High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial

Almudena Zapatero, Araceli Guerrero, Xavier Maldonado, Ana Alvarez, Carmen Gonzalez San Segundo, Maria Angeles Cabeza Rodríguez, Victor Macias, Agustí Pedro Olive, Francesc Casas, Ana Boladeras, Carmen Martín de Vidales, Maria Luisa Vazquez de la Torre, Salvador Villà, Aitor Perez de la Haza, Felipe A Calvo

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See Comment page 244

Hospital Universitario de la Princesa, Madrid, Spain (A Zapatero PhD, C Martín de Vidales PhD); **Hospital Son Espases, Palma de Mallorca, Spain** (A Guerrero MD); **Hospital Universitari Vall d'Hebron, Barcelona, Spain** (X Maldonado MD); **Hospital General Universitario Gregorio Marañón, Madrid, Spain** (A Alvarez MD, C Gonzalez San Segundo PhD, Prof F A Calvo PhD); **Hospital Universitario 12 de Octubre, Madrid, Spain** (M A Cabeza Rodríguez MD); **Hospital General de Catalunya, Sant Cugat del Vallès and Hospital Universitario de Salamanca, Salamanca, Spain** (V Macias PhD); **Hospital Plató, Barcelona, Spain** (A Pedro Olive MD); **Hospital Clinic, Barcelona, Spain** (F Casas PhD); **Institut Català d'Oncologia, Barcelona, Spain** (A Boladeras MD, S Villà PhD); **Hospital Do Meixoeiro, Vigo, Spain** (M L Vazquez de la Torre MD); **and Apices Data Management and Biostatistics Centre, Madrid, Spain** (A Perez de la Haza MSc)

Correspondence to:
Dr Almudena Zapatero, Radiation Oncology Department, Hospital Universitario de la Princesa, Health Research Institute IIS, 28006 Madrid, Spain
almudena.zapatero@salud.madrid.org

Summary

Background The optimum duration of androgen deprivation combined with high-dose radiotherapy in prostate cancer remains undefined. We aimed to determine whether long-term androgen deprivation was superior to short-term androgen deprivation when combined with high-dose radiotherapy.

Methods In this open-label, multicentre, phase 3 randomised controlled trial, patients were recruited from ten university hospitals throughout Spain. Eligible patients had clinical stage T1c–T3b N0M0 prostate adenocarcinoma with intermediate-risk and high-risk factors according to 2005 National Comprehensive Cancer Network criteria. Patients were randomly assigned (1:1) using a computer-generated randomisation schedule to receive either 4 months of androgen deprivation combined with three-dimensional conformal radiotherapy at a minimum dose of 76 Gy (range 76–82 Gy; short-term androgen deprivation group) or the same treatment followed by 24 months of adjuvant androgen deprivation (long-term androgen deprivation group), stratified by prostate cancer risk group (intermediate risk *vs* high risk) and participating centre. Patients assigned to the short-term androgen deprivation group received 4 months of neoadjuvant and concomitant androgen deprivation with subcutaneous goserelin (2 months before and 2 months combined with high-dose radiotherapy). Anti-androgen therapy (flutamide 750 mg per day or bicalutamide 50 mg per day) was added during the first 2 months of treatment. Patients assigned to long-term suppression continued with the same luteinising hormone-releasing hormone analogue every 3 months for another 24 months. The primary endpoint was biochemical disease-free survival. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT02175212.

Findings Between Nov 7, 2005, and Dec 20, 2010, 178 patients were randomly assigned to receive short-term androgen deprivation and 177 to receive long-term androgen deprivation. After a median follow-up of 63 months (IQR 50–82), 5-year biochemical disease-free survival was significantly better among patients receiving long-term androgen deprivation than among those receiving short-term treatment (90% [95% CI 87–92] *vs* 81% [78–85]; hazard ratio [HR] 1·88 [95% CI 1·12–3·15]; p=0·01). 5-year overall survival (95% [95% CI 93–97] *vs* 86% [83–89]; HR 2·48 [95% CI 1·31–4·68]; p=0·009) and 5-year metastasis-free survival (94% [95% CI 92–96] *vs* 83% [80–86]; HR 2·31 [95% CI 1·23–3·85]; p=0·01) were also significantly better in the long-term androgen deprivation group than in the short-term androgen deprivation group. The effect of long-term androgen deprivation on biochemical disease-free survival, metastasis-free survival, and overall survival was more evident in patients with high-risk disease than in those with low-risk disease. Grade 3 late rectal toxicity was noted in three (2%) of 177 patients in the long-term androgen deprivation group and two (1%) of 178 in the short-term androgen deprivation group; grade 3–4 late urinary toxicity was noted in five (3%) patients in each group. No deaths related to treatment were reported.

Interpretation Compared with short-term androgen deprivation, 2 years of adjuvant androgen deprivation combined with high-dose radiotherapy improved biochemical control and overall survival in patients with prostate cancer, particularly those with high-risk disease, with no increase in late radiation toxicity. Longer follow-up is needed to determine whether men with intermediate-risk disease benefit from more than 4 months of androgen deprivation.

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Introduction

Several randomised trials done during the past two decades have shown a significant improvement in biochemical control and overall survival with the combination of androgen deprivation and conventional-dose radiotherapy (≤70 Gy) in patients with high-risk[1–7] and intermediate-risk prostate cancer.[8,9] Similarly, advances in external beam radiotherapy have enabled dose escalation with substantial improvements in biochemical outcome.[10–15] Because randomised trials showing a significant clinical benefit with androgen deprivation and radiotherapy use exclusively conventional dose levels of 65–70 Gy, the optimum duration of androgen deprivation to use in combination with high-dose radiotherapy remains unresolved.[16] Thus,

we aimed to determine whether long-term androgen deprivation was superior to short-term androgen deprivation for patients receiving high-dose radiotherapy.

Methods

Study design and participants

In this open-label, multicentre, phase 3 randomised controlled trial, patients were recruited from ten university hospitals throughout Spain (appendix). Patients aged 18 years or older with histologically confirmed clinical stage T1c–T3b adenocarcinoma of the prostate, N0, M0 with intermediate-risk and high-risk factors according to National Comprehensive Cancer Network criteria, serum PSA concentration less than 100 ng/mL, a Karnofsky performance score of 70 or greater, and a life expectancy of more than 5 years were eligible for inclusion. Patients with T4 tumours, regional lymph-node involvement, distant metastatic disease, previous pelvic radiotherapy or surgery, neoadjuvant hormonal treatment for more than 3 months, or concomitant use of chemotherapy were excluded from the trial. Severe psychiatric or medical conditions that could hamper both treatment and follow-up and major malignancies were also considered exclusion criteria. Patients with a previous history of cancer that had been controlled for 5 years or more and patients with cutaneous basal cell or squamous-cell carcinoma were not excluded. Pretreatment evaluation included a digital rectal examination, transrectal ultrasound, abdominal-pelvic CT, and bone scan. Review of pathology specimens was not centralised.

The study was approved by the independent review board at each participating centre and conducted according to the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent before participating in the trial. The full study protocol can be viewed online.

Randomisation and masking

Before randomisation, patients were screened to verify the study selection criteria and stratified based on prostate cancer risk subgroups (intermediate risk: T1–T2 with a Gleason score of 7, or PSA concentration of 10–20 ng/mL, or both; high risk: T3 with Gleason score of 8–10, or PSA concentration of >20 ng/mL, or both) and the participating centre.

Patients were randomly assigned (1:1) to receive 4 months of neoadjuvant and concomitant androgen deprivation combined with three-dimensional conformal radiotherapy (short-term androgen deprivation group) or the same treatment followed by 24 months of adjuvant androgen deprivation (long-term androgen deprivation group). Randomisation was centralised at the Health Research Institute of Hospital Universitario de la Princesa (Madrid, Spain). After eligibility screening, the research coordinator assigned eligible patients using a randomisation schedule generated by means of the SAS programme (version 9.1) and an interactive web response system. The research coordinator then faxed the investigator of the participating centres, reported the number, and informed the investigator about the assigned treatment. No blocks were used. Neither the participants nor the investigators were masked to treatment allocation, because blinding was not feasible.

Procedures

See Online for appendix

Radiotherapy was administered with three-dimensional conformal radiotherapy techniques done with a six-field isocentric beam setup based on a CT scan. The target volume included the prostate and the seminal vesicles. In view of the controversy regarding the role of prophylactic pelvic radiotherapy and the absence of definitive data, elective pelvic radiotherapy was left to the criteria of each participating centre. The radiation dose was specified at the intersection of the beam axes (isocentre) according to the guidelines of the International Commission on Radiation Units.[17] Treatment was provided in daily 2 Gy fractions at a minimum dose of 76 Gy (range 76–82 Gy). The median isocentre radiation dose to the prostate was 78 Gy for both groups, and the corresponding dose to the seminal vesicles was 56 Gy. Beams were shaped with multileaf collimators or customised shaped blocks, and treatment was delivered with 6–18 MV photons. Dose constraints for normal tissues have been described elsewhere.[18] Treatment was verified with electronic portal image devices according to the quality assurance protocols at each centre.

The hormone therapy regimen was based on that used in the RTOG 9202 trial[4] and on the usual clinical practice in Spain. Patients assigned to the short-term androgen deprivation group received 4 months of neoadjuvant and concomitant androgen deprivation with subcutaneous goserelin (in both groups, goserelin was given subcutaneously at 3·6 mg; after 1 month, it was given subcutaneously at 10·8 mg subcutaneously every 3 months). Treatment started 2 months before high-dose radiotherapy, and was then given for 2 months combined with radiotherapy. Anti-androgen therapy (flutamide 750 mg per day or bicalutamide 50 mg per day) was added during the first 2 months of treatment. Patients assigned to long-term suppression continued with the same luteinising hormone-releasing hormone analogue every 3 months for another 24 months.

For the **protocol** see http://www.gicor.es/invest003/resumen.pdf

Follow-up visits were at intervals of 3 months after radiotherapy during the first year, every 6 months for 5 years, and yearly thereafter. PSA concentrations, serum testosterone concentration, and a complete blood count were obtained at every visit. Specifically, 12 PSA measurements were obtained during the first 5 years of follow-up to enable systematic assessment of the lowest PSA value achieved (PSA nadir) after completion of treatment. Imaging (abdominal-pelvic CT and bone scan) was repeated in cases in which clinical or biochemical progression was suspected. Decisions on salvage therapy