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Efficacy and safety of combined sequential treatment with radiofrequency ablation and sorafenib in patients with hepatocellular carcinoma in intermediate stage ineligible for tace: a prospective randomized open study

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Introduction: TACE is considered the gold standard for patients (pts) with Hepatocellular Carcinoma in Intermediate Stage (BCLC-B HCC). Pts with contraindications or ineligible for TACE are candidates for Sorafenib (S). Aim of the present study is to verify efficacy and safety of a combined treatment Radiofrequency Ablation (RFA)and S in pts with BCLC-B HCC ineligible for TACE. Primary Endpoint: Overall Survival in both groups. Secondary Endpoints: validation of CEUS for evaluation of RFA efficacy; safety and efficacy of combined RFA+S.

Methods: A prospective randomized open-label study is expected to enroll during 12 months 124 pts with BCLC-B HCC (3-5 HCCs nodules \geq 3cm \leq 5 cm), not eligible for TACE or who refused TACE. Pts will be randomized 1:1 into two arms: Group A: S 400 mg bid; Group B: combined sequential treatment RFA+S. In Group B S will be administered for 2 weeks; then S will be stopped from 15th to 19th day to perform RFA scheduled on day 17. CEUS to assess the extent of necrosis and biochemical tests will be performed 24 hours after RFA. In case of complete necrosis, pts will re-take S 2 days after the RFA and will be followed-up. In case of incomplete necrosis, 2 days after RFA, pts will start again S at full dosage for 11 days, then drug will be stopped 2 days before the 2th RFA and resumed 2 days after procedure (up to 3 sessions of RFA; up to 2 nodules or a single nodule up to 5 cm, for session). Seven days after the last RFA therapeutic efficacy will be evaluated with CEUS and three-phase contrast-enhanced (CE- CT). Fig.1 shows the follow-up flow-chart .

Results: From December 2014 up to March 2015, 18 pts for group were enrolled. To date, statistical evaluation in terms of survival, safety and efficacy of treatment in the 2 group is impossible due to the too small sample size and the short time of observation.

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Morphofunctional Inactivation of Jurkat T-cells by the Titanium Oxides Coating

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We have examined response of human leukemic T-lymphoblastoid cells (Jurkat T-cells) to 24-h in vitro cultivation with titanium substrates (12*12*1 mm³) covered by titanium oxides (TiO, TiO₂) bilateral coating was prepared by microarc method from an aqueous solution of 20 mass % orthophosphoric acid. 27-98 % of immortalized cells had CD3+CD4+CD71+CD45RA+ immunophenotype and secreted IL-2, IL-4, IL-8, IL-10 and TNF α , but not IL-1b and IL-6. Other cell markers (CD8, CD16, CD56, CD25, CD95) were found at 0 - 2.5% of the cell population. Jurkat T-cells contact with titanium oxides coating reduced statistically CD3, CD4, CD8 and CD95 membrane markers presentation and decreased IL-4 and TNF α secretion. Structural (antigens expression) and functional (cytokines secretion) inactivation of Jurkat T-cells was not connected with the generation of intracellular reactive oxygen species (ROS), and was not mediated by TiO₂ nanoparticles (diameter of 14±8 nm; doses of 1 mg/L or 10 mg/L). Spearman's correlation analysis showed the inhibiting action of the oxide surface roughness in the range of Ra=2.2-3.7 μ m on the number of viable Jurkat T-cells (rs = - 0.95; n=9; p<0.0001) due to an elevating portion of necrotic forms in the cellular population, mainly. In turn, magnitude of negative electrostatic potential of the oxide surface rose linearly (r = 0.6; p<0.000001, n=60) with the Ra roughness index. The roughness of the titanium oxides coating induces its surface voltage that seems to promote morphofunctional suppression of tumor immune cells by electrostatic/biological mechanisms are not connected with intracellular ROS generation.

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