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CLINICAL TRIAL PROTOCOL

Rationale and protocol of AIRC IG-13218, short-term radiotherapy for early prostate cancer with concomitant boost to the dominant lesion

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ABSTRACT

Introduction: Of the different treatments for early prostate cancer, hypofractionated external-beam radiotherapy is one of the most interesting and studied options.
Methods: The main objective of this phase II clinical study is to evaluate the feasibility, in terms of the incidence of acute side effects, of a new ultra-hypofractionated scheme for low- or intermediate-risk prostate cancer patients treated with the latest imaging and radiotherapy technology, allowing dose escalation to the dominant intraprostatic lesion identified by multiparametric magnetic resonance imaging. Secondary endpoints of the study are the evaluation of the long-term tolerability of the treatment in terms of late side effects, quality of life, and efficacy (oncological outcome).
Results: The study is ongoing, and we expect to complete recruitment by the end of 2016.
Conclusions: Like in previous studies, we expect ultra-hypofractionated radiation treatment for prostate cancer to be well tolerated and effective.
Trial registration: ClinicalTrials.gov identifier: NCT01913717.

Keywords: Biomarkers, Dominant intraprostatic lesion (DIL), High-precision radiotherapy, Hypofractionated radiotherapy, Magnetic resonance imaging (MRI), Prostate cancer

Introduction

Prostate cancer (PCa) is the most common malignancy in European men. Approximately 70% of patients with a new diagnosis of PCa are affected by organ-confined disease. The treatment options in these patients include radical prostatectomy, external-beam radiotherapy, brachytherapy, and active surveillance (1). All active treatments available present similar risks of side effects, although the type of toxicity differs between treatments. The right treatment should be the most effective and least toxic for the individual patient in a personalized medicine scenario, and the most convenient for both the patient and the treatment center. Also the patient's quality of life has been more and more investigated recently, and is taken into account in daily clinical practice. Stratification of patients into risk categories according to the guidelines of the US National Comprehensive Cancer Network (NCCN) is widely used to assess the most appropriate treatment and to compare outcomes (2).

The maximum delivered radiation dose to the tumor influences its eradication and thus the patient's prognosis. A dose escalation benefit has been demonstrated in several randomized trials and 1 meta-analysis (3). However, further dose escalation is limited by toxicities to the surrounding

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normal tissues. Recently developed imaging techniques allow better definition of the tumor area (4), so the concept of dose escalation (boost) to the dominant lesions seems appealing. Such an approach might allow better sparing of normal tissues surrounding the target. Nowadays magnetic resonance imaging (MRI) fused with planning computed tomography (CT) is strongly recommended for contouring the PCa treatment plan volumes, because CT overestimates the volume of the prostate by about 30%. In order to improve radiation treatment planning with the help of MRI information, the MR images need to be registered to the treatment planning CT, taking into account also organ motion due to variability in rectum and bladder filling (5). As part of 3D conformal radiation therapy, the dose to the target can be further conformed by modern techniques of intensity-modulated radiotherapy, which can be delivered with the latest generation of accelerators providing modulated arc delivery (e.g., RapidArc® by Varian Medical Systems) (6) or with newly developed machines such as the Vero™ system (Mitsubishi Heavy Industries Ltd. and Brainlab AG) (7). On the other hand, the use of protons in the treatment of PCa finds its rationale in the spatial characteristics of the dose deposition of these charged particles compared to x-rays: a low dose at the entrance of the beam, the maximum dose delivered to the tumor target, and virtually no dose at the exit of the beam (8).

Because of the higher safety of PCa treatment by these new technological developments and particle therapies, novel alternative schemes of radiation therapy fractionation have been investigated. The linear-quadratic model represents the basis for predicting the clinical effects of alternative fractionation schemes in radiotherapy. In this model, the tissue response to altered fractionation is determined by the tissue α/β ratio. Tissue with a high α/β ratio is less sensitive to a high dose per fraction or hypofractionated external-beam radiotherapy (HEBRT) than tissue with a low α/β ratio. In clinical practice, most tumors have a high α/β ratio; therefore, these tumors are treated with the standard fractionation of 2 Gy/fraction, or with a hyperfractionated regimen. In the last decade, experimental and clinical data suggesting an α/β ratio value of 1.5 Gy for PCa (9, 10) have led to numerous clinical trials testing hypofractionated regimens delivered over 1 to 5 weeks (11-13). A recent review analyzing data from available series of PCa patients treated with 33.5-50 Gy in 5 fractions showed that HEBRT is a well-tolerated and effective treatment (11). The feasibility, efficacy and very good toxicity profile have also been demonstrated by our group using a hypofractionated scheme delivered with CyberKnife in the re-treatment of PCa up to 30 Gy in 5 fractions (14).

