OFFICIAL TITLE OF THE STUDY:

A SINGLE CENTER EXPERIENCE: SAFETY AND EFFICACY OF DEB-TACE PERFORMED WITH A NOVEL REFLUX-CONTROL MICROCATHETER IN PATIENTS WITH EARLY AND INTERMEDIATE HCC.

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BACKGROUND:

Hepatocellular carcinoma is the fifth most frequent cancer in the world, with a diagnosis of more than 500,000 new cases per year. It is considered the third leading cause of cancer mortality and presents well-defined risk factors. Liver cirrhosis is the main risk factor for developing HCC, therefore screening programs in cirrhotic patients will allow the early diagnosis of this neoplasia. Despite this, most HCCs are diagnosed at a stage in which the application of curative therapies is no longer possible.

Hepatic transarterial chemoembolization (TACE) belongs to the arterially directed embolization therapies for the treatment of unresectable early-to-advanced hepatocellular carcinoma (HCC). It is the only therapy that has shown to improve survival in intermediate-stage HCC.
Drug-eluting beads (DEB)-TACE has shown to provide slow drug elution, reduced liver and systemic toxicity, increased local drug concentration, and tissue necrosis.
Aside from TACE, other transarterial options include bland embolization, or hepatic artery embolization (HAE), and transarterial radioembolization (TARE). All have an acceptable safety profile, and each has its associated procedural and peri-procedural complications. One potential complication that may occur during all embolization procedures is when the embolic material migrates outside of the desired treatment area, leading to non-target embolization (NTE). In fact, when collateral vessels are embolized, there is a risk that these may be feeders of non-target tissue or organs. NTE following TACE in particular may lead to a double-layer problem: dangerous components affecting healthy tissue, one ischemic and one related to cytotoxicity from the chemotherapeutic agent, which may have clinical consequences, and potential incomplete treatment of the lesion (due to beads being "deviated" from target).

NTE is highly recognized, but often thought to be uncommon, and although different complications can be caused by it, there may appear to be no evidence of NTE during the intraprocedural imaging.
To avoid the complications due to NTE, apart from the importance of the pre, intra and post-procedural imaging, and the thorough study of the anatomical picture, the catheters/microcatheters should also be chosen with reason and care. In particular, selective catheterization should be achieved by placing the microcatheter tip as close as possible to the target, through the specific branch/branches supplying it.
However, even with the microcatheter selectively positioned in the vessel to be embolized, the risk of NTE might not be eliminated, since it could happen as a result of changes in flow dynamics that occur during embolization, particularly when the endpoint is stasis. These changes could result in reflux into non-target territories and, as such, might be better prevented with the use of microcatheters intended to reduce reflux. To this purpose, the use of a dedicated delivery device should be taken into consideration, in order to optimize and save time during the procedure.

Microcatheters are commonly used during most arterial embolization procedures, and as explained above, there is a strong rationale to use a reflux-control microcatheter – like SEQURE® (Guerbet, Roissy-France) – for DEB-TACE.

The main expectation is to achieve technical success with SEQURE ® in all patients with a reachable target lesion, with the intent not only to minimize potential damage to surrounding tissue, but also to potentially deliver more treatment embolics, as all the beads are (re)directed towards the target.
The use of small diameter particles (100 micron-TANDEM ® spheres- Varian Medical Devices, Palo Alto, CA, US), induces superior tumor necrosis response (*Urbano et al.*, European Journal of Radiology, 2020); with the synergistic effect of being administered through the SEQURE anti-reflux protection system, there is reason to believe that it will be possible to administer maximum doses of doxorubicin, while avoiding the occlusion of non-target arterial segments (SYNERGIC EFFECT).

