Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials.

Prostate Cancer Trialists' Collaborative Group

Authors' objectives
To determine the effect on survival of maximum androgen blockade (MAB) compared with androgen suppression (AS) alone.

Searching
Electronic databases, trial registers, meeting abstracts and reference lists were searched. Investigators, trial groups and pharmaceutical companies were contacted (see Other Publications of Related Interest no.1).

A secretariat and collaborative group (The Prostate Cancer Trialists' Collaborative Group) was established to identify trials and undertake the meta-analysis.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) that began before December 1989.

Specific interventions included in the review
Studies that compared MAB with AS alone were eligible for inclusion. MAB was defined as AS plus immediate administration of an anti-androgen given for at least one year or until disease progression.

In the included studies MAB comprised: orchiectomy plus nilutamide, flutamide, or cyproterone acetate; leuprolide plus flutamide or nilutamide; goserelin plus flutamide or cyproterone acetate; and decapeptyl plus cyproterone acetate. MAB was given for 18, 24 or 36 months, or until disease progression. The AS comparators were: orchiectomy; orchiectomy plus cyproterone for 14 days; leuprolide; leuprolide plus flutamide for 15 days; goserelin; buserelin; and buserelin plus cyproterone for 14 days.

Participants included in the review
Studies of men with advanced prostate cancer were eligible for inclusion. Men with metastatic (88%) and locally advanced (12%) cancer were included. The men's ages ranged from younger than 65 years to older than 75 years.

Outcomes assessed in the review
Duration of survival was the main outcome of interest. The outcomes reported were overall mortality, 5-year survival, and an analysis of non-prostate cancer deaths.

How were decisions on the relevance of primary studies made?
The authors mentioned undertaking a further investigation of randomisation and duration of anti-androgen administration in MAB, but no further details were reported.

Assessment of study quality
The data were checked for completeness and consistency, and the trial investigators were contacted to clarify any anomalies. One potentially eligible study was excluded when further investigation found that it was not randomised, but no details of the procedure were reported.

Data extraction
Investigators were asked to provide data for each individual patient in their trial. The data included age, stage of
disease, date and cause of death. Updated data were requested for trials that were included in an earlier analysis (see Other Publications of Related Interest no.2). The data were adjusted to balance uneven randomisation: the number of deaths and number of patients was counted twice for the AS group for one trial that compared two MAB treatment groups with one AS group; and the numbers were halved for the AS group for one trial that compared one MAB group with two groups who received AS.

Methods of synthesis
How were the studies combined?
The main analysis was of all-cause mortality. A meta-analysis was used to combine the studies by pooling the log rank statistic for mortality, and its variance, which were calculated for each trial. A meta-analysis stratified by years of follow-up, age, and stage of disease was also conducted. Survival curves were plotted to determine 5-year survival. All of the analyses were conducted by intention-to-treat and a 2-sided P-test was used to test for statistical significance. Deaths reported to arise from other causes (i.e. not prostate cancer) were analysed separately in a subsidiary analysis.

How were differences between studies investigated?
A chi-squared test was used to test for statistical heterogeneity in the meta-analyses. In the main analysis of all-cause mortality, the trials were grouped according to whether MAB included nilutamide, flutamide or cyproterone acetate.

Results of the review
Data from 8,275 men in 27 RCTs were included. IPD could not be obtained for 183 participants in four other trials. The authors reported that the typical duration of follow-up was almost 5 years. Data for cause of death were obtained for only 20 of the 27 trials.

There were 5,932 (72%) deaths overall. Heterogeneity in the treatment effect across all 27 trials was not statistically significant. The absolute difference in survival at 5 years was 1.8% (standard error, SE=1.3; log rank 2P=0.11). The difference was not statistically significant. The difference was also not statistically significant on omission of non-prostate cancer deaths from the analysis (2P=0.06).

There was no significant difference in overall mortality between metastatic and locally advanced disease, or between the age groups less than 65 years, 65 to 74 years, and 75 years and over, or according to whether AS was achieved by orchiectomy or drugs.

Based on 20 trials, 2,778 (80%) of the 3,475 deaths were attributed to prostate cancer. There was a non significant excess of non-prostate cancer deaths among men treated with MAB, but no association was found between this and age, stage, anti-androgen, or years of follow-up.

Trials of nilutamide (8 RCTs, 1,688 men; n adjusted) or flutamide (12 RCTs, 4,803 men) showed an absolute increase in 5-year survival of about 3% with MAB, whereas trials of cyproterone acetate (37 RCTs, 1,784 men; n adjusted) showed a 3% decrease. Some of the excess mortality among men treated with cyproterone acetate was accounted for by an excess of other deaths (i.e. not prostate cancer) in the cyproterone acetate trials, although non-prostate cancer deaths were not clearly significantly different between MAB and AS (2P=0.05).

Authors’ conclusions
MAB (addition of an anti-androgen to AS) improved 5-year survival in men with advanced prostate cancer by about 2% (analysis including trials of cyproterone acetate) or 3% (analysis excluding trials of cyproterone acetate). The range of uncertainty was approximately 0 to 5%.

CRD commentary
Some aspects of the methodology of this review were described in earlier publications (see Other Publications of Related Interest nos.1-2). The inclusion criteria were clearly defined and considerable effort was applied to identify trials. A collaborative group of trial investigators was established to maximise the retrieval of IPD. The authors reported
the number of trials that were identified for which IPD could not be retrieved; this represented only 2% of the data identified. The validity of eligible trials was assessed by checking the raw data and attempting to resolve any problems encountered by communication with the trial investigators. The data were analysed using appropriate statistical techniques and heterogeneity was explored. The authors’ conclusions are balanced and, given the rigour of the review, are likely to be reliable. This review is an update of a previous analysis (see Other Publications of Related Interest no.2).

Implications of the review for practice and research
Practice: The authors explicitly made no comment about whether the difference of 2 or 3% they have shown in 5-year survival, if real, is clinically significant.

Research: The authors stated that future randomised trials seeking to determine a difference in survival duration should recruit several thousands of patients. The authors also suggested that there remains a need for research to identify prostate cancers that are most likely to respond to prolonged hormonal treatment, and then to determine whether other hormonal regimens could improve survival more than the addition of an anti-androgen to AS.

Bibliographic details

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Other publications of related interest

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