Prognostic value of the levels of circulating tumor cells (CTCs) in peripheral blood in patients with prostate cancer at high risk (Clinical Stages IIB-III) treated radically with radiotherapy and hormone therapy

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Prognostic value of the levels of circulating tumor cells (CTCs) in peripheral blood in patients with prostate cancer at high risk (Clinical Stages IIB-III) treated radically with radiotherapy and hormone therapy.

HYPOTHESIS:

The detection and quantification of Circulating tumor cells CTCs in peripheral blood of patients with prostate adenocarcinoma may be useful at least for:

- Getting a correct stratification of patients with high-risk prostate cancer (PCa).

- Set the prognosis at baseline.

- Evaluate the response to different treatments (predictive value and monitoring).

- Establish individualized therapies.

MAIN AIM:

Primary Objective:

To evaluate the proportion of patients with high-risk prostate cancer (NCCN 2011), IIB-III AJCC staging, that expresses circulating prostatic tumor cells (CTCs) in the peripheral blood (PB).

SECONDARY AIMS:

To establish whether the expression of CTCs a) following neoadjuvant androgen deprivation (AD) prior to radiotherapy (RT) and b) following RT, predict for biochemical relapse, overall survival and distant metastasis.

METHODOLOGY:

Prospective analysis of biologic samples from peripheral blood of 65 patients with localized high-risk PCa (NCCN 2011) treated with RTC-3D-IMRT combined with AD.

Following the sign of the informed consent of the patient, the blood samples will be analyzed for CTCs using an immunomagnetic method based on the CellSearch system (Veridex), in 3 periods of time:

a) prior to any treatment;

b) Following AD and prior to RT; and

c) Following the end of RT (1-3 months afterwards).

4) 6-12 months following the end of RT in those patients with 0 CTCs in the first determination and positive CTCs in the following determinations. A cut off of 0 vs ≥ 1CTCs/7.5 mL blood was defined as a threshold for negative versus positive CTCs status.

Comparison between the expression of CTCs in peripheral blood before and following AD and RT will be performed. The quantification of the CTCs obtained in these phases of treatment will be correlated with the treatment results in terms of biochemical failure according to Phoenix definition, distant metastasis rate and overall survival to identify a significant prognostic relationship and to determine the potential effect of the treatment in the number of CTCs

Our working group will include 65 patients because the amount is based on routine clinical activity can be safely enrolled in the project development time by the participating centers.

NUMBER OF PATIENTS:

65 patients

CONDITION:

This research project will take place in the context of clinical practice, without the need of complementary extras or additional visits. Treatment given standard treatment is recommended in clinical practice guidelines. Finally, the extraction of 7.5 ml of blood needed will be in the same procedure as usual veno-puncture for clinical testing for the diagnosis and monitoring of patients.

After obtaining informed consent shall be the removal of SP samples (7.5 ml) for detection of CTCs by immunomagnetic method based on the CellSearch system (Veridex) in three time periods:

a) Prior to the start of any treatment-DA initially neoadjuvant

b) Prior to the start of RT (DA after neoadjuvant)

c) At the end of RT (1-3 months)

The analysis-quantification of CTCs obtained in these phases, will correlate with treatment outcomes in terms of biochemical failure (BF) according to the criteria of Phoenix 2006 and overall survival to identify potential prognostic value. Likewise determinations are compared before and after CTCs DA and RT to evaluate the effect of such treatments on modular quantifying CTCs

The assignment of a patient to a particular therapeutic strategy is independent prior to the decision to include the patient in the study. The study period is after the start of the investigation.

INTERVENTION:

This is a multicenter, prospective, observational, single-arm, phase IV.

Prospective analysis of biological material from samples of peripheral blood (PB) of patients diagnosed with prostate cancer at high risk (NCCN 2011), AJCC stage IIB-III, treated with 3D-CRT, IMRT dose escalation (with androgen deprivation (DA))

After obtaining informed consent shall be the sampling of peripheral blood (PB) for detection of CTCs in three treatment periods:

- Before starting any treatment-DA initially neoadjuvant
- Prior to the start of RT (DA after neoadjuvant)
- At the end of RT (1-3 months)

The analysis-quantification of CTCs obtained in these phases, will correlate with treatment outcomes in terms of biochemical failure (BF) according to the criteria of Phoenix 2006 and overall survival and metastasis-free to identify potential prognostic value. Likewise determinations are compared before and after CTCs DA and RT to evaluate the effect of such treatments on modular quantifying CTCs (predictive value).

PHASE:

A multicenter, prospective, observational, single-arm, phase IV.

STUDY TYPE: STUDY DESIGN:

A multicenter, prospective, observational, single-arm, phase IV.

Prospective analysis of biological material from samples of peripheral blood (PB) of 65 patients diagnosed with prostate cancer at high risk (NCCN 2011), AJCC stage IIB-III, treated with 3D-CRT, IMRT dose escalation and androgen deprivation (DA).

OFFICIAL TITLE:

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PRIMARY OUTCOME MEASURE:

The expression of circulating tumor cells in the peripheral blood of patients with high-risk prostate cancer (NCCN 2011) (Initially a cutoff point of 3 or more circulating cells per 7.5 ml of blood will be taken as the reference baseline).

SECUNDARY OUTCOME MEASURES:

- Radiation dose

- Duration and type of hormone therapy

- Gleason sum

- Pretreatment PSA

- Clinical T stage

- Biochemical failure-free survival ("Phoenix definition": PSA ≥ 2 ng/ml over the nadir PSA).

- Overall Survival defined as death due to any cause

- Metastasis-free survival defined as imaging documented evidence of distant spread of disease;

ARMS:

Not applicable

ASSIGNED INTERVENTIONS:

The experimental approximations that will be develop in this project are enumerated below:

Patients that satisfy inclusion criteria, and after signing informed consent, will extract 1 blood sample (7.5 mL):

a) prior to any treatment;

b) Following AD and prior to RT; and

c) Following the end of RT (1-3 months afterwards).

4) 6-12 months following the end of RT in those patients with 0 CTCs in the first determination and positive CTCs in the following determinations. A cut off of 0 vs ≥ 1CTCs/7.5 mL blood was defined as a threshold for negative versus positive CTCs status.

The quantification of CTC in blood samples will be done with the CellSearch® system.

ELIGIBILITY:

AGES ELIGIBLE FOR STUDY:

Patients aged > 18

GENDERS ELIGIBLE FOR STUDY:

Male

INCLUSION CRITERIA:

- Patients aged > 18 with capacity to give informed consent.
- Patients with histologically confirmed prostate cancer.
- Patients with a high risk factor: PSA> 20 ng / ml, Gleason 8-10 and / or stage T3a-b, N0M0 (NCCN 2011, stage IIB-III AJCC classification 2010).

  Staging by: Histology-Gleason score-, PSA, TR, ECO TR, CT, MRI.
- Patients who accept radical treatment with radiotherapy.
- Patients who give written informed consent to participate in the study.

EXCLUSION CRITERIA:

a) Any patient diagnosed with prostate cancer, which does not meet the prerequisites.

b) Any patients with another malignancy diagnosed in the past 5 years (except basal cell or squamous cell carcinoma of skin).

c) Any patient who has prostate biopsy performed 7 days prior to study entry.

d) Patients who have received prior treatment with hormonal therapy, chemotherapy or radiotherapy.

e) Patients with PSA> 100 ng / ml.

f) Any situation or condition of the patient which in the opinion of the investigator, advised against participation in the study.

STATISTICAL METHODS

The frequency of expression of CTCs was estimated with its 95% confidence interval (CI). Initially a cutoff point of ≥3 CTCs/7.5 mL of blood was taken as the

reference baseline. Because of the low CTC counts observed and for statistical purposes, we empirically established a cut-off of 0 vs ≥1 CTCs/7.5 mL blood as the thresholds between negative and positive CTC status. The association between the presence and development of CTCs over time and well-known clinicopathological features was assessed using the □2 test or Fisher exact test. Overall survival, metastasis-free survival, and biochemical failure–free survival were estimated using the Kaplan-Meier method. The curves were compared using the log-rank test. All events were defined as time until death from any cause (OS), distant metastasis (MFS), biochemical failure (bFS), or date of last follow-up visit. Cox regression models were constructed to estimate the hazard ratio and 95% CI as a measure of the effect and were adjusted for potential confounding variables (P ≤ 0.20)..All hypothesis tests were performed using 2-tailed alternatives. Statistical significance was set at P < 0.05.

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