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ILI Protocol

Prospective observational study on isolated limb perfusion of
melphalan in treating patients with metastasis or recidivism of limb
melanoma or sarcoma that are not operable

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1. Background

In-transit metastases occur in approximately 3% of melanoma patients, can be very symptomatic and the survival in this group may be prolonged. In-transit melanoma metastases are often confined to a limb. In this circumstance, treatment by isolated limb perfusion or isolated limb infusion can be a remarkably effective regional treatment option. Isolated limb infusion (ILI) was introduced in 1992 and is a technique used to deliver regional chemotherapy to treat advanced melanoma confined to a limb. Regional chemotherapy with melphalan delivered by isolated limb perfusion (ILP) or ILI are effective treatment options for in-transit melanoma and are generally well tolerated.

ILI is a less invasive and simpler alternative to ILP. Complete response rates are 45- 69% for ILP and 23-44% for ILI. The limb is often warmed to lower temperatures in ILI compared to ILP and the limb becomes progressively more hypoxic and acidotic during ILI, each of these parameters potentially having an effect on outcome. ILP & ILI are used primarily as palliative options when excision of in-transit metastases is unfeasible but can be used as an adjunctive procedure to surgery, for other tumour types such as merkel cell carcinoma, and can be repeated if indicated. For ILI correction of melphalan dose for ideal body weight has been shown to substantially decrease the rates of severe local toxicity while maintaining complete response rates, but overall response rate is reduced.

Response to ILI, moreover, is different in upper and lower limbs. ILI for Upper limbs disease is associated with similar complete response rates but lower toxicity than ILI for Lower limbs E disease and with different physiologic sequelae despite comparable methods. The Upper limbs appears relatively resistant to toxic effects of melphalan-based ILI as currently performed, which suggests a potential for further optimization of drug dosing for Upper limbs ILI.

Regional therapy is an excellent therapeutic modality for disease limited to a limb and furthermore serves as an excellent model for scientific investigation, both clinical and translational. In this study we want to collect data on isolated limb infusion of chemotherapy to monitor efficacy and

tolerability in patients with melanoma metastases of the arm or leg that cannot be removed by surgery.

2. Study Design and Objectives

2.1 Study Design: Prospective observational study .

Primary objective: To collect data on tumor response and progression free survival after administration of melphalan.

2.2 Secondary objectives: To collect data on survival rate, time to progression, morbidity tolerability of treatment, number of treatment required to achieve objective response and improvement of quality of life (Edmonton questionnaire) [19].

3. Patient selection

3.1 Inclusion criteria

1. Histologically proven primary or recurrent, regional melanoma or soft tissue sarcoma that is not amenable to surgical resection
2. Majority (greater than 95%) of disease must be distal to the apex of the femoral triangle in the lower limb and the deltoid insertion in the upper limb
3. Bidimensionally measurable disease in the extremity
4. Patients with disease beyond the limb are eligible if their extremity disease requires palliative treatment in the judgment of their physician
5. Age: more than 18
6. Karnofsky 70-100%
7. Life expectancy: At least 6 months
8. Hematopoietic: WBC at least 3,000/mm³
9. Renal: Creatinine less than 2.0 mg/dL
10. At least 4 weeks since prior antitumor therapy and recovered
11. At least 2 weeks since prior antibiotics

3.2 Exclusion criteria

1. Signs or symptoms of vascular insufficiency (no history of claudication or other ischemic peripheral vascular disease)

2. pregnant or nursing
3. other concurrent serious illness
4. severe diabetes
5. prior extremity complications due to diabetes

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

Patients undergo fluoroscopic placement of angiographic arterial and venous catheters into the appropriate extremity in order to infuse the drug (artery) and to stop the out flow (venous with balloon catheter). Melphalan 1mg/kg is rapidly infused into the isolated limb via the arterial catheter after the inflation of venous balloon catheter. Then the circulation of the limb is blocked with a pneumatic cuff at the root of the limb . Patients with little or no response at 8 weeks may receive up to 2 additional treatments at the discretion of the treating physician.

Patients are followed at 1-2 weeks, 3-4 weeks, 6-8 weeks, and then every 3-6 months thereafter as deemed necessary by the treating physician.

Day -1 Melphalan 1mg/ Kgr has been prepared 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)

Day +1:

- Upon admittance to the radiology room, 1 vial of tropisetron (diluted in 100ml of physiological solution) administered by slow drip.
- During infusion of the Melphalan into the artery, 1 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 with 1 vial of verapamil diluted in 4 ml of normal saline solution followed by 4 ml of lidocaine.
- Intra femoral infusion of Melphalan at the dosage 1mg/ Kg
- Second ILI treatment could be repeated at side effects recovery (following oncologist ' s planning of cure).
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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 Melphalan are the following: nausea, vomiting, oral ulceration, bone marrow suppression, including decreased white blood cell count causing increased risk of infection, decreased platelet count causing increased risk of bleeding. Less common side effects include: severe allergic reactions, pulmonary fibrosis (scarring of lung tissue) including fatal outcomes (usually only with prolonged use), hair loss, interstitial pneumonitis, rash, itching, irreversible bone marrow failure due to melphalan not being withdrawn early enough, cardiac arrest.

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:

- Limb-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.

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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

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 ILI 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 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.

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.