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DEBDOX Protocol

Observational Prospective Study on Chemoembolization Using Doxorubicin Drug-eluting Bead in Patients With Unresectable Hepatocellular Carcinoma

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1. Background

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer in men and the seventh in women and is the third most common cause of death from cancer worldwide [<http://globocan.iarc.fr>]. The overall incidence of HCC remains high in developing countries and is steadily rising in most industrialized countries [Shariff MI et al., 2009].

In unresectable hepatocellular carcinoma, transcatheter arterial chemoembolization (TACE) using Lipiodol/anti cancer agent emulsion is the standard treatment and reported as a significantly better treatment through randomized comparison study like Llovet, etc. than conservative treatment. Recently, doctors do transarterial chemoembolization with drug-eluting bead, and it is proved to induce less side effect and better efficacy.

TACE is a new method in terms of response in the treatment of hepatocellular carcinoma (HCC), and is widely performed in 32% of patients with unresectable HCC at initial diagnosis and in 58% of those with recurrent HCC. It appears, moreover, to be particularly useful if carried out with new embolization materials, such as doxorubicin.

Doxorubicin-eluting bead TACE (DEB-TACE) has recently been developed as a novel therapy option for HCC. In order to maximize its therapeutic efficacy, doxorubicin-loaded drug-eluting beads have been developed to deliver higher doses of the chemotherapeutic agent and to prolong contact time with the tumor. The comparison of efficacy and safety of drug-eluting bead (DC bead®) TACE in comparison with conventional TACE (cTACE) showed that response in the DC bead® group was significantly higher than that of the cTACE group ($p < 0.001$). The time to progression was significantly better in the DC bead® group than in the cTACE group (11.7 and 7.6 months, respectively, $p = 0.018$). Subgroup analysis showed that in intermediate-stage HCC, DC bead® treatment resulted in a significantly better treatment response and longer time to progression than cTACE ($p < 0.001$ and 0.038, respectively). There was no significant difference in hepatic treatment-related toxicities. DC bead® TACE thus appears to be a feasible and promising approach to the treatment of HCC. (Song 2012)

We have been using this method from 2006 and now we want to collect data on time to progression and tolerability. This study's purpose is evaluating treatment efficacy, survival rate and safety of DEB-TACE using doxorubicin for unresectable hepatocellular carcinoma.

Study Design and Objectives

2.1 Study Design: Prospective observational study .

Primary objective: To collect data on tumor response after administration of Dc-Beads microspheres preloaded with Doxorubicin.

2.2 Secondary objectives: To collect data on survival rate, time to progression, tolerability of treatment, number of treatment required to achieve objective response and improvement of quality of life (Edmonton Symptom Assessment System (ESAS)) [16].

3. Patient selection

3.1 Inclusion criteria

1. Patients with confirmed diagnosis of HCC
2. Patient with HCC not suitable for radical therapies such as resection, liver transplantation or percutaneous therapies or patient is indicated for these therapies but there is a contraindication for them or patient himself rejects above treatments and wants to do TACE (Indication for hepatectomy, liver transplantation, local ablation is decided by doctors of each center)
3. Multinodular or single nodular tumor over 5cm, (In the case of single nodule less than 5cm, if curative treatment is contraindicated or the patient rejects curative treatment)
4. Hypervascular lesion showing contrast enhancement in the early stage at the contrast media bolus injection CT or MRI.
5. At least one uni-dimensional lesion measurable according to the Modified RECIST criteria by CT-scan or MRI
6. No invasion in the blood vessel (hepatic portal, hepatic vein) or bile duct by the CT or MR
7. Eastern Cooperative Oncology Group performance status is 0 - 1
8. Proper blood, liver, renal, heart function
9. more than 18 years old
10. Expected survival more than 6 months
11. Prior written patient consent

3.2 Exclusion criteria

1. Extrahepatic metastasis (Any lymph nodes measuring ≥ 10 mm along the short axis)
2. Tumor burden involving more than 50% of the liver
3. History of biliary tract repair or endoscopic biliary tract treatment
4. Clinically important refractory ascites or pleural fluid
5. Any contraindications for hepatic embolization procedures
6. Any contraindication for doxorubicin administration