The introduction of such schemes has brought – apart from the potential radiobiological benefits in terms of tumor control – a reduction of the overall treatment time, with increased patient compliance and a positive economic impact on health facilities; this can shorten waiting lists and increase the total number of treatments per operation unit. In order to safely implement hypofractionated treatments, reduction of the safety margins around the target volume (to limit the toxicity to the surrounding organs at risk [OARs]) is necessary. The only way to reduce the safety margins is by accurate target volume localization during each treatment session, together with accurate identification of the target in the planning phase. The highest accuracy in patient immobilization is also important, and is possible thanks to the availability of modern in-room imaging and target localization devices.

In this context of rapid advances in PCa conformal radiotherapy, a major clinical dilemma is to prospectively identify which patients will benefit from HEBRT schemes, so that the remaining patients might be directed towards conventional treatment modalities and doses. Molecular markers that can describe the radiobiological characteristics of prostate tumors need to be identified in order to assign each patient to the safest and most effective treatment. In this respect, thanks to the remarkable progress of the discipline of molecular pathology and the availability of high-throughput technologies, translational radiobiological research is increasingly focusing on the evaluation of markers of vascular proliferation (vascular endothelial growth factor), hypoxia (hypoxia inducible factor-1), tumor proliferation (Ki67, MCM2-7), and tumor progression (osteopontin and matrix metalloproteinases) (15). The availability of microarray technology has made it possible to examine the expression of thousands of genes simultaneously in order to isolate genetic tumor fingerprints. Combining these data with those obtained by modern functional imaging methods is essential to characterize the tumor in respect to the normal tissue, and acquire information about candidate genes responsible for a more aggressive tumor phenotype.

Study rationale

New radiotherapy technologies have been developed in recent years, which have led to further research into high-precision hypofractionated treatments. This means that radiotherapy schedules can be shortened from the 7-8 weeks of the past to a mere 1-2 weeks, which is highly convenient both for patients and radiotherapy centers. Furthermore, the availability of multiparametric MRI (mpMRI) allows to identify the dominant intraprostatic lesion (DIL), so that a high-precision boost dose can be delivered to the tumor instead of treating the whole prostate at the same dose. The rationale for the selected dose is based on recent feasibility studies, on stereotactic CyberKnife treatment to the whole prostate (11), and on the tomotherapy conventionally fractionated dose escalation scheme to the DIL (16, 17). This dose level to the whole prostate seems feasible (18), and the feasibility of dose escalation to the MRI-identified DIL using several extreme-precision strategies represents an innovative aspect of the study. From a radiobiological point of view, the low prostate α/β ratio (estimated to be around 1.5) would benefit from a higher dose per fraction. The aim of our study is to evaluate the feasibility and safety of an ultra-hypofractionated scheme for early-stage PCa with innovative technology in order to improve the treatment of localized PCa. Increasing attention to patients' quality of life and resource optimization is prompting shorter treatment schedules like the one proposed in this protocol. Also important is the economic impact on treatment centers, as the new approaches can shorten waiting lists and facilitate access to treatment for more patients.

Patients and methods

Study design

The study is divided into 4 tasks:

1. In silico study to assess the optimal dose delivery technique selection between RapidArc®, Vero™, CyberKnife® and proton therapy
2. Phase II, prospective, single-arm, single-center clinical trial
3. Evaluation of modeling and organ motion through a new semiautomatic deformable image registration algorithm
4. Molecular biomarker study to investigate predictive models to be used for stratification of patients.

The in silico study on 10 test PCa patients was performed by comparing competitive treatment plans to assess the technique that provides the maximum target coverage with the minimum dose to the surrounding OARs between RapidArc®, Vero™, CyberKnife® and proton therapy. Excellent coverage was observed with all techniques (19), but because of logistic issues proton therapy was not planned to be used in the clinical study, and RapidArc® (Varian Medical Systems) and CyberKnife® (Accuray Inc.) were chosen for the prospective phase II trial.

Enrollment started in June 2015, and the recruitment of 65 consecutive patients should be completed by the end of 2016.

The primary endpoint of the study is feasibility in terms of the incidence of acute effects, i.e., within a month of the end of treatment. Toxicity will be clinically assessed once a week during radiotherapy and 1 month thereafter. According to the Radiotherapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scale (20), every grade 3 or 4 event will be considered as "failure". Acute toxicity will also be registered according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) (21).

Secondary endpoints include:

- Late toxicity, evaluated at 6, 12 and 24 months after treatment completion, according to CTCAE v4.0 and the RTOG/EORTC scale
- Biochemical response through trimestral PSA evaluation
- Time to biochemical failure, defined according to the Phoenix criterion (nadir PSA + 2 ng/mL)
- Disease-free survival, both local and distant
- Cause-specific survival
- Overall survival
- Treatment-related quality of life, according to EORTC questionnaires QLQ-C30 and QLQ-PR25, the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IEEF-5)
- Role of mpMRI in identifying the tumor and in guiding treatment planning
- Identification of molecular prognostic factors for aggressive PCa.

The inclusion and exclusion criteria are listed in Table I.

TABLE I - Inclusion and exclusion criteria

Inclusion criteria	Histologically confirmed adenocarcinoma of prostate
	Very low, low and intermediate NCCN risk categories
	Age >18 years
	Good performance status (ECOG <2)
	No previous pelvic radiotherapy
	No previous prostatectomy
	Good urinary flow (peak flow >10 mL/s)
	Ability to complete questionnaires about quality of life
	Written informed consent signed
Exclusion criteria	Extracapsular tumor or locally advanced disease (cT3-cT4)
	Nodal involvement or distant metastasis (cN1 and/or cM1)
	IPSS questionnaire >20
	Concomitant inflammatory bowel disease
	Important systemic diseases or oral anticoagulant therapy ongoing
	Nonconformity to dose constraints at treatment planning
	Previous invasive cancer (apart from nonmelanoma skin cancer), unless the patient has been free from disease for at least 3 years
	Mental diseases that cannot ensure valid informed consent

NCCN = National Comprehensive Cancer Network; ECOG = Eastern Cooperative Oncology Group; IPSS = International Prostate Symptom Score.

Treatment planning

Pelvic mpMRI is performed, including diffusion-weighted and perfusion MRI imaging, as well as conventional T2-weighted imaging, before CT treatment simulation for each patient in the same treatment position in order to assure accurate image registration. The combined analysis of diffusion-weighted and perfusion imaging, along with T2-weighted images, facilitates the detection and localization of the DIL and allows better characterization of tumors in terms of cellularity and vascularization. At the time of treatment planning, mpMRI is coregistered with the simulation CT to define the DIL to be boosted (gross tumor volume, GTV). The clinical target volume (CTV) is represented by the whole prostate identified on fusion imaging. A margin of 3 mm posteriorly and 5 mm in all other directions is added to create the planning target volume (PTV) for the prostate and 3 mm in all directions for the DIL (PTV-DIL). PTV should be covered by at least 95% of the prescription dose ($D_{95\%}$ = 95% for the prostate and 98% for the DIL).

We consider and delineate as OARs the following structures: urinary bladder, rectum, posterior rectal wall, anal canal, urethra, peritoneal cavity/bowel bag, penile bulb, penis, testis, femoral heads and necks, and cauda equina.

Dose-volume histograms are calculated for GTV/CTVs, PTVs and OARs in order to evaluate the feasibility of the treatment plan according to the dose constraints (11, 22-24).

Treatment schedule

The whole prostate is treated to a dose of 36.25 Gy in 5 fractions (7.25 Gy/fraction), corresponding to 90.6 Gy in 45 fractions according to the linear quadratic model, assuming $\alpha/\beta = 1.5$ Gy for PCa. The DIL receives a simultaneous integrated boost of 37.5 Gy in 5 fractions (7.5 Gy/fraction), equivalent to 96.4 Gy with conventional fractionation. The treatment is delivered every other day. Time between fractions should not be less than 36 hours or more than 8 days.

Treatment delivery

The treatment is delivered either by the Trilogy® system (Varian Medical Systems) with RapidArc technology or by CyberKnife. During each treatment session with Trilogy, the image-guided radiation therapy tool (cone-beam computed tomography, CBCT) is used for localization of the target volume, and a clinician performs real-time control and adjusts positioning (if needed) in order to ensure treatment precision despite possible intrafraction errors. The short beam-on time allowed by the RapidArc technology (less than 5-6 minutes) does not usually require checking of intrafraction errors or organ motion. With CyberKnife, the fiducial markers placed in the gland enable real-time verification of organ position through orthogonal electronic x-ray imaging devices, thereby providing intrafractional tracking. We decided not to implant fiducials in patients to be treated with RapidArc because the procedure is quite invasive, time-consuming, and not completely free from complications.

Patients are trained to present for radiotherapy with an empty rectum and full bladder. If this condition appears not to be satisfied at CBCT, the treatment is not performed until the rectum and bladder are similar to the planning CT scan. The use of α-1 blockers and low doses of steroids is recommended to lower the risk of urinary obstruction and minimize inflammatory effects.

Identification of molecular prognostic markers

At the time of enrollment the patient is informed about the possibility to undergo MRI-guided biopsy of the DIL to investigate the presence of aggressive phenotype markers. An immunohistochemical assay will be performed to determine a panel of biomarkers (Ki67, phosphatase and tensin homolog [PTEN]) known to be involved in PCa progression (25-27). The aim is to find a possible correlation between tumor aggressiveness and clinical outcomes and to generate molecular predictive models to be used for patient stratification.

Statistical methods

CTCAE v4.0 and RTOG/EORTC criteria are employed to classify treatment-related acute and late side effects. The primary endpoint of the trial is acute toxicity, which will be tested by counting the number of patients who are free from cumulative 1-month acute toxicity. The trial will be conducted according to Simon's optimal 2-stage design for phase II clinical trials (28). For sample size calculation, alpha level and power are assumed to be 5% and 80%, respectively; a rate of success (patients with no cumulative acute toxicity grade ≥3) of 95% is considered sufficient to warrant further investigation, whereas a rate of success of 85% or less (or even 1 event of rectal/urinary bladder necrosis) is considered unacceptable. To test this hypothesis, stage I of the study will require 13 patients and the treatment schedule will be rejected if the success rate is <11. In other words, the treatment schedule will be rejected and the study prematurely closed if 2 grade 3 or 4 acute toxicities or more will be detected in this first stage. By contrast, if at least 12 patients have been event free (and all 13 are necrosis free), the trial will proceed to stage II by recruiting an additional 52 patients until a total of 65 patients is reached. If more than 59 event-free patients will be reported, then the treatment schedule will be considered worthy of further phase III investigation.

Ethical aspects

The study will be conducted according to the Declaration of Helsinki/Tokyo and to Good Clinical Practice guidelines. The protocol has been presented to and approved by the ethics committee of the European Institute of Oncology of Milan. After complete explanation of the objectives and modalities of the study, each patient is required to give written informed consent for participation in the study. Separate written informed consent is required for tissue samples. (This is optional, i.e., mpMRI-guided biopsy is performed only in those patients who will give their consent). Patients can at any moment drop out of the study with no need for explanation.

Abbreviations

CBCT	cone-beam computed tomography
CT	computed tomography
CTV	clinical target volume
DIL	dominant intraprostatic lesion
EORTC	European Organization for Research and Treatment of Cancer
GTV	gross tumor volume
HEBRT	hypofractionated external-beam radiotherapy
IEEF-5	International Index of Erectile Function
IPSS	International Prostate Symptom Score
mpMRI	multiparametric MRI
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OAR	organ at risk
PCa	prostate cancer
PTEN	phosphatase and tensin homolog
PTV	planning target volume
RTOG	Radiotherapy Oncology Group

Disclosures

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Conflict of interest: The authors declare they have no conflict of interest related to this study.

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