Briefing Paper
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Upfront zoledronic acid for men with prostate cancer

Current treatment of hormone-sensitive prostate cancer

Prostate cancer is the second most common cancer worldwide in men, with more than one million diagnoses and 307,000 deaths from the disease each year. In the UK, there are around 41,000 new cases each year, and it is responsible for around 10,000 deaths.

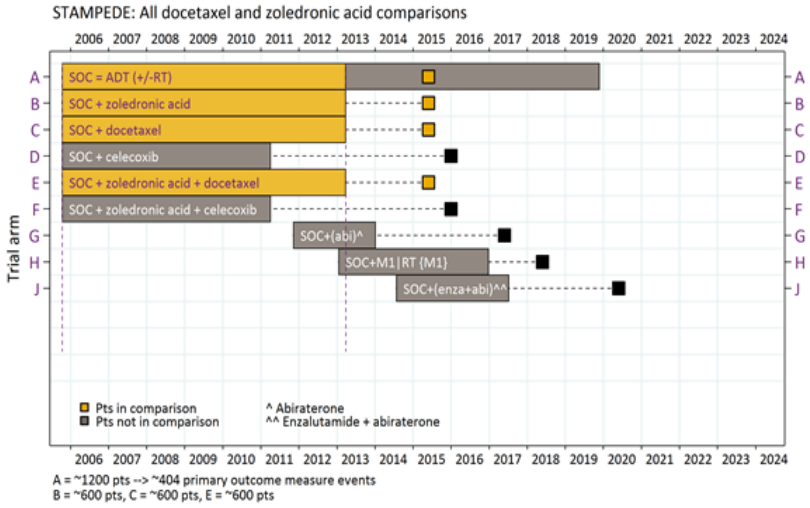
Four in ten men diagnosed with prostate cancer in the UK have very aggressive local disease or metastatic disease at diagnosis (around 16,000 to 17,000 men each year). Treatment for these men has been long-term hormone therapy and has not changed significantly in decades, until the recent introduction of radiotherapy for men with non-metastatic disease. In most men with clinically non-metastatic disease and in all those with metastatic spread, the disease eventually stops responding to hormone therapy and progresses (termed castrate-refractory prostate cancer).

A number of new treatments have been approved for use in men whose disease has already stopped responding to hormone therapy. In these men, zoledronic acid reduces the risk of skeletal complications from bone metastases.

Recently, a number of trials have been conducted to test whether using zoledronic acid may be beneficial if given earlier, alongside

The evidence on upfront zoledronic acid

The STAMPEDE trial compared 593 men who were allocated to receive standard-of-care (hormone therapy with or without radiotherapy) plus zoledronic acid, to 1,184 men who were allocated to receive standard-of-care without zoledronic acid. The trial also included 593 men who were allocated to receive standard-of-care plus both zoledronic acid and docetaxel. Six in ten men on the trial had metastatic disease. Median follow-up was around 3.5 years.



The meta-analysis looked at men with metastatic and non-metastatic disease separately. It was able to include survival results from 2,462 men with metastatic disease from two trials testing zoledronic acid (89% of all men randomised). This includes 365 men from the STAMPEDE trial who were randomised to receive both docetaxel and zoledronic acid. Median follow-up for these trials ranged from 2 to 3.6 years.
For men with non-metastatic disease, the meta-analysis was able to include survival results from 3,608 men from three trials that tested zoledronic acid (63% of all men randomised). This includes 228 men who were randomised to receive both docetaxel and zoledronic acid. Median follow-up for these trials ranged from 3.6 to 7.3 years.

Key points

- Adding zoledronic acid to hormone therapy provides no significant survival benefit for men starting long-term hormone therapy for the first time
- There is no evidence that adding zoledronic acid to docetaxel plus hormone therapy provides any additional survival benefit to just docetaxel plus hormone therapy
- While adding zoledronic acid did not seem to increase reports of severe side-effects overall, compared to hormone therapy alone or hormone therapy plus docetaxel, it did seem to increase cases of osteonecrosis of the jaw
- Adding zoledronic acid to hormone therapy did not affect the time to first skeletal-related event

long-term hormone therapy, rather than waiting until the disease stops responding to hormone therapy.

How was zoledronic acid used in these trials?

In the STAMPEDE trial, zoledronic acid was given for six three-weekly cycles, followed by four-weekly cycles until disease progression for a maximum of two years. Each cycle involved an infusion of 4mg over 15 minutes. All men also received an oral supplement of 500mg calcium and 400IU vitamin D daily. In the other trials included in the meta-analysis, zoledronic acid was also given at a dose of 4mg, either every three to four weeks, or every three months for up to four years.

Does zoledronic acid improve survival?

The STAMPEDE results

The STAMPEDE trial found that there was no evidence that adding zoledronic acid to the standard-of-care improved survival or delayed treatment failure (biochemical progression; local, lymph node or distant metastases progression; or death from prostate cancer).

There was no evidence of any difference in treatment effect on overall survival or treatment failure between particular groups of men (eg. men with metastatic vs non-metastatic disease).

A combination of zoledronic acid and docetaxel in addition to standard-of-care did significantly improve overall survival compared to standard-of-care alone, with 60% of men alive at five years, versus 55% in the standard-of-care arm. However, this benefit was no greater than that of adding just docetaxel to standard-of-care (where 63% of men were alive at five years – see recommended reading for further information).

The meta-analysis results

Men with metastatic disease

The meta-analysis found no clear evidence of a survival benefit from zoledronic acid for men with metastatic disease. The trials which have not yet reported survival results have fewer than 400 men, so are unlikely to alter these results. If there is any survival benefit from zoledronic acid it is likely to be small at best.

Men with non-metastatic disease

The meta-analysis found no evidence of a survival benefit from zoledronic acid for men with non-metastatic disease. Data from ongoing trials that may report survival are unlikely to change this conclusion.

Side-effects from zoledronic acid seen in the STAMPEDE trial

In STAMPEDE, adding zoledronic acid to the standard-of-care either alone or with docetaxel did not seem to increase the proportion of men who reported severe side-effects (Grade 3 or above).

However, there were 10 reports of osteonecrosis of the jaw amongst patients on the zoledronic acid plus standard-of-care arm, and 20 reports amongst patients on the zoledronic acid plus docetaxel and standard-of-care arm. This compares to no reports in both the standard-of-care alone arm and the docetaxel plus standard-of-care arm.

Does upfront zoledronic acid reduce skeletal-related events?

The STAMPEDE trial found no evidence of an improvement in time to first skeletal-related event from adding zoledronic acid to the standard-of-care. Among the sub-group of men who had bone metastases when joining the trial, adding zoledronic acid to hormone therapy did not affect time to first skeletal-related event.

Conclusions

Neither STAMPEDE nor the meta-analysis found substantial evidence that upfront zoledronic acid improves survival. Furthermore, STAMPEDE did not find any evidence that it delays time to either treatment failure or skeletal-related events. There may potentially be a small survival advantage for men with metastatic disease, but this is not significant or clinically important, especially in the context of the survival gains seen from adding docetaxel to the standard-of-care. Based on this current data we would conclude that zoledronic acid should not become part of the standard-of-care for men starting long-term hormone therapy for the first time.

Further information

James ND, Sydes, MR, Clarke NW, et al. Adding docetaxel and/or zoledronic acid for hormone-naive prostate cancer (STAMPEDE): survival results from an adaptive multi-arm multi-stage platform randomised controlled trial. The Lancet. 2016.

Vale CL, Burdett S, Rydzewska LHM et al. Adding docetaxel or bisphosphonates to standard-of-care in men with localised or metastatic hormone-sensitive prostate cancer; a systematic review and meta-analysis of aggregate data. Lancet Oncology. 2016.

Watch a short film about these results.

Credits

This briefing document was written by Annabelle South, Sarah Burdett, Noel Clarke, Clare Gilson, Nicholas James, Malcolm Mason, Mahesh Parmar, Melissa Spears, Matthew Sydes and Claire Vale on behalf of the STAMPEDE team.

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