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Visceral fat area predicts survival in patients with advanced hepatocellular carcinoma treated with tyrosine kinase inhibitors

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ABSTRACT

Background: Anthropometric measurements have been linked to resistance to anti-angiogenic treatment and survival.
Methods: Patients with advanced hepatocellular carcinoma treated with sorafenib or brivanib in 2008–2011 were included in this retrospective study. Anthropometric measurements were assessed using computed tomography and were correlated with drug toxicity, radiological response, and overall survival.
Results: 52 patients were included, Barcelona Clinic Liver Classification B (38%) and C (62%), with a mean value of α-fetoprotein of 29,554 ± 85,654 ng/mL, with a median overall survival of 10.5 months. Sarcopenia was associated with a greater rate of hand–foot syndrome ($P = 0.049$). Modified Response Evaluation Criteria In Solid Tumours (mRECIST) and Choi criteria were significantly associated with survival, but RECIST criteria were not. An absence of hand–foot syndrome and high-visceral fat area were associated with progressive disease as assessed by RECIST and mRECIST criteria. In multivariate analyses, high visceral fat area (HR = 3.6; $P = 0.002$), low lean body mass (HR = 2.4; $P = 0.015$), and presence of hand–foot syndrome (HR = 1.8; $P = 0.004$) were significantly associated with overall survival. In time-dependent multivariate analyses; only high visceral fat area was associated with survival.
Conclusion: Visceral fat area is associated with survival and seems to be a predictive marker for primary resistance to tyrosine kinase inhibitors in patients with advanced hepatocellular carcinoma.

1. Introduction

Hepatocellular carcinoma (HCC) is the third cause of cancer-related death worldwide. It is associated with various aetiologies, including hepatitis B virus, hepatitis C virus, high alcohol intake, and metabolic syndrome. The Barcelona Clinic Liver Classification (BCLC) is the main staging system used in Western countries to assess a patient's prognosis and to guide curative or palliative treatment.

Sorafenib, a tyrosine kinase inhibitor that targets the vascular endothelial growth factor (VEGFR), platelet-derived growth factor receptors (PDGFR), RAS and RAF, is to date the only systemic

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therapy that can improve survival in advanced HCC [1]. Despite this breakthrough in clinical care, the prognosis for patients with advanced HCC is still poor and new treatments are warranted [2]. Recently, brivanib, a tyrosine kinase inhibitor that targets VEGFR and FGFR, failed to improve survival in first-line or second-line treatments of advanced HCC, despite increased progression-free survival [2,3]. In addition, other phase III randomized trials, using everolimus, sunitinib, erlotinib, or linifanib, have failed to show clinical efficacy in first-line regimens [2–4]. Consequently, sorafenib remains the first and sole systemic treatment approved for advanced HCC [5]. However, not all patients benefit from sorafenib: in the pivotal SHARP trial 27% of patients showed progressive disease at the first evaluation and the median time to radiological progression was 5.5 months [6]. Consequently, it is important to decipher the determinants of susceptibility and resistance to sorafenib and to other tyrosine kinase inhibitors [2].

Both the tumour and host can determine the response to targeted therapies. Like other cancers, HCC is derived from malignant transformation of hepatocytes caused by accumulation of somatic genetic alterations in passenger and driver genes [7]. In solid tumours, somatic genetic alterations can predict the response to targeted therapy, such as tyrosine kinase inhibitors (TKI) that target *EGFR* mutations, including gefitinib, erlotinib, and afatinib to treat non-small-cell lung cancer; vemurafenib which targets BRAF V600 mutations; dabrafenib that targets melanoma or EML4-ALK translocation; and the ALK inhibitor crizotinib or ceritinib to treat non-small-cell lung cancer.

These genetic alterations can also predict resistance to treatments against mutations of *KRAS*, *NRAS*, and *HRAS*, as well as resistance to the EGFR antibodies cetuximab and panitumumab in metastatic colorectal cancer. So far, no genetic mutation of HCC has been robustly linked to a response to sorafenib.

In contrast, a host factor may determine the resistance and susceptibility to tyrosine kinase inhibitors and anti-angiogenic treatments [8]. Much more than obesity, the repartition of fat (visceral fat area and subcutaneous fat area) has been linked to the response to anti-angiogenic treatment. A high visceral fat area is associated with resistance to anti-angiogenic therapy and tyrosine kinase inhibitors in several types of cancer [9–11]. In addition, sarcopenia has been linked to a prognosis of gastrointestinal cancer [12–14] and with drug toxicity in patients with HCC treated by sorafenib [15]. However, the predictive value of anthropometric measurements that combine visceral fat area, subcutaneous fat area, lean body mass, and sarcopenia has not been tested in advanced HCC treated with tyrosine kinase inhibitors.