STUDY PROPOSAL:

Investigators propose a prospective observational study with data collection from a single center (Virgen de las Nieves University Hospital-Granada), for a period that ranges October 2020-December 2021. Here summarized the inclusion criteria and contraindications:

Inclusion criteria

- BCLC B and or some case BCLC A
- Both genders
- Over 18 years.
- Bilirubin less than 3 gr/dl.
- No contraindications to the use of iodinated contrast
- Absence of chronic kidney disease
- ECOG 0-1.
- Absence of encephalopathy.
- Informed consent.

Contraindications

- Advanced liver disease.
- Thrombosis or reversal of portal flow.
- Vascular invasion.
- Extrahepatic spread.
- Contraindication to administration of cytostatics.
- Contraindication to angiographic procedure.

HYPOTHESIS:
The use of 100 micron-TANDEM ® spheres will be studied with the synergistic effect of being administered through SEQURE® microcatheter anti-reflux protection system, which may allow the administration of the maximum doses of doxorubicin, avoiding the undesired occlussion of collateral arterial segments (SYNERGIC EFFECT). Other variables to study are: access route, procedural time and fluoroscopy time.

The information will be collected through the electronic database of the patient (includes laboratory data). Patients will be evaluated starting from the date of inclusion as candidates for TACE treatment, and followed up for 6 months (unless patients are lost to clinical follow-up or death occurs). Mortality data are obtainable by searching the electronic history of the patient.
Changes in the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphatase (ALP), bilirubin, albumin and patients' complete hematological profile, as well as serum lipase and amylase levels within the 1st week post-TACE to detect pancreatitis, will be evaluated at the following time-points: pre-embolization, at one month, three months, and six months. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) with contrast will be performed at the same time-points as just indicated; modified Response Evaluation Criteria in Solid Tumors (m-RECIST) will be used, and images will be assessed by two experienced radiologists (any discordant interpretation will be solved through team consensus). All serologic toxicities would be classified according to common terminology criteria for adverse effects. On this scale, severe hepato-toxicity (grade 3) is classified as the increase of up to 5 times the normal limit of AST, ALT, FA or the increase of bilirubin level to over 3 g/dl.

PATIENT SELECTION:

Between October 2020 and December 2021, and expected number of 30 patients will be treated. The diagnosis of Hepatocellular carcinoma (HCC) will confirm in accordance with the American Association for the Study of Liver Diseases guidelines and HCC staged according to Barcelona Clinic Liver Cancer (BCLC) system.

DEB-TACE is indicated according to clinical practice guidelines referred above.

TECHNICAL PROCEDURE:

The embolization will be performed using TANDEM ® spheres (each cc of spheres can be loaded with up to 50 mg of doxorubicin. The maximum dose of doxorubicin used per procedure was 150 mg, corresponding to 3 cc of spheres) and SEQURE ® microcatheter in a super-selective tumour´s arterial position avoiding undesired arterial branches. The procedure will consider super-selective when the micro-catheter tip reached the tumour feeding artery. Each cc of microspheres will mix with 7-10 cc of non-ionic contrast medium. Embolization endpoint is considered vascular stasis or 150 mg of Doxorubin administered.

OBJECTIVES AND END-POINTS:

Efficacy:

- Technical success will be defined as a composite outcome measurement: ability to place the microcatheter inside the required vascular segment and qualitative assessment of microspheres deposition in the target tumour.

- Time to Progression (TTP) [Time Frame: 6 months]. Time at which progression is first observed in a tumor assessment according to mRECIST as assessed by CT or MRI.

- Objective Response Rate (ORR) and Disease Control Rate (DCR) [Time Frame: Assessed at 1, 3, and 6 months after first treatment]. ORR is defined as a complete or partial response among the total number of cases and DCR is defined as a complete, partial response or stable disease among the total number of cases , according to mRECIST evaluated by CT or MRI. Time to retreatment included as consequential secondary objective.

