

Upfront docetaxel 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).

In recent years, a number of new treatments have been approved for use in men whose disease has already stopped responding to hormone therapy. Docetaxel is one of those treatments and was the first to become a treatment option after hormone therapy failure when two trials showed that it improved survival among these men. Following this, a number of trials were started to test whether using docetaxel earlier, when men are starting long-term hormone therapy for the first time, improves survival. This briefing paper summarises new evidence from the largest of these trials, STAMPEDE, and a meta-analysis that brings together the results from all the trials evaluating this treatment approach that have reported so far.

How was docetaxel used in these trials?

In the STAMPEDE trial docetaxel was given at 75mg/m² for six three-weekly cycles with prednisolone or prednisone (10mg) daily, and standard premedication before each injection.

In the other trials included in the meta-analysis, docetaxel was given at the same dose and frequency as STAMPEDE but for six to nine cycles.

The evidence on upfront docetaxel

The STAMPEDE trial compared 592 men who received standard-of-care treatment (hormone therapy with or without radiotherapy) plus docetaxel, to 1,184 men who received standard-of-care alone. Of these men, 60% had metastatic disease and 40% non-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 2,992 men with metastatic disease from three trials, representing 93% of all men randomised across all identified trials. Median follow-up ranged from 2.4 to 6.9 years. For men with non-metastatic disease, the meta-analysis was able to include survival results from 2,120 men from three trials, representing 51% of all men randomised across all identified trials. Median follow-up ranged from 3.3 to 6.9 years.

Key points

- Docetaxel improves survival and delays treatment failure for men with metastatic prostate cancer who are starting long-term hormone therapy for the first time.
- For men with non-metastatic disease who are starting long-term hormone therapy for the first time, there is good evidence that docetaxel delays treatment failure, but there is less evidence for or against an effect on overall survival at this time. This position may change as further data becomes available.
- Use of docetaxel does increase the proportion of men reporting severe side-effects related to the addition of chemotherapy such as neutropenia, but these side-effects are temporary.
- Docetaxel is a commonly-used, inexpensive drug, so the shift to using it upfront in men starting long-term hormone therapy should be feasible, but this will require adjustments to patients' treatment pathways.

Does docetaxel improve survival?

The STAMPEDE results

The STAMPEDE trial found that, overall, docetaxel significantly improved median survival by 10 months (from 71 months to 81 months). The proportion of men alive five years after joining the trial increased from 55% in those who received the standard of care alone to 63% in those who had docetaxel in addition to the standard-of-care.

Docetaxel also delayed treatment failure (biochemical progression; local, lymph node or distant metastases progression; or death from prostate cancer). In the standard-of-care alone arm, the median time to treatment failure was 20 months, with only 28% of men not having experienced treatment failure by five years. In the group of men who also received docetaxel, the median time to treatment failure was 37 months (17 months later), and 38% of men survived five years without experiencing treatment failure.

The effect of docetaxel on overall survival did not appear to differ in different groups of men. Among the subgroup of men with metastatic disease, median survival increased from 45 months in the standard-of-care alone arm to 60 months with the addition of docetaxel. At five years, 50% of men with metastatic disease who received docetaxel were still alive, compared to 39% of those who received standard-of-care alone. There was strong evidence that this difference was not just due to chance.

The overall survival results for the subgroup of men with non-metastatic disease are not yet mature, as there are fewer deaths in both the standard-of-care and docetaxel groups. The STAMPEDE results suggest that docetaxel significantly delayed time to treatment failure as much for men with non-metastatic disease as for the metastatic subgroup.

Docetaxel also significantly increased the time to first skeletal

related event, such as spinal cord compression, fracture, bone pain or radiotherapy to bone, with mean survival time (restricted to the first 84 months on trial) increased by around seven months in those on docetaxel.

The meta-analysis results

Men with metastatic disease

The meta-analysis found that docetaxel significantly improved survival at four years from 40% to 49%. Docetaxel also reduced treatment failures from 80% to 64% at four years.

Men with non-metastatic disease

The meta-analysis found evidence that docetaxel significantly reduced treatment failures, from 30% to 22% at four years in men with non-metastatic disease. However, survival rates in this group are quite high so there are not yet enough data to reliably assess whether docetaxel improves survival in these men. The results currently available suggest that it may improve survival at four years from 80% to 82%, but the confidence interval is wide and the results are not statistically significant. Continued follow-up and reporting of those men who did not have metastatic disease at diagnosis is needed to answer this question with confidence. These trials will provide that data in a few years without the need for new trials.