7. Contrast media allergy contraindicating angiography
8. Acute or active cardiac, hepatic or renal diseases
9. Pregnant, nursing or childbearing age women and men who are sexually active and don't want to or can't do contraception

4. Clinical staging

4.1 Examinations foreseen for staging and re-assessment

- physical examination
- chest-abdomen CAT scan with and without contrast medium, based on the following specifications:

64-slice Multidetector CAT scan

Acquisition phase	Contrast medium bolus	Thickness	Increment	Delay
Arterial	100-130 ml	2 mm	1 mm	Bolus track
Portal		2 mm	1 mm	40-50''

- standard laboratory tests (complete hemochrome, hepatic and renal function)
- cancer markers (CEA, CA 19.9)

Other examinations may be carried out at the discretion of the investigator.

All baseline evaluations must be performed as close as possible to the date of initiation of treatment, and in any case no earlier than 4 weeks previously.

Re-assessment will be performed on Day 30, Day 90 and Day 120 from the start of treatment by repeating the CAT scan as well as any other examination returned positive during the staging process (20-23),

5. Treatment modalities

Day -1 Doxorubicin at a dose of 35/50 mg/m² has been charged onto 2 ml of 70-150 µm M1 microspheres at Pharmacy. It is suggested to dissolve Doxorubicin powder with 2 ml of contrast medium. The charging time of Dc-Beads is at least 30 minutes.

Day 0: prehydration, antibiotic prophylaxis and setting up of a therapeutic scheme appropriate for analgesic prophylaxis (3-day duration) as previously reported (17)

Day +1:

- Upon admittance to the radiology room, 1 vial of tropisetron (diluted in 100ml of physiological solution) and 1 vial of morphine hydrochloride diluted in 100 ml i.v. are administered by slow drip.
- One vial of morphine hydrochloride diluted in 100 ml i.v. to be repeated one hour after the procedure and if necessary also after 6 hours.
- Tropisetron i.v. if needed.

- Intra-arterial premedication (optional) with 1 vial of verapamil diluted in 4 ml of normal saline solution followed by 4 ml of lidocaine.
- Tumor Infusion (segment/s with dominant disease) of Doxorubicin at a dose of 35/50 mg/m² preloaded into 2 ml of 70-150 µm M1 microspheres.
- A second tumor infusion is allowed if other lesions are present (daughter tumor), using Doxorubicin at a dose of 35/50 mg/m² preloaded into 2 ml of 70-150 µm M1 microspheres (following radiologist and oncologist ' s planning of cure).

Day +30: The above procedure is repeated.

Day +90: In case of response, a third administration following the above procedures will be repeated

6. Toxicity

Most common adverse events associated with Doxorubicin are the following: congestive heart failure (CHF), acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS), fever, asthenia, nausea, vomiting, neutropenia, thrombocytopenia.

7. Evaluation of response

Response must be assessed by repeating the following examinations, at Day 30, Day 90 and Day 120 after start of treatment:

- Chest-abdomen CAT scan with and without contrast medium (refer to Section 4).
Evaluation will be based on RECIST criteria [18-22]
- cancer markers (CEA, CA 19.9)

8. Assessment of quality of life

The Edmonton Symptom Assessment System (ESAS) is used to monitor health conditions and quality of life.

The questionnaire must be filled in by the patient unaided by family members or by health care personnel, over a period of about 15 minutes. Assessment of quality of life will be performed during the baseline visit and at Day 30, Day 60 and Day 120 from start of treatment.

It is important for the questionnaire to be completed by the patient before undergoing the physical examination, in other words before discussing with the physician about any examinations, which might give an indication of the favorable or unfavorable course of the disease. In providing the questionnaire to the patient, the physician will explain how to complete it without discussing the contents of the questions, and once the patient has completed the questionnaire, the physician will check that all questions have been answered.