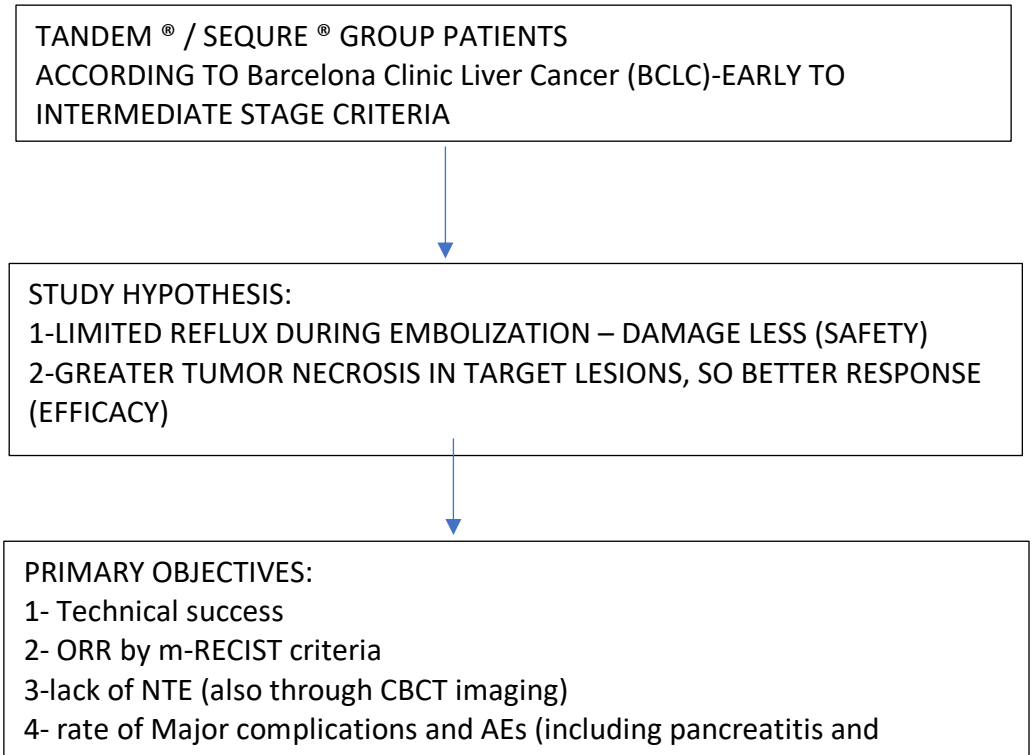
Safety:

- Adverse Events (AEs) and Serious Adverse Events (SAE) [Time Frame: Assessed at 1, 3, and 6 months after first treatment. The incidence of emerging AE and SAE will be summarized according to standardized qualification criteria [Journal of Vascular Interventional Radiology (JVIR) SAE], including pancreatitis, cholecystitis, clinical presentations, postembolization syndrome (PES), etc.

- Non Target embolization (NTE) by thorough angiographic assessment of the whole liver vasculature after TACE, as well as Cone Beam Computed Tomography (CBCT) **performed immediately following embolization (within 30 minutes from the end of procedure) to evaluate off-target distribution.**

- Health-Related Quality of Life questionary (HRQOL): pre-treatment and post-treatment quality of life assessment using the specific questionnaire for functional assessment for cancer treatment (FACT-G).

Study flowchart



SECONDARY OBJECTIVES:
1-TTP
2-HRQOL
3-Time to retreatment

DEB-TACE PROCEDURES:

The embolization will be performed according to routine clinical practice, with drug-eluting microspheres (100-micron TANDEM ® spheres), pre-loaded with 50 mg doxorubicin per ml (1 syringes of 3 ml). Injection will be according to manufaturer recommendations, with a selective or superselective approach depending on lesion and feeder localization.

RECIST	mRECIST for HCC
CR = Disappearance of all target lesions	CR = Disappearance of any intratumoral arterial enhancement in all target lesions
PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD = Any cases that do not qualify for either partial response or progressive disease	SD = Any cases that do not qualify for either partial response or progressive disease
PD = An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD = An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.