Prostate

High-dose radiotherapy and risk-adapted androgen deprivation in localised prostate cancer (DART 01/05): 10-year results of a phase III randomised, controlled trial

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BACKGROUND

The optimal duration of androgen deprivation combined with high-dose radiotherapy in prostate cancer remains controversial. The DART 01/05 trial was designed to determine whether long-term androgen deprivation is superior to short-term androgen deprivation when combined with high-dose radiotherapy. The five-year results showed that two years of adjuvant androgen deprivation combined with high-dose radiotherapy significantly improved biochemical control, metastasis, and overall survival, especially in patients with high-risk disease. In this report, we present the 10-year final results of the trial.

METHODS

This open-label, phase III, randomised, controlled trial was done in ten hospitals in Spain. The eligibility criteria included patients aged 18 years or older with histologically confirmed T1c to T3, N0, and M0 adenocarcinoma of the prostate, according to the 2002 classification of the American Joint Committee on Cancer, with intermediate-risk and high-risk factors, prostate-specific antigen (PSA) less than 100 ng/mL, and a Karnofsky performance score of at least 70%. Patients were randomly assigned (1:1) to receive four months of neoadjuvant and concomitant short-term androgen deprivation (STAD) plus high-dose radiotherapy (minimum dose 76 Gy; median dose 78 Gy) or to receive the same treatment followed by 24 months of adjuvant long-term androgen deprivation (LTAD), via a randomisation scheduled generated by Statistical Analysis Software programme (version 9.1) and an interactive web response system. Patients assigned to the STAD group received four months of neoadjuvant and concomitant androgen deprivation (oral flutamide 750 mg per day or oral bicalutamide 50 mg per day) with subcutaneous goserelin (two months before and two months combined with high-dose radiotherapy). Anti-androgen therapy was added during the first two months of treatment. Patients assigned to LTAD continued with goserelin every three months for another 24 months. The primary endpoint was biochemical disease-free survival at five years. For this 10-year study we analysed overall survival, metastasis-free survival, biochemical disease-free survival, and cause-specific survival. Analysis was by intention to treat. This trial is closed and is registered at ClinicalTrials.gov (NCT02175212) and in the EU Clinical Trials Register (EudraCT 2005-000417-36).

FINDINGS

Between 7 Nov 2005, and 20 Dec 2010, 355 patients were enrolled. One patient in the STAD group withdrew from the trial, hence 354 participants were randomly assigned to STAD (n=177) or LTAD (n=177). The median follow-up was 119·4 months (IQR 100·6-124·3). The 10-year biochemical disease-free survival for LTAD was 70·2% (95% CI 63·1-77·3) and for STAD was 62·3% (54·9-69·7; hazard ratio [HR] 0·84; 95% CI 0·50-1·43; p=0·52). At 10 years, overall survival was 78·4% (72·1-84·8) for LTAD and 73·3% (66·6-80·0) for STAD (HR 0·84; 95% CI 0·55-1·27; p=0·40), and metastasis-free survival was 76·0% (69·4-82·7) for LTAD and 70·9% (64·0-77·8) for STAD (HR 0·90; 95% CI, 0·37-2·19; p=0·81). For the subgroup of high-risk patients, the 10-year biochemical disease-free survival was 67·2% (57·2-77·2) for LTAD and 53·7% (43·3-64·1) for STAD (HR 0·90; 95% CI 0·49-1·64; p=0·73), the 10-year overall survival was 78·5% (69·6-87·3) for LTAD and 67·0% (57·3-76·7) for STAD (HR 0·58; 95% CI 0·33-1·01; p=0·054), and the 10-year metastasis-free survival was 76·6% (95% CI 67·6-85·6) for LTAD and 65·0% (55·1-74·8) for STAD (HR 0·89; 95% CI 0·33-2·43; p=0·82). Only 11 (3.0%)

of 354 patients died from prostate cancer, all of them in the high-risk subgroup (five in the LTAD group and six in the STAD group). 76 (21%) patients died from other causes (mainly second malignancies in 31 [9%] and cardiovascular disease in 21 [6%]). No treatment-related deaths were observed.

INTERPRETATION

After an extended 10-year follow-up, we were unable to support the significant benefit of LTAD reported at five years. However, the magnitude of the benefit was clinically relevant in high-risk patients. Intermediate-risk patients treated with high-dose radiotherapy do not benefit from LTAD. A biological characterisation with the inclusion of genomic testing is needed in the decision-making process.