Side-effects from docetaxel seen in the STAMPEDE trial

Severe side-effects (Grade 3 or above) were reported by 52% of men who received docetaxel in addition to the standard-of-care, compared to 32% of those who received the standard-of-care alone. This confirms that standard hormone therapy carries a significant treatment burden. Additional side-effects due to chemotherapy were common with docetaxel, but most patients were able to complete all six cycles of docetaxel in a timely fashion and with good

dose intensity. Common severe side-effects that were reported more often in the docetaxel plus standard-of-care group than the standard-of-care alone group were:

- **Febrile neutropenia** (reported in 15% of men in the docetaxel group, vs 1% in the standard-of-care alone group)
- **Neutropenia** (reported in 12% of men in the docetaxel group, vs 0% in the standard-of-care alone group)
- **General disorder:** lethargy, fever, asthenia (reported in 7% of men in the docetaxel group, vs 4% in the standard-of-care alone group)
- **Gastro-intestinal disorder:** diarrhoea, abdominal pain, constipation, vomiting (reported in 8% of men in the docetaxel group, vs 3% in the standard-of-care alone group)

These differences in severe side-effects occurred during the first six months, the great majority settling thereafter. After this there was no difference in the proportion of men reporting severe side-effects between the docetaxel plus standard-of-care group and the group who received standard-of-care alone.

Many men not treated with upfront docetaxel would end up receiving it later in their disease, and therefore be exposed to the same side-effects, but at a time when they are less well.

It should be noted that the men included in all three trials are on average younger and fitter than many men with advanced prostate cancer, therefore these results may not be applicable to all men. Clinicians and patients will need to decide on a case-by-case basis whether they are fit enough to undergo chemotherapy, and whether the potential benefits of docetaxel for them outweigh the additional side-effects. There will be a NICE Rapid Evidence Review and NHSE Policy statement published on this topic in the near future.

Implementing upfront docetaxel

Docetaxel is a widely-used drug in later stages of prostate cancer and in other cancers such as breast and lung; oncology units around the world are familiar with how to administer it. The main change to using it upfront, rather than once first-line hormone therapy fails, is that only six cycles are required, rather than the 10 usually recommended at relapse. A potential benefit of using docetaxel earlier is that more men may be able to tolerate it than when it is used for the first time later in the disease.

Docetaxel is included on the World Health Organisation's List of Essential Medicines, which means it is recognised as a drug that should be available within all health systems. Branded Taxotere is still available but docetaxel is now available as a generic drug, so its costs are low compared to many new cancer treatments. The evidence on the use of upfront docetaxel has relevance to high, middle and low-income countries.

Implementing upfront docetaxel as part of the standard of care for all suitable men presenting with metastatic disease should be feasible but will have implications for the clinical pathway and for resources in urology clinics and oncology clinics managing prostate cancer. The increased demand is likely to manifest as a greater need for oncology input at the point of diagnosis and increased demands on chemotherapy units.

As docetaxel delayed relapse and reduced symptomatic skeletal events by up to 40% there may be durable cost savings from implementation to offset the upfront costs. A Health Economic evaluation is in progress and will be published in 2016-7.

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.](#)

CONCLUSIONS

There is clear evidence that giving docetaxel at the time men with metastatic prostate cancer are starting long-term hormone therapy for the first time substantially improves their survival and delays treatment failure.

There is currently insufficient evidence from STAMPEDE alone, or when combined with other trials, to be certain whether docetaxel improves survival for men with non-metastatic disease starting long-term hormone therapy. However, there is clear evidence that it does delay treatment failure for these men. These gains in survival need to be weighed against an increase in side-effects. While docetaxel is associated with

more side-effects, once treatment with docetaxel has finished the numbers of men continuing to experience side-effects are similar to those who received hormone therapy alone. Docetaxel is a commonly prescribed chemotherapy and clinicians are experienced at helping patients to manage the side-effects.

Docetaxel is a relatively cheap, widely-used drug that is already common in the treatment of castrate-refractory prostate cancer. The evidence from STAMPEDE and the meta-analysis show that it should swiftly be incorporated into the standard of care for all suitable men starting long-term hormone therapy for the first time.

RECOMMENDATIONS

- Docetaxel should be incorporated into the standard of care for men with metastatic prostate cancer who are starting long-term hormone therapy for the first time and are fit enough to receive chemotherapy
- The increased risk of short-term severe side-effects should be discussed with patients, along with how these side-effects can be prevented or treated
- Further evidence is needed for men with non-metastatic prostate cancer; trials that are looking at upfront docetaxel for these men should continue to collect and report survival data, and consider contributing data to relevant individual participant data meta-analyses
- In the meantime, clinicians may wish to consider the use of upfront docetaxel for selected men with high-risk non-metastatic prostate cancer on the basis of the significant delay in time to treatment failure

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.