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CHOLANGIO Protocol

International Registry on Cholangiocarcinoma treatment

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1. Background

Cholangiocarcinoma is a rare and very aggressive neoplasm that arises from the biliary epithelium, constitutes approximately 2% of all reported cancer, and accounts for about 3% of all gastrointestinal malignancies (1). Up to date, there are many modalities to diagnosis and treat with a range of sensitivity and specificity, and also the advantage and disadvantage of its modality. As physicians, we should be able to assess and choose promptly which modality is best for our patient, even for paliative care. Treatment modalities are surgery and non-surgery like adjuvant chemotherapy, radiation, chemoradiation, radiotherapy, TACE, intra-arterial chemoinfusion, intralesional PEI, photodynamic therapy, liver transplantation, and palliative therapy (1). The choice of treatment varies individually.

Cholangiocarcinoma has a poor prognosis. Surgical resection offers the only curative option and usually requires a major hepatic resection in addition to resection of the cholangiocarcinoma (2). Unfortunately, curative resection is possible in only about 30% of patients due to locally advanced disease, distant metastases or comorbidity in elderly patients (2). Even after resection, the recurrence rate is approximately 60%, resulting in a low 5-year overall survival (OS).

Patients with intra-hepatic Cholangiocarcinoma (ICC) have a very limited benefit from systemic chemotherapy, indeed, in unresectable cholangiocarcinoma OS with systemic chemotherapy is less than 1 year (2). Since most cholangiocarcinoma patients develop distant metastases at late stages only, locoregional therapy is an interesting therapeutic strategy.

Locoregional therapy studies in patients with intrahepatic cholangiocarcinoma employing radiofrequency ablation (RFA), transarterial chemoembolization (TACE) or external as well as internal radiation therapy yielded promising results in the last couple of years (3-9).

Locoregional therapies have been shown to be effective in patients with ICC. TACE, moreover, is safe in patients with normal liver function, and results in a prolongation of progression free survival (PFS) and OS (10). Local tumour control may prolong OS and can be achieved by locoregional interventions applied either sequentially or in combination with systemic chemotherapies (11).

TACE is also used as postoperative adjuvant therapy for cholangiocarcinoma, resulting in prolonged survival in patients with tumour size ≥ 5 cm or advanced TNM stage (8, 12).

TACE offers also greater survival benefits than supportive treatment for the palliative treatment of unresectable ICC (13).

TACE is safe and may be effective for prolonging the survival of patients with nonresectable combined HCC-cholangiocarcinoma, as compared with the historically reported survivals of these patients. Tumor vascularity is highly associated with tumor response. The patient survival period after TACE for combined HCC-cholangiocarcinoma is significantly dependent on tumor size, tumor vascularity, Child-Pugh class, and presence or absence of portal vein invasion (14-16).

Currently, few centers perform TACE therapy for unresectable Cholangiocarcinoma. Several European studies have reported the efficacy and safety TACE for ICC.

The establishment of a registry to obtain the majority of Cholangiocarcinoma cases treated with locoregional approach within and outside Europe can help the investigators evaluate a larger and non-ambiguous sample population. This would help the investigators evaluate the technical success rates, clinical success rates, feasibility and safety of TACE for ICC.

All hospitals of IGEVO operating on patients with cholangiocarcinoma are eligible to take part in the Registry.

2. Study Design and Objectives

2.1 Study Design: Prospective observational study .

Primary objective: This is a data collection study where the main purpose is to collect information about the treatments that patients receive for their unresectable cholangiocarcinoma.

2.2 Secondary objectives: To create an international Registry including patients undergoing locoregional treatments, to correlate tumour characteristics with outcome, survival and prognosis; to identify criteria for guiding therapy including TACE, chemoinfusion and other locoregional treatments

3. Patient selection

3.1 Inclusion criteria

Inclusion Criteria:

1. The diagnosis of cholangiocarcinoma will be established preoperatively by at least one of the following criteria: a) positive brush cytology or biopsy result obtained at the time of cholangiography; b) Fluorescence in situ hybridization demonstrating aneuploidy; c) serum CA 19-9 value greater than 100 U/mL in the presence of a radiographically characteristic malignant stricture in the absence of cholangitis.
2. Tumor is above the cystic duct and is unresectable.
3. Patient is a suitable candidate for the study by a radiation oncologist, a medical oncologist, and the liver surgeon

4. Maximum Eastern Cooperative Oncology Group performance status of 2 and a minimum daily caloric intake of 1200kcal.
5. No evidence of metastatic disease.
6. Between ages 18 - 75.
7. Patient must provide written informed consent.

3.2 Exclusion Criteria:

1. Patients with intrahepatic metastasis presenting liver involvement more than 75%
2. Patients with uncontrolled infections (sepsis)
3. Evidence of extrahepatic disease, including local lymph node metastasis (except perihilar nodes).
4. History of another malignancy diagnosed within 5 years, excluding "in situ" skin and cervical cancers, without metastases.

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 blood count, 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 for TACE

5.1 Day -1 Doxorubicina 50-75 mg/mq has been charged onto 2 ml of 70-150 µm M1 microspheres at Pharmacy.

Day -1 : prehydration, antibiotic prophylaxis and setting up of a therapeutic scheme appropriate for analgesic prophylaxis (3-day duration) as previously reported (25) *1 vial of tropisetron (diluted in 100ml of physiological solution) administered by slow drip*

Day 0: Upon admittance to the radiology room, the patient receive morphine hydrochloride 10 mgr diluted in 100 ml of salin solution 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 with 2.5 mgr of verapamil 2.5 mgr diluted in 4 ml of normal saline solution followed by 4 ml of lidocaine 2%.
- Selected arterial Infusion (considering tumor uptake and dominant disease) of doxorubicina 50-75 mg preloaded into 2 ml of 70-150 μ m M1 microspheres.
- Second infusion of doxorubicin at the same dose into 2 ml of 70-150 μ m M1 microspheres can be administered in a further TACE (following IR 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 and dose reduction

6.1 TACE

Most common adverse events associated with doxorubicin are the following: Fever, asthenia, nausea,vomiting,neutropenia, thrombocytopenia, anemia, alopecia, abdominal pain.

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 [20-24]
- 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 issues

We will use descriptive statistics to describe the characteristics of the enrolled population, both through qualitative and quantitative variables. There will not be statistical tests except to demonstrate the variability and trends of the response to treatment.

10. Inclusion into the study

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

Patients will receive treatment with conventional TACE, or TACE- Dc-Beads at the Unit of Interventional Radiology

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 Italian National Health Service. As regards administration of drugs and monitoring of treatment, such procedures are part of normal clinical practice and no additional costs are therefore foreseen.

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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.

Target lesion– 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.