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EURECA (European Research on Electrochemotherapy in head and neck Cancer) PROJECT

CLINICAL STUDY PROTOCOL

TITLE:
Local treatment of HN cancer by ECT.
Analysis of the efficacy of the procedure in tumor control and survival

COORDINATING INVESTIGATORS	M. Benazzo, G. Bertino, A. Occhini Dept. Of Otolaryngology Head Neck Surgery IRCCS S. Matteo Foundation University of Pavia V.le Golgi 19 27100 Pavia Italy Tel. +39 0382526218 Fax +39 0382528184 Email: m.benazzo@smatteo.pv.it

Confidential Statement

This protocol contains information that is property of the Department of Otolaryngology Head Neck Cancer – IRCCS Policlinico S. Matteo Foundation – University of Pavia, in the person of Prof. Marco Benazzo (Coordinating Investigator), and therefore is provided to you in confidence for review by you, your staff, and applicable ethics committee/institutional review board, and regulatory authorities. It is understood that this information will not be disclosed to others without the written approval from the Coordinating Investigator.

Data management: All the personal data will be property of the different centers and each center will be free to use them (presentation at Scientific Meetings, publication, etc.).

The data of each center will be inserted in the INSPECT database sofware. The access to the data of each center will be made possible only by means of a protection password.
A monitor will verify the completeness of the collected data. He will make a report of the data collection during each meeting of the European Working Group.

Each publication including all the data of the EURECA Project must contain all the names of the members of the European Working Group.

Any other new center that will participate to the EURECA Project will have to receive the approval by the European Working Group.

This study will be conducted in compliance with Good Clinical Practice and the Declaration of Helsinki (with amendements), in accordance with local legal and regulatory requirements and in compliance with the applicable parts of _____ Regulations

SYNOPSIS

TITLE	**Local treatment of HN cancer by ECT.** **Analysis of the efficacy of the procedure in tumor control and survival**
COORDINATING INVESTIGATORS	M. Benazzo, G. Bertino, A. Occhini Dept. Of Otolaryngology Head Neck Surgery IRCCS S. Matteo Foundation University of Pavia V.le Golgi 19 27100 Pavia Italy Tel. +39 0382526218 Fax +39 0382528184 Email: m.benazzo@smatteo.pv.it
DISEASE	Recurrent HN cancer (any type of histology). Standard treatment options must be offered to the patients Metastatic HN cancer. Standard treatment options must be offered to the patients Primary HN cancer (any type of histology) not eligible for surgery or radiotherapy because of patient's clinical condition or because of expectation of too large morbidity or patient's preference Primary HN cancer in patients who refuse any other kind of treatment
RATIONALE	Recurrent or primary extended neoplasms of the head and neck can be challenging for the surgeon and debilitating for the patient, especially when important anatomical structures are involved. Surgical treatment of these lesions could be disfiguring and followed by functional impairment. Moreover (chemo)radiotherapy can be associated with anatomical and functional complications. For these reasons therapies that preserve organ functionality in combination with effective local tumor control, like ECT, are therefore of great interest. ECT has proven to be effective in the treatment of tumors of the skin, subcutaneous and mucosal tissue. The main advantages of ECT include: - High success rate in local tumor control (74% complete regression, 11% partial response after 1 treatment) - Limited damage to healthy tissue thanks to the specificity of the procedure for the dividing tumor cells - Good cosmetic and functional results. In fact, surgery and radiotherapy could be associated with not only a scar, but also volume loss, retraction and other deformities, even for small tumors. ECT, by leaving the treated tissue in site for resorption by the body, without stroma and vascular destruction, allows progressive healing with limited compromise of aesthetics or loss of function. - Limited side effects - Advantageous cost/benefit ratio. The technology involved and the

