Title: circulating DNA monitoring in patients treated with transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC)


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Introduction:
Morphological evaluation is currently the gold standard for assessing the efficacy of transarterial chemoembolization (TACE) in patients treated for hepatocellular carcinoma (HCC). The aim of this pilot study was to assess the prognostic value of detecting circulating DNA (cDNA) in patients treated with TACE.

Patients and methods:
A blood sample was prospectively taken from all patients treated with TACE at baseline (D-1 before TACE), D+2 and at 1-month evaluation (M1). Circulating total DNA (ctotDNA) was quantified by a fluorimetric method and circulating tumor DNA (ctumDNA) by a Digital PCR method (dPCR) (Qx200® ddPCR system, Bio-Rad) targeting recurrent TERT mutations (c.228 C> T and c.250 C> T) reported in approximately 50% of HCC. Spiral computed tomography/magnetic resonance imaging were centrally reviewed by an expert radiologist blindly to biological results. The main objective was to explore the variation of cDNA (ctotDNA and ctumDNA) around the TACE procedure. The secondary objectives were to evaluate the correlation between these variations and tumor response (according to the mRECIST criteria (complete response (CR) vs partial response (RP), stability (S) and progression (P)) as well as with the progression-free survival (PFS).

Results:
A total of thirty-eight patients was included from March 2018 to March 2019 with a median follow-up of 9.1 months. At M + 1, 15/38 (39.5%) patients had CR, 16/38 (42.1%) PR, 6/38 (15.8%) S and 1/38 (2.6%) P. The median PFS was 5.9 months. The mean levels of ctotDNA were 26.0, 160.5 and 40.4 ng/ml at baseline, D+2 and M1, respectively. A significant variation was observed between baseline vs D+2 (p < 0.0001) and D+2 vs M+1 (p < 0.0001). A circulating TERT mutation was detected at baseline in 20/38 (52.6%) patients (mutation c.228C>T; n=17/20 (85%) and c.250 C>T; n=3/20 (15 %)), 19/38 (50%) at D+2 and 11/38 (32.3%) at M+1. The mean allelic frequency of ctumDNA was 0.70% at D-1, 8.83% at D+2 and 0.34% at M+1. A significant variation was present between baseline vs D+2 (p = 0.0002) and D+2 vs M+1 (p = 0.0003). No significant association was observed between ctotDNA and ctumDNA values at the different times as well as their variations with the response at M+1. The ctumDNA detection at M+1 and the ctumDNA increase between baseline and M+1 were significantly associated with worse PFS (median PFS = 3.2 vs 8.9 months, p = 0.04 and 1.3 vs 10.1 months, p = 0.05, respectively).

Conclusion:
Our results suggest that there are significant variations of ctotDNA and ctumDNA following the TACE procedure. ctumDNA detection at M+1 is significantly associated with worse PFS. Analysis of these biomarkers detection at M+1 is significantly associated with worse PFS. Analysis of these biomarkers should prospectively be evaluated to define the treatment strategy beyond the first TACE.