In this study, we aimed to explore the association between anthropometric measurements assessed by a computed tomography (CT) scan and treatment response, survival, and toxicity in patients with advanced HCC treated with tyrosine kinase inhibitors.

2. Materials and methods

2.1. Selection of patients

All consecutive patients treated with tyrosine kinase inhibitors between 2008 and 2011 for advanced HCC at a single institution (Henri Mondor Hospital, Liver Unit, Creteil, France) were included in this retrospective study. Inclusion criteria were: HCC diagnosed histologically or by non-invasive imaging criteria from EASL [5] and AASLD guidelines [16]; HCC classified as BCLC B with progressive disease after at least two chemoembolizations or classified as BCLC C (tumour portal thrombosis and/or metastasis); treatment with tyrosine kinase inhibitors sorafenib or brivanib; a Child–Pugh score of A or B; or a performance status of 0–2. The study was approved by the local institutional review board (CPP Ile de France IX) and all patients gave their informed written consent according to French law.

For all patients, the following clinical data were recorded: age, gender, height, weight, body-mass index (BMI), previous treatments received, status of the non-tumorous liver, aetiology, ascites, performance status, diabetes, and hypertension. The following biological criteria were also recorded: platelet count, prothrombin time, creatinine, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl-transpeptidase (GGT), total bilirubin, alpha-fetoprotein, Child–Pugh score, BCLC classification, the presence of tumour portal thrombosis, and the presence of metastasis.

Sorafenib was started at 400 mg twice daily, brivanib at 800 mg once per day, and patients were monitored at day 15 and then every month. Doses were modified according to the occurrence of any drug-related toxicity, which was classified according to the National Cancer Institute's Common Toxicity Criteria NCI-CTC v3.0.

2.2. Assessment of radiological response

A CT scan and/or magnetic-resonance imaging (MRI) were used to assess the response to treatment at 6–8-week intervals. All images were reviewed by two expert radiologists (FP and AL) who were blinded to the patients' outcomes and their initial data. Patients were classified according to their best radiological response and were divided into having progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR), using the Response Evaluation Criteria In Solid Tumours (RECIST) criteria [17] and the Modified Response Evaluation Criteria In Solid Tumours (mRECIST) criteria [18]. Patients were also classified according to Choi criteria [19,20] as being responders or non-responders.

2.3. Anthropometric measurements

Visceral fat area, subcutaneous fat area, lean body mass, and sarcopenia were measured in all patients (Fig. 1). Both visceral fat area, subcutaneous fat area, sarcopenia, and lean body mass were assessed from a pre-treatment CT. Among the 52 included patients, 45 underwent a CT-scan at <1 month before the start of tyrosine kinase inhibitor therapy, and were therefore available for anthropometric measurements. The other seven patients underwent a CT scan at >1 month before tyrosine kinase inhibitor (TKI) was started, and so were excluded from all CT anthropometric measurements. In addition, four patients with ascites were included for the assessment of sarcopenia and lean body mass but were excluded from assessments of visceral fat and subcutaneous fat, following international consensus recommendations [14].

Two radiologists, blinded to all clinical and biological characteristics and the follow-up findings, measured total muscle area (cm^2) using manual segmentation on a dedicated post-treatment station (Advantage Window v4.6, GE Healthcare, Buc, France). They used enhanced CT scans, i.e., a portal venous phase with 0.625-mm collimation, at 1.25 contiguous slice thicknesses.

The Skeletal Muscle Index (SMI) and lean body-mass measurements were assessed in 45 patients. The total muscle area (TMA) was measured from axial CT sections through the 3rd lumbar vertebrae when both pedicles were visible and with a pre-established density threshold of −29 to +150 Hounsfield units. SMI was defined by the TMA normalized for stature (cm^2/height m^2) [21]. According to international guidelines, sarcopenia was defined by a SMI of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women [14]. Lean (fat-free) body mass was calculated using the TMA on L3 as follows: total lean body mass (kg) = 0.30 × (TMA at L3 [cm^2]) + 6.06 [12].

Visceral fat area and subcutaneous area were assessed in 41 patients. Visceral fat area and subcutaneous area were assessed at