Up-front abiraterone for men with prostate cancer

Current treatment of hormone-naïve prostate cancer

Around 47,000 men are diagnosed with prostate cancer in the UK each year. Three to four in 10 men diagnosed with prostate cancer in the UK have very aggressive local disease or metastatic disease at diagnosis (around 15,000 to 19,000 men).

Long-term hormone therapy has been the mainstay of treatment for these men for decades. In recent years, adding radiotherapy has been shown to improve survival for men with locally-advanced disease. In 2015, results from the STAMPEDE trial and a meta-analysis on the use of the chemotherapy drug docetaxel were published. These showed a clear survival benefit of adding docetaxel to hormone therapy for men with metastatic prostate cancer, extending overall survival by 10 months. This approach is now being used in the NHS.

While docetaxel has a clear survival benefit, this comes at the cost of increased side-effects. Around half of men who had docetaxel reported severe side-effects (grade 3 or higher), compared to a third of men who had hormone therapy alone. The most common additional side-effects from docetaxel were febrile neutropenia, neutropenia, general disorder and gastro-intestinal disorders.

The STAMPEDE trial has continued to evaluate other treatments that may improve outcomes for men with prostate cancer. This briefing paper explores the results on adding abiraterone to hormone therapy.

Key points

- Adding abiraterone with prednisolone (“abiraterone”) to hormone therapy for men starting long-term hormone therapy significantly improves survival and delays disease progression
- The clinical evidence is strong enough to make adding abiraterone to long-term hormone therapy a new standard of care for men starting long-term hormone therapy for the first time
- Abiraterone is an expensive drug, so evidence on the cost-effectiveness of using it for men starting long-term hormone therapy for the first time is needed
- There may be benefits from combining docetaxel and abiraterone for these patients; further evidence on this is needed

About abiraterone

Abiraterone (also known as abiraterone acetate and Zytiga) is a type of hormone therapy that works by inhibiting the CYP17 enzyme, which is involved in the production of testosterone. It is currently licensed to treat metastatic castration resistant prostate cancer either before or after chemotherapy. Trials in these settings have shown that abiraterone has an overall survival benefit of around four months. Abiraterone is given with steroids, usually prednisolone.

The STAMPEDE trial looked at using abiraterone upfront, rather than once resistance to standard hormone therapy has developed, to test the hypothesis that it may be even more active in combination with first-line hormone therapy, and prevent or delay the development of castrate refractory disease.
Does abiraterone improve survival?

STAMPEDE found that abiraterone substantially improved overall survival. There was a relative reduction of 37% in deaths, after a median follow up of 40 months. Three year survival increased from 76% in the control arm to 83% in the abiraterone arm. This difference was statistically significant.

There is no evidence that the treatment effect varies by metastatic status; there is currently more evidence from the metastatic patients but this is because men with non-metastatic disease tend to live longer, so it takes longer for the information to accumulate. There was no good evidence of the efficacy of abiraterone varying by other characteristics either.

As well as improving overall survival, abiraterone significantly improved failure free survival, delaying the first treatment failure event (PSA progression or radiological progression or clinical progression) in the first 54 months after randomisation by around 14 months. Three year failure free survival was improved from 45% in the control arm to 75% in the abiraterone arm. Abiraterone improved progression free survival by 60%, and reduced skeletal related events by 54%.

Side-effects

One in three patients in the control arm reported severe side-effects, compared to nearly one in two patients in the abiraterone arm. The types of side-effects seen were those that are expected in patients taking long-term androgen deprivation therapy and abiraterone. The table on the next page gives details of the most common severe side-effects reported.

One in five of the men who stopped taking abiraterone say they did so because of side-effects.

Implementation

As abiraterone is taken in tablet form, it is relatively straightforward to implement in principle.

Affordability is more likely to be a barrier to implementation. We are awaiting results of cost-effectiveness analysis based on the STAMPEDE trial data. The manufacturers, Janssen, have a commercial access agreements with NHS England for abiraterone to treat metastatic hormone-relapsed prostate cancer, prior to or after chemotherapy. Given the size of effect abiraterone has when used upfront, clinicians and patients are likely to be keen that the NHS and Janssen come to an agreement on price that would allow patients to benefit from abiraterone upfront.

Marketing authorisation

Abiraterone has a UK marketing authorisation for use with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men. The STAMPEDE trial looked at using abiraterone at an earlier stage than this, outside its marketing authorisation. The manufacturers may wish to apply to the FDA and EMA to extend the license of the drug to include hormone-naïve disease.

About the STAMPEDE trial

The STAMPEDE trial is a multi arm multi stage phase III randomised controlled trial protocol serving as a platform to evaluate a number of approaches which may improve outcomes for men with hormone-naïve locally advanced or high risk prostate cancer.

In the “abiraterone comparison”, 957 men who were randomised to receive standard of care (hormone therapy with or without radiotherapy) were compared to 960 men who were randomised to receive abiraterone (4 pills a day) plus prednisolone plus standard of care (hormone therapy with or without radiotherapy). Of these