9. Statistical analysis

Assuming as a negative result (p_0) a 50% rate of subjects with no evidence of progression (or with controlled disease) at Month 4 and as favorable and desirable result (p_1) a 70% rate of subjects without any evidence of progression at Month 4 (increase versus standard of an absolute rate of 20%) having established that $\alpha=10\%$ and $\beta=10\%$ (appropriate for a phase II study), the sample size for the study is established as follows, based on the two-step Simon model (Minimax method):

Step 1: 23 patients are recruited; if at Month 4 only 11 or less patients are free from progression, recruitment is to be discontinued based on sufficient evidence of non-efficacy; if at Month 4 more than 11 subjects are still free from progression, continue to Step 2.

Step 2: further 16 patients will be recruited, reaching an overall number of 39 patients; if at Month 4 more than 23 out of the 39 patients are still free from progression, it may be concluded that the treatment is effective and that therefore further investigation is warranted.

10. Inclusion into the study

Patients will be adequately informed and will sign a written informed consent.

Patients will receive treatment with Dc-Beads at the Unit of Interventional Radiology of the IGEVO Hospitals.

11. Insurance coverage

this is an observational study, no insurance coverage for compensation of any damages incurred by subjects due to study-related activities is required, since there are no experimental procedures involved.

12. Administrative Procedures

The drugs foreseen by the study protocol will be used in accordance with the indications listed in the summary of product characteristics. This is an observational study, therefore, the drugs will be dispensed by the National health System. As regards administration of drugs and monitoring of treatment, such procedures are part of normal clinical practice and no additional costs are therefore foreseen.

Bibliography

1. Gao S, Yang Z, Zheng Z, Yao J, Deng M, Xie H, Zheng S, Zhou L. Doxorubicin-Eluting Bead versus Conventional TACE for Unresectable Hepatocellular Carcinoma: A Meta-Analysis. *Hepatogastroenterology*. 2013 Jan 3;60(126). doi: 10.5754/hge121025. [Epub ahead of print]
2. Takayasu K. Transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: recent progression and perspective. *Oncology*. 2013;84 Suppl 1:28-33. doi: 10.1159/000345886. Epub 2013 Feb 20.
3. Cotoi CG, Khorsandi SE, Pleşea IE, Quaglia A. Histological aspects of post-TACE hepatocellular carcinoma. *Rom J Morphol Embryol*. 2012;53(3 Suppl):677-82.
4. Song MJ, Chun HJ, Song do S, Kim HY, Yoo SH, Park CH, Bae SH, Choi JY, Chang UI, Yang JM, Lee HG, Yoon SK. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Hepatol*. 2012 Dec;57(6):1244-50. doi: 10.1016/j.jhep.2012.07.017. Epub 2012 Jul 20.
5. Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocellular carcinoma (HCC). *J Surg Oncol*. 2010 May 1;101(6):476-80.
6. Malagari K, Pomoni M, Kelekis A, Pomoni A, Dourakis S, Spyridopoulos T, Moschouris H, Emmanouil E, Rizos S, Kelekis D. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol*. 2010 Jun;33(3):541-51. Epub 2009 Nov 24.
7. Malagari K, Pomoni M, Spyridopoulos TN, Moschouris H, Kelekis A, Dourakis S, Alexopoulou E, Koskinas J, Angelopoulos M, Kornezos J, Pomoni A, Tandeles S, Marinis A, Rizos S, Kelekis D. Safety Profile of Sequential Transcatheter Chemoembolization with DC Bead(™): Results of 237 Hepatocellular Carcinoma (HCC) Patients. *Cardiovasc Intervent Radiol*. 2010 Dec 24; [Epub ahead of print]
8. Nicolini A, Martinetti L, Crespi S, Maggioni M, Sangiovanni A. Transarterial chemoembolization with epirubicin-eluting beads versus transarterial embolization before liver transplantation for hepatocellular carcinoma. *J Vasc Interv Radiol*. 2010 Mar;21(3):327-32. Epub 2010 Jan 22.

