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TACETUX Protocol

Observational Study on Second line treatment of hepatic metastases from colorectal carcinoma in K-RAS wild type patients by hepatic intra-arterial chemoembolization with Dc Beads 70-150 μ m M1 microspheres preloaded with irinotecan 200 mgr plus systemic cetuximab

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1. Background

Colorectal malignancies represent one of the main health care issues/leading cancer diseases in developed countries. Despite screenings being performed to identify early stage disease, the incidence of patients presenting with advanced phase malignancy even at diagnosis still remains high. Radical surgery is possible in only 20% of patients with hepatic metastases.

Hepatic intra-arterial locoregional therapy using mainly FUDR has shown significant activity achieving response rates of about 45%, in unresectable hepatic metastases from colorectal cancer (CRC-LM) but the method of delivery and the use of implantable pumps resulted as cumbersome and not feasible in the vast majority of centers (1). New drugs such as Irinotecan and Oxaliplatin administered by intravenous infusion in combination with Fluorouracil and folinic acid, have been demonstrated to achieve interesting responses in approximately 40-50% [2-5]. The hepatic metabolism of irinotecan has been amply investigated and appears to be suitable for locoregional delivery [6-12]

Although metastases curability rates have improved in the past decade, patient treatment outcomes are still far from satisfactory. A proportion of patients does respond to new protocols however require a second and third line treatment because of recurrence or liver progression.

Drugs such as fluorouracil, Mitomycin-c, fluorodeoxyuridine, oxaliplatin and irinotecan are well known to produce novel responses when administered by locoregional intra-arterial delivery, thanks to the established pharmacological advantages that the hepatic circulatory-metabolic system offers to locoregional delivery versus systemic administration [13].

The recently introduced chemoembolization has been considered to be a very attractive new method in terms of response in the treatment of liver metastases from neuroendocrine tumors [14]. It appears to be particularly useful if carried out with the new embolization materials. An 80% response rate was reported using TACE with DC Beads loaded with 100 mgr of Irinotecan in patients with liver metastases from colon cancer pretreated with 2 or more lines of chemotherapy [15].

Intra-arterial administration of Irinotecan and the pharmacokinetic profile of the drug have been recently evaluated and there is evidence supporting its efficacy in terms of response and toxicity [16].

Fiorentini et al reported in 2012 a statistical significant advantage in term of survival, PFS and QoL in a randomized study comparing FOLFIRI vs DEBIRI (17).

Based on such observations and on the need to offer new therapeutic options to these patients, the use of DC-Bead microspheres preloaded with Irinotecan via locoregional delivery appears to be of great interest.

Based on a randomized, phase II clinical trial which demonstrated greater activity produced by a combination of Cetuximab and Irinotecan versus Cetuximab in monotherapy, the European Agency for the Evaluation of Medicinal Products (EMA) has granted authorization to the use of Cetuximab in association with irinotecan in the treatment of irinotecan-refractory CRC-LM [19]. We have been using this method from 2006 and now we want to collect data on time to progression and tolerability.

2. Study Design and Objectives

2.1 Study Design: Prospective observational study .

Primary objective: To collect data on time to progression (local and/or distant progression) after administration of Dc-Beads microspheres preloaded with Irinotecan 200 mgr via hepatic intra-arterial locoregional delivery (TACE) in/without association with standard weekly therapy with Cetuximab.

2.2 Secondary objectives: To collect data on tolerability of treatment and improvement of quality of life (Edmonton Symptom Assessment System (ESAS)) [19].

3. Patient selection

3.1 Inclusion criteria

1. Unresectable hepatic metastases from colorectal carcinoma (CRC-LM)
2. Progression of disease after first line therapy containing Irinotecan completed at least one month previously
3. PS 0-2
4. Biochemistry parameters within normal limits (ALT and gamma-GT not exceeding three times the upper limit of normal, total bilirubin not exceeding 2.5 mg/ml)
5. Adequate information and subsequent written informed consent
6. Life expectancy > 3 months
7. Patients K-RAS wild type

3.2 Exclusion criteria

1. Extension of disease greater than 50% of the parenchymal liver (confirmed by CAT scan or MRI)
2. Brain metastases
3. Severe and confirmed vascular diseases
4. Other concomitant malignancies except for cutaneous basal cell carcinoma or carcinoma in situ of the uterine cervix
5. Evidence of significant diseases such as uncontrolled diabetes, congestive heart failure, chronic renal insufficiency (CRI)
6. Known hypersensitivity reactions towards components of the study drugs
7. Pregnant or breastfeeding women or women of childbearing potential not making use of effective contraceptives
8. Family, psychological, social or geographical circumstances preventing the patient from undergoing follow-up and from complying with protocol procedures
9. Patients K-RAS mutant

