteria in Solid Tumor (mRECIST), Choi and European Association for the Study of the Liver (EASL) evaluations to assess the response to sorafenib for hepatocellular carcinoma (HCC).

The second aim was to describe the evolution of HCC and to identify whether some imaging features are predictive of the absence of response.

Materials and methods: This retrospective study included 60 patients with advanced HCC treated with sorafenib. Patients must have undergone a scan prior to treatment to identify the number of lesions, size, enhancement and endoportal invasions, and repeat scans thereafter. Computed tomography (CT) scans were analyzed using RECIST 1.1, mRECIST, Choi and EASL criteria. Overall survival was analyzed.

Results: The median overall survival was 10.5 months. On the first CT reevaluation, the sorafenib response rates were 20%, 5%, 7% and 3% according to Choi, EASL, mRECIST and RECIST 1.1. The responders based on Choi exhibited significantly better overall survival compared with non-responders (20.4 months; hazard ratio (HR) 0.042, 95% confidence interval (CI): 0.186–0.94, $p = 0.035$). A modification of imaging findings was observed in 48.3% of patients, and necrosis was present in 44.1% of patients.

Conclusion: This study found a significant difference between Choi versus RECIST 1.1, mRECIST and EASL when evaluating the response to sorafenib in HCC patients.

1. Introduction

The RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria are considered to be the standard method for tumor responses assessment in clinical trials and are representative of survival outcome in patients with solid tumors [1,2].

The Study of Heart and Renal Protection (SHARP) trial [3] demonstrated a significant improvement in overall survival (OS) (median 10.7 versus 7.9 months) and in the mean time to radiological progression (5.5 versus 2.8 months) in patients with advanced-stage hepatocellular carcinoma (HCC) treated with sorafenib (Nexavar®, Bayer Healthcare Pharmaceuticals). However, the response rate on follow-up examination was only 2% according to RECIST. Phase III trials also showed a low radiological response rate (3.3%) using the RECIST 1.1 criteria, despite an improvement in overall survival [4,5]. Moreover, in the SHARP trial, no significant difference was noted between the sorafenib and placebo groups with respect to objective responses (complete plus partial) or stable disease based on RECIST 1.1 (2% and 71%, respectively, in the

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sorafenib group; 1% and 67%, respectively, in the placebo group) [3].

The European Association for the Study of the Liver (EASL) proposed a set of criteria that considers the antitumoral activity of local therapies used in HCC, such as radiofrequency ablation and chemoembolization [6].

The emergence and validation of systemic therapies called for new criteria to assess tumor responses [7,8], giving rise to the modified RECIST criteria (mRECIST) [6,9–12]

Choi et al. developed a composite endpoint for gastrointestinal stromal tumors (GIST) treated with imatinib, including tumor size and enhancement [13]. This evaluation tool is also potentially relevant to HCC.

The main objective was to determine which criteria (RECIST 1.1, mRECIST, Choi or EASL) correlates best with OS among patients with HCC treated with sorafenib. The secondary objectives were to describe morphological changes in tumors treated with sorafenib and their correlation with pretreatment characteristics to identify predictors of non-response.

2. Materials and methods

2.1. Data collection

This retrospective monocentric observational study was conducted from November 2007 to January 2014 in HCC patients treated with sorafenib.

The following inclusion criteria were utilized for this study:

- Baseline thoracic and abdominopelvic imaging available within 6 weeks before sorafenib administration; and
- Imaging available during sorafenib therapy (>4 weeks after initiation).

The exclusion criteria were as follows:

- Concomitant specific treatment; or
- Prior specific treatment of HCC ending less than 8 weeks before sorafenib administration.

HCC was diagnosed according to Barcelona Clinic Liver Cancer (BCLC) and American Association for the Study of Liver Diseases guidelines (6,14) based on imaging or histology.

Imaging was based on thoraco–abdominal–pelvic computed tomography (CT) using a Lightspeed VCT 64-detector (GE Healthcare) with the same multiphase acquisition protocol: unenhanced phase, hepatic arterial phase, venous portal phase and late phase at the time of three minutes. The following CT parameters were used: detector configuration 64×0.625 mm, 120 KVp, 250–300 mAs. Section thickness was 3 mm without section overlap. Patients received 1.5 mL/kg total body weight of an intravenous contrast medium. The contrast medium was administered with a mechanical power injector at a rate of 3–5 mL/s.

At baseline, the target lesions had to be at least 1 cm at their widest point. Non-target lesions could be smaller than 1 cm. A maximum of 2 lesions per organ and 5 lesions in total were selected. Target lesions could be extra-hepatic.

The following imaging data were collected:

- Multifocal, infiltrative HCC, and the number of lesions (1, 2 or $\geq$3);
- Vascular invasion: invasion of a portal branch, the portal vein, suprahepatic vein or other veins (inferior vena cava, mesenteric vein) and the nature of vascular thrombosis (endovascular tumor bud or fibrin-cruoric thrombus);
- Presence and topography of metastases;
- Cirrhotic dysmorphia;
- Ascites;
- Portal hypertension;
- Size and number of lesions;
- Bilobular hepatic involvement;
- Sum of the largest diameters (SLD) using RECIST 1.1 and mRECIST criteria;
- Arterial enhancement relative to baseline intensity; and
- Necrosis presence, topography (central, periphery, diffuse) and extension.

2.2. Data collection after sorafenib initiation

All patients had at least one follow-up examination. All images were reviewed by two radiologists who specialized in gastrointestinal imaging.

For OS analysis, only the first follow-up CT results were considered.

The following data were collected and repeated for each follow-up examination:

- Time from sorafenib initiation;
- Tumor response according to RECIST 1.1, mRECIST, EASL and Choi;
- Nature of progression; and
- Tumor morphological changes: decreased vascularity, necrosis appearance assessed in one axial slice.

Each patient was classified as having a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (P) according to each set of criteria. Patients were also classified as objective response (OR) or progressive disease according to the Choi criteria.

2.3. Statistical analysis

OS was measured from the date of treatment initiation to either the patient's date of death or their last follow-up visit. Survival curves were constructed using the Kaplan–Meier method and compared using the Mantel–Cox log-rank test based on the final data. Cox hazard ratios were used to compare survival according to the radiological response as defined by RECIST 1.1, mRECIST, EASL and Choi. All tests were two-sided, and p values below 0.05 were considered to denote significant differences. In addition, 95% confidence intervals (95% CI) were calculated.

Fisher's test and Student's t-test were used. Analysis of variance (ANOVA) and the Pearson χ^2 test were used to identify baseline imaging characteristics predictive of the radiological response.

3. Results

In total, 84 patients were treated with sorafenib during the study period, of whom 60 were eligible for inclusion. The median follow-up was 10.3 months (1–45 months).

The female:male sex ratio was 1:9. The average age was 60 years (39–79 years) (Table 1).

In total, 40 patients received prior treatment: chemoembolization ($n = 32$), radioembolization ($n = 6$), radiofrequency ablation ($n = 4$), cyberknife ($n = 1$), surgical tumor resection ($n = 6$), and liver transplantation ($n = 2$).

Sorafenib treatment lasted a mean of 8.3 months (1.5–43 months) and a median of 5.7 months.

3.1. Tumor response assessment

According to RECIST 1.1 (Fig. 1), 2 patients exhibited PR (3.3%), 28 exhibited SD (46.7%) and 30 exhibited P (50%).