	drug used do not require large investments. Furthermore the treatment can be completed under local or general anesthesia and may not require hospitalization. Usually only one session of treatment is required.
STUDY TYPE	Phase II observational study of intravenous administration of bleomycin combined with electroporation in patients with recurrent and/or metastatic HN cancer or HN cancer for which only regular treatment with extensive morbidity is available.
PRINCIPAL AIM	Evaluation of tumor response (only one target lesion)
SECONDARY AIMS	Safety (toxicity) of the procedure Analysis of overall and progression free survival PET-CT uptake change between pre treatment and 8 weeks post treatment "Quality of life" (EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D)
INCLUSION CRITERIA	1. Histologically verified cancer of any type 2. Progressive and/or metastatic disease 3. Primary disease not eligible for surgery for patient's general conditions or for the need of extensive surgery 4. Patients must have offered standard treatments 5. Measurable lesions suitable for application of electric pulses 6. Age> 18 yrs 7. Performance status (Karnofsky $\geq$ 70; WHO $\leq$ 2) 8. Life expectancy> 3 months 9. Treatment free interval of at least 4 weeks after previously applied chemo- or radiotherapy to the target lesions 10. Patients must be mentally capable of understanding the information given and sign informed consent
EXCLUSION CRITERIA	1. Other symptomatic lesions not under control 2. Lesions not suitable for ECT (bony invasion, large vessels infiltration, etc.) 3. Acute lung infection 4. Symptoms of poor lung function necessitates DLCO and patient can not be treated if this is abnormal 5. Severe coagulation disorders not correctable 6. Previous allergic reactions to bleomycin 7. If cumulative dose of 240000 IU BLM/m^2 was previously exceeded 8. Chronic renal dysfunction (creatinine > 150 µmol/L) 9. Pregnancy or lactation
PRE-OPERATIVE EVALUTATION	1. CT and/or MRI for tumor staging 2. Identification of the target lesion 3. PET-CT 4. Photographic documentation of the lesions 5. QOL assessments
PROCEDURE	Intravenous administration of 15000 IU BLM/m^2 within 1 min After 8 min electroporation of the lesion with a 1 cm of safe margin Procedure has to be finished within 30 min Description of the electrodes used (data of the Cliniporator)
POST-OPERATIVE EVALUATION	Diary pain VAS during hospitalization and at every F-U visit Recording of the type of drugs used to control pain

	Recording of the duration of hospitalization
ASSESSMENT CRITERIA	**4 weeks after procedure** CT or MRI (same imaging as pre-operative evaluation) Evaluation of tumor response in accordance with RECIST criteria (version 1.1) Photographic documentation QOL assessments (EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D) In case of residual disease a second ECT can be considered (if residual disease after the 2nd ECT other treatment options must be considered). **8 weeks after procedure** CT or MRI and PET-CT Evaluation of tumor response in accordance with RECIST criteria (version 1.1) Photographic documentation QOL assessments (EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D) Biopsy on indication In case of residual disease a second ECT can be considered (if residual disease after the 2nd ECT other treatment options must be considered).
FOLLOW-UP PERIOD	All the CR must be followed up at 4, 8, 12 months after treatment
PROGRESSIVE DISEASE	Re-staging of the lesion Consider the possibility of further ECT Other treatment options (patients off study)
NUMBER OF PATIENTS	29 patients for each referral center
NUMBER OF REFERRAL CENTERS	M. Benazzo (m.benazzo@smatteo.pv.it), G. Bertino (giulia.bertino@tin.it), A. Occhini (antonio.occhini@alice.it) Dept. of Otolaryngology Head Neck Surgery University of Pavia IRCCS S. Matteo Foundation, Pavia, Italy Renè Leemans (cr.leemans@vumc.nl), Remco De Bree (r.debree@vumc.nl) Dept. of Otolaryngology / Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands Juan Grau (jjgrau@clinic.ub.es) Oncologic Service Hospital Clinic, Barcelona, Spain Julie Gehl (juge@heh.regionh.dk), Irene Wessel (wessel@ofir.dk) Dept. of Oncology, Dept. of Otolaryngology, Head Neck Surgery, Copenhagen University Hospital, Denmark
EXPECTED ACCRUAL TIME	36 months

I. INTRODUCTION AND RATIONALE OF THE STUDY

Recurrent or primary extended neoplasms of the head and neck can be challenging for the surgeon and debilitating for the patient, especially when important anatomical structures are involved.
Surgical treatment of these lesions could be disfiguring and followed by functional impairment. Moreover (chemo)radiotherapy can be associated with anatomical and functional complications.
Therapies that preserve organ functionality in combination with effective local tumor control are therefore of great interest.

ECT description
ECT delivers a specific current into the tissue through percutaneous needle electrodes. This current causes cell membrane poration, allowing highly efficient but not-permeable cytotoxic agents (i.e. bleomycin) to enter the cells and selectively kill the tumor cells.
The result of this original procedure is specific tumor cell destruction in the electrode's application field.

ECT has proven to be effective in the treatment of tumors of the skin, subcutaneous or mucosal tissue. The main advantages of ECT include:

-High success rate in local tumor control (74% complete regression, 11% partial response after 1 treatment)

-Limited damage to healthy tissue thanks to the specificity of the procedure for the dividing tumor cells

-Good cosmetic and functional results. In fact, surgery and radiotherapy could be associated with not only a scar, but also volume loss, retraction and other deformities, even for small tumors. ECT, by leaving the treated tissue in site for resorption by the body, without stroma and vascular destruction, allows progressive healing with limited compromise of aesthetics or loss of function.

-Limited side effects.

