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...
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).

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.

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.

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


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.

The STAMPEDE trial was funded by Cancer Research UK, Medical Research Council, Astellas, Janssen, Novartis, Pfizer and Sanofi-Aventis.