9. Poon RT, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, Fan ST. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. *Clin Gastroenterol Hepatol*. 2007 Sep;5(9):1100-8. Epub 2007 Jul 12.
10. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R; PRECISION V Investigators. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol*. 2010 Feb;33(1):41-52. Epub 2009 Nov 12.
11. Takayasu K, Arai S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology*. 2006 Aug;131(2):461-9.
12. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ; Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst*. 2008 May 21;100(10):698-711. Epub 2008 May 13. Review.
13. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005 Nov;42(5):1208-36. No abstract available.
14. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol*. 2007 Mar;46(3):474-81. Epub 2006 Nov 29.
15. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Sola R, Rodes J, Bruix J; Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002 May 18;359(9319):1734-9.
16. Bagha SM, Macedo A, Jacks LM, Lo C, Zimmermann C, Rodin G, Li M. The utility of the Edmonton Symptom Assessment System in screening for anxiety and

- depression. *Eur J Cancer Care (Engl)*. 2013 Jan;22(1):60-9.
- 17.** Fiorentini G, Aliberti C, Benea G, Montagnani F, Mambrini A, Ballardini PL, Cantore M: TACE of liver metastases from colorectal cancer adopting irinotecan-eluting beads: beneficial effect of palliative intra-arterial lidocaine and post-procedure supportive therapy on the control of side effects. *Hepatogastroenterology* 55(88):2077-82,2008.
- 18.** Miller AB, Hoogstraten B, Staquet M et al. Reporting results of cancer treatment. *Cancer* 1981; 47 (1): 207-14
- 19.** Brown DB, Gould JE, Gervais DA, Goldberg SN, Murthy R, Millward SF, Rilling WS, Geschwind JF, Salem R, Vedantham S, Cardella JF, Soulen MC: Transcatheter therapy for hepatic malignancy: standardization of terminology and reporting criteria. *J Vasc Interv Radiol* 20(7 Suppl):S425-34,2009.
- 20.** Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216,2000.
- 21.** Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, Benjamin RS: Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 25:1753-1759,2007.
- 22.** Common Terminology Criteria for Adverse Events v3.0 (CTCAE). August 9, 2006. <http://ctep.cancer.gov/CTCAEv3>

Appendice 1 - Criteri RECIST

Measurable lesion	Longest diameter \geq 20 mm, using conventional techniques or \geq 10 mm using spiral CAT scan or MRI.
Non-measurable lesions	Longest diameter < 20 mm or < 10 mm (depending on the method used) and all bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, previously irradiated lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total per single patient, chosen as being representative of all involved organs. Lesions chosen based on dimension of longest diameter and the expected possibility of subsequent evaluations; the sum of the longest diameters of all target lesions recorded at baseline will be used as reference for subsequent re-evaluations
Non target lesions	All other lesions or sites of diseases identified during the baseline visit. Measurements of these lesions are not required but the presence/absence should be reported during follow-up.

Lesioni target – Definition of objective response

CR	Complete response	Disappearance of all target lesions, confirmed by 2 separate evaluations with an interval of at least 4 weeks; no appearance of new lesions
PR	Partial response	At least 30% reduction in the sum of the longest diameter of target lesions, versus the baseline value, confirmed by 2 separate evaluations with an interval of at least 4 weeks. No appearance of new lesions.
PD	Progressive Disease	At least 20% increase in the sum of the longest diameter of target lesions versus the smallest sum of the diameters recorded ever since treatment started or appearance of new lesions
SD	Stable Disease	All cases that cannot be defined as CR, PR or PD, confirmed by 2 separate evaluations with an interval of at least 6-8 weeks

Non target lesions – Definition of objective response

Complete response	Disappearance of non target lesions and normalization of cancer markers, confirmed by 2 separate evaluations with an interval of at least 4 weeks. No appearance of new lesions.
Incomplete response or stable disease	Persistence of one or more non target lesions and/or persistence of high cancer markers levels
Progression	Appearance of one or more lesions and/or unequivocal progression of existing non target lesions

Overall response

Lesions			Global response
Target	Non target	New	
CR	CR	no	CR
CR	Non PD	no	PR
PR	Non PD	no	PR
SD	Non PD	no	SD
PD	any	Yes/no	PD
any	PD	Yes/no	PD
any	any	yes	PD

Best response: The response recorded and confirmed by the subsequent measurements since treatment started up to recurrence of progression of disease.

Duration of response: From the time when all measurement criteria allow to define CR or PR until the first date when PD or recurrence of diseases is objectively documented.

Duration of stable disease: Measured from the time when treatment started.