-Advantageous cost/benefit ratio. The technology involved and the drug used do not require large investments. Furthermore the treatment can be completed under local or general anesthesia and may not require hospitalization. Usually only one session of treatment is required.

Local control
With ECT as with other percutaneous therapies, there is significant concern regarding leaving potentially untreated disease, leading to local recurrence.
For this reason the ability to image precisely tumor volume in order to guide the introduction of the electrodes is mandatory. A 1 cm margin of healthy tissue around the lesion will be also included in the field to be treated in order to minimize the risk of local recurrence.
In this study CT, MRI and PET-CT will be applied before and after procedure to evaluate tumor response. In case of doubt, biopsy of the treated field will be performed.

Cosmesis and follow-up
Cosmetic results of the treatment will be objectively evaluated with photographic documentation. The impact of the treatment results on the quality of life of the patients will be evaluated with the EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D questionnaires delivered before the procedure and during follow-up.
A 1 year follow-up period is provided to evaluate tumor control, overall and progression-free survival.

II. STUDY OBJECTIVES

A. Primary objective

Evaluation of tumor response according to RECIST criteria (version 1.1). In case of multiple lesions all of them will be treated but only one (the most significant) will be considered for evaluation.

B. Secondary objectives

- Safety (toxicity) of the procedure
- Analysis of overall and progression free survival
- PET-CT uptake change between pretreatment and 8 weeks post-treatment
- Evaluation of quality of life of the patients by means of the EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D questionnaires

III. METHODOLOGY

Phase II observational study of intravenous administration of bleomycin combined with electroporation in patients with recurrent and/or metastatic head and neck cancers.
At least 116 patients will have to be enrolled.

Pre treatment	CT, MRI and PET-CT Identification of the target lesion Photographic documentation EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5Dquestionnaires
Day 0-15*	ECT under local/general anesthesia (*ECT must be performed as soon as possible after the diagnosis)
Hospitalization	VAS for pain Recording of the drugs used for pain control Recording of the duration of hospitalization
Day 28	CT,MRI (same imaging as pre-operative evaluation) Evaluation of tumor response according to RECIST criteria (version 1.1) Photographic documentation VAS for pain EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5Dquestionnaires In case of residual disease a second ECT will be considered (if residual disease after the 2nd ECT other treatment options will beconsidered).
Day 56	CT or MRI Evaluation of tumor response according to RECIST criteria (version 1.1) PET-CT Photographic documentation VAS for pain EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5Dquestionnaires Biopsy on indication
Months 4,8,12	Clinical evaluation Photographic documentation VAS for pain EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5Dquestionnaires

Progressive disease	Re-staging of the lesion Consider the possibility of further ECT Other treatment options (patients off study).

IV. SELECTION OF PATIENTS

A. Inclusion criteria

1. Histologically verified cancer of any type
2. Progressive and/or metastatic disease
3. Primary disease not eligible for surgery for patient's general conditions or for the need of extensive surgery
4. Patients must have offered standard treatments
5. Measurable lesions suitable for application of electric pulses
6. Age> 18 yrs
7. Performance status (Karnofsky ≥ 70; WHO ≤ 2)
8. Life expectancy> 3 months
9. Treatment free interval of at least 4 weeks after previously applied chemo- or radiotherapy to the target lesions
10. Patients must be mentally capable of understanding the information given and sign informed consent

B. Exclusion criteria

1. Other symptomatic lesions not under control
2. Lesions not suitable for ECT (bony invasion, large vessels infiltration, etc.)
3. Acute lung infection
4. Symptoms of poor lung function necessitates DLCO and patient can not be treated if this is abnormal
5. Severe coagulation disorders not correctable
6. Previous allergic reactions to bleomycin
7. If cumulative dose of 240000 IU BLM/m^2 was previously exceeded
8. Chronic renal dysfunction (creatinine > 150 µmol/L)
7. Pregnancy or lactation

V. TREATMENTS

A. Study treatment

ECT is a dual treatment including the injection of an anticancer drug (bleomycin) followed by the delivery of electric pulses using appropriate electrodes and appropriate electric pulses generator.

1. Chemotherapy

Only bleomycin injected intravenously will be used. This administration route ensures that the whole tumor field will be infiltrated by the drug. It also ensures a concentration of bleomycin in the interstitial tissue sufficient to kill all the dividing tumor cells while completely sparing the normal non-dividing cells.

Bleomycin is active on any type of tumor because electroporation affect all the cell types and, once cells are electropermeabilized, it can enter all the cells and interact with the cell DNA in the same way whatever the cell type and whatever the genetic expression of the cell.

Bleomycin will be prepared in the pharmacy of each Institution using the standard procedures for this drug. It will be injected in a bolus within 30-60 seconds at a dose of 15000 IU/m^2.

Appropriate electrodes will be inserted in and around the lesions 8 minutes after the end of the bolus injection of bleomycin.

2. Electric pulses
The electric pulses will be generated by a Cliniporator™ (IGEA srl, Carpi (MO), Italy). It generates train of pulses of 100 μs duration at a repetition frequency of 5000 Hz. The electric pulses are delivered by means of specific electrodes. Different electrodes exist with different number, spatial distribution and length of the needles. The choice of the electrodes will be based on the volume and site of the lesion to be treated.
For each treatment, description of the electrodes used and number of insertions performed for each lesions will have to be registered.

B. Dosage and schedule of treatment
Bleomycin injection must be performed on a different venous access respect of that used for delivering of the other drugs necessary for sedation, general anesthesia, etc.
If the procedure is performed under local anesthesia, it will be induced between bleomycin injection and the beginning of the electrodes insertion; while if the procedure is performed under general anesthesia, bleomycin injection will follow the induction of anesthesia itself.
Eight minutes after the end of bleomycin injection, needles will be inserted into and around the tumor lesion including 1 cm of safe margin. The procedure can require one ore more insertions and pulses and must be completed within 30 minutes from the end of bleomycin injection.

C. Concomitant treatments
Pain will be treated by continuous iv perfusion of opiates or anti-inflammatory non-steroid drugs for 24-48 hours or with oral paracetamol according to its intensity evaluated by means of a visual analog scale.
If necessary, antibiotics can be administered.

VI. BASELINE AND FOLLOW-UP ASSESSMENTS

A. Baseline assessments
Haematological examination
Chest X-ray
CT or MRI of the H&N lesion
PET-CT
Photographic documentation
EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D questionnaires

B. Follow-up assessments

4 weeks after the treatment
Clinical examination
Photographic documentation
Same radiologic examination as pre-operative evaluation
VAS for pain
EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D questionnaires

8 weeks after the treatment
Clinical examination
Photographic documentation
Same radiologic examination as pre-operative evaluation
PET-CT
Biopsy on indication

VAS for pain
EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D questionnaires

Complete responders will be evaluated at 4, 8, 12, months after the treatment with clinical examination, photographic documentation, VAS for pain EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D questionnaires.
In case of recurrence re-staging of the lesion will be performed.

C. Tumor assessment
Tumor response will be evaluated by means of clinical and radiological examination. Biopsy with histological examination will be performed on indication.

VII. EVALUATION CRITERIA

A. Primary criteria
Evaluation of tumor response will be performed in accordance with RECIST criteria (version 1.1).
Complete response (CR): disappearance of all target lesions.
Partial response (PR): at least a 30% decrease in the sum of diameters of target lesion, taking as reference the baseline sum diameters.
Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
The appearance of one or more new lesions is also considered progression.
Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

B. Secondary criteria

1. Safety (toxicity) of the procedure
There is no specific toxicity to be expected, with no side effects out of pain and muscular contraction just during the treatment and pain thereafter.
However, cautious follow-up will be made during the first 2 post-procedure days in order to register any serious adverse event. This is any untoward medical occurrence that at any dose:
- results in death or
- is life-threatening or
- requires patient hospitalization or prolongation of existing hospitalization or
- is medically significant

Intensity of adverse events not listed in this classification will be evaluated according to the NCI-CTC classification (version 3.0):
- Mild (grade 1): does not affect the patient's usual daily activities
- Moderate (grade 2): perturbs the patient's usual daily activities
- Severe (grade 3): prevents the patient carrying out his usual daily activities
- Very severe (grade 4): necessitates intensive care or is life-threatening
- Death (grade 5)

2. PET-CT uptake change at 0 and 8 weeks
Measurement of PET-CT uptake change at baseline and 8 weeks will be performed and will be statistically correlated with tumor response.

3. Quality of life
Quality of life will be measured by means of the EORTC QLQ-C30, EORTC QLQ-H&N35, EQ_5D questionnaires at the time of inclusion, 4 and 8 weeks after treatment and at follow-up visits.

4. Analysis of overall and progression free survival
During the 1 year follow-up period duration of complete regression of the tumor, appearance of recurrence and its response to salvage treatment, causes of death will be recorded. Overall and progression-free survival will be evaluated with Kaplan-Meyer estimation analysis.

VIII. DATA COLLECTION AND STATISTICAL ANALYSIS

All the data will be recorded on the INSPECT database software that will be furnished to every referral center. Statistical analysis of the data collected will be performed by the coordinating investigator.

IX. STUDY DISCONTINUATION

The study could be interrupted or terminated by the sponsor in agreement with the coordinator and with competent authority for the following reasons:
- frequency and/or unexpected severity of the toxicity,
- recruitment of patients too low,
- poor quality of the data collected

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