Prostate

Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase III trials of the STAMPEDE platform protocol

Gerhardt Attard, Laura Murphy, Noel W Clarke, William Cross, Robert J Jones, Christopher C Parker et al.

Lancet Vol 399, Issue 10323, P447-460, Jan 29, 2022

BACKGROUND

Men with high-risk non-metastatic prostate cancer are treated with androgen-deprivation therapy (ADT) for three years, often combined with radiotherapy. We analysed new data from two randomised controlled phase III trials done in a multiarm, multistage platform protocol to assess the efficacy of adding abiraterone and prednisolone alone or with enzalutamide to ADT in this patient population.

METHODS

These open-label, phase III trials were done at 113 sites in the UK and Switzerland. Eligible patients (no age restrictions) had high-risk (defined as node positive or, if node negative, having at least two of the following: tumour stage T3 or T4, Gleason sum score of 8–10, and prostate-specific antigen [PSA] concentration ≥40 ng/mL) or relapsing with high-risk features (≤12 months of total ADT with an interval of ≥12 months without treatment and PSA concentration ≥4 ng/mL with a doubling time of <6 months, or a PSA concentration ≥20 ng/mL, or nodal relapse) non-metastatic prostate cancer, and a WHO performance status of 0–2. Local radiotherapy (as per local guidelines, 74 Gy in 37 fractions to the prostate and seminal vesicles or the equivalent using hypofractionated schedules) was mandated for node negative and encouraged for node positive disease. In both trials, patients were randomly assigned (1:1), by use of a computerised algorithm, to ADT alone (control group), which could include surgery and luteinising-hormone-releasing hormone agonists and antagonists, or with oral abiraterone acetate (1000 mg daily) and oral prednisolone (5.0 mg daily; combination-therapy group). In the second trial with no overlapping controls, the combination-therapy group also received enzalutamide (160 mg daily orally). ADT was given for three years and combination therapy for two years, except if local radiotherapy was omitted when treatment could be delivered until progression. In this primary analysis, we used meta-analysis methods to pool events from both trials. The primary endpoint of this meta-analysis was metastasis-free survival. Secondary endpoints were overall survival, prostate cancer-specific survival, biochemical failure-free survival, progression-free survival, and toxicity and adverse events. For 90% power and a one-sided type 1 error rate set to 1·25% to detect a target hazard ratio for improvement in metastasis-free survival of 0·75, approximately 315 metastasis-free survival events in the control groups was required. Efficacy was assessed in the intention-to-treat population and safety according to the treatment started within randomised allocation. STAMPEDE is registered with ClinicalTrials.gov, NCT00268476, and with the ISRCTN registry, ISRCTN78818544.

FINDINGS

Between 15 Nov 2011, and 2016, 1974 patients were randomly assigned to treatment. The first trial allocated 455 to the control group and 459 to combination therapy, and the second trial, which included enzalutamide, allocated 533 to the control group and 527 to combination therapy. Median age across all groups was 68 years (IQR 63–73) and median PSA 34 ng/ml (14·7–47); 774 (39%) of 1974 patients were node positive, and 1684 (85%) were planned to receive radiotherapy. With median follow-up of 72 months (60–84), there were 180 metastasis-free survival events in the combination-therapy groups and 306 in the control groups. Metastasis-free survival was significantly longer in the combination-therapy groups (median not reached, IQR not evaluable [NE]–NE) than in the control groups (not reached, 97–NE; hazard ratio [HR] 0·53, 95% CI 0·44–0·64, p<0·0001). 6-year metastasis-free survival was 82% (95% CI 79–85) in the combination-therapy group and 69% (66–72) in the control group. There was no evidence of a difference in metastasis-free survival when enzalutamide and abiraterone acetate were administered concurrently compared with abiraterone acetate alone (interaction HR 1·02, 0·70–1·50, p=0·91) and no evidence of between-trial heterogeneity (I^2 p=0·90). Overall survival (median not reached [IQR NE–NE] in the combination-therapy groups *vs* not reached [103–NE] in the control groups; HR 0·60, 95% CI 0·48–0·73, p<0·0001), prostate cancer-specific survival (not reached [NE–NE] *vs* not reached [NE–NE]; 0·49, 0·37–0·65, p<0·0001), biochemical failure-free-survival (not reached [NE–NE] *vs* 86 months [83–NE]; 0·39, 0·33–0·47, p<0·0001), and progression-free-survival (not reached [NE–NE] *vs* not reached [103–NE]; 0·44, 0·36–0·54, p<0·0001) were also significantly longer in the combination-therapy groups than in the control groups. Adverse events grade 3 or higher during the first 24 months were, respectively, reported in 169 (37%) of 451 patients and 130 (29%) of 455 patients in the combination-therapy and control groups of the abiraterone trial, respectively, and 298 (58%) of 513 patients and 172 (32%) of 533 patients of the combination-therapy and control groups of the abiraterone and enzalutamide trial, respectively. The two most common events more frequent in the combination-therapy groups were hypertension (abiraterone trial: 23 (5%) in the combination-therapy group and six (1%) in control group; abiraterone and enzalutamide trial: 73 (14%) and eight (2%), respectively) and alanine transaminitis (abiraterone trial: 25 (6%) in the combination-therapy group and one (<1%) in control group; abiraterone and enzalutamide trial: 69 (13%) and four (1%), respectively). Seven grade 5 adverse events were reported: none in the control groups, three in the abiraterone acetate and prednisolone group (one event each of rectal adenocarcinoma, pulmonary haemorrhage, and a respiratory disorder), and four in the abiraterone acetate and prednisolone with enzalutamide group (two events each of septic shock and sudden death).

INTERPRETATION

Among men with high-risk non-metastatic prostate cancer, combination therapy is associated with significantly higher rates of metastasis-free survival compared with ADT alone. Abiraterone acetate with prednisolone should be considered a new standard treatment for this population.