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

This is an observational study and the treatment is related to the experiences and economical availability of each center. The study consists of :

Program A (for all patients)

5.1 Day -1 Irinotecan has been charged onto 2 ml of 70-150 μ m M1 microspheres at Pharmacy.

Day 0: 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 +1:

- 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%.
- Lobar Infusion (lobe with dominant disease) of Irinotecan 100 mg preloaded into 2 ml of 70-150 μ m M1 microspheres.
- Second lobar infusion of Irinotecan 100 mg preloaded into 2 ml of 70-150 μ m M1 microspheres can be administered at the same time controlaterally or 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

Program B (for Centers in which Cetuximab is available)

5.2 Cetuximab administered as per standard scheme:

Day -15: loading dose with 400 mg/mq i.v. over a 2-hour period

Day +21 and subsequent weekly administrations: 250 mg/mq i.v. over a one hour period.

It is pointed out that administration of Cetuximab will be continued following the timeline of the first infusion relative to the intra-arterial administration.

6. Toxicity and dose reduction

6.1 TACE

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

6.2 Cetuximab

6.2.1 Dose reduction in case of allergic/hypersensitivity reactions (NCI-CTCAE v3.0) [24].

| NCI classification of reaction | Treatment |
|---|---|
| Grade 1 Rash or transient flushing; fever < 38°C | Reduce by 50% Cetuximab infusion and closely monitor the patient to avoid any worsening. Total duration of weekly infusion must not exceed 240 minutes |
| Grade 2 Rash ; flushing ; urticaria; dyspnea ; fever ≥ 38°C | Discontinue Cetuximab infusion. Administer bronchodilators, oxygen, etc. as per normal clinical practice Resume infusion decreased by 50% once allergic/hypersensitivity reaction has resolved or is assessed to be a grade 1 reaction, and closely monitor the patient. |
| Grade 3 or Grade 4 Symptomatic bronchospasm, with or without urticaria; appropriate parenteral treatment, edema/angioedema correlated with allergic reaction; hypotension Anaphylaxis | Immediately discontinue cetuximab infusion and unhook the patient from the IV line. Administer epinephrine, bronchodilators, glycocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as per normal clinical practice The patient must immediately interrupt infusion and no further treatment with Cetuximab will be administered. |

6.2.2 Continuation of treatment after allergic/hypersensitivity reactions

Once the Cetuximab infusion has been reduced due to an allergic/hypersensitivity reaction, it is recommended to accordingly reduce all subsequent infusions. Should the patient experience a second allergic/hypersensitivity reaction during the reduced dose infusion, infusion must be interrupted and Cetuximab discontinued definitively. In case of grade 3 or 4 reactions, at any given time, Cetuximab must be definitively discontinued.

6.2.3 Cutaneous toxicity

- In case of grade 3 toxicity (NCI-CTCAE v3.0), therapy with Cetuximab may be postponed

for up to two consecutive infusions without changing the dose.

- In case of grade 1 or 2 acne, treatment with topical antibiotics (eg. benzoyl peroxide, erythromycin) or systemic antibiotics (oral tetracyclines such as doxycycline 100mg day) will be taken into consideration.
- For patients presenting with a reaction classified to be \geq grade 3, a dermatological consultation will be required. In case of itching, an oral antihistamine is recommended, while in case of cutaneous dryness, the patient will benefit from the use of emollient creams, and in case of cracked and chapped skin from the use of topical preparations.
- If after treatment, toxicity should resolve to grade 2 or less, therapy with Cetuximab may be resumed.
- After the second or third grade 3 cutaneous toxicity episode, therapy with Cetuximab may again be postponed for up to two consecutive weeks, while concomitantly reducing the dose to 200 mg/mq and 150 mg/mq, respectively.
- Cetuximab dose reductions are permanent. Patients will definitively discontinue treatment with Cetuximab in case therapy is postponed by more than two consecutive weeks or in case of a fourth episode of grade 3 cutaneous toxicity, despite the dose being appropriately reduced.
 - In any case, if the investigator feels it to be necessary to interrupt therapy with Cetuximab, the patient will be immediately withdrawn from the protocol.

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

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 and Cetuximab will be administered at the oncologic Day Hospital.

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.

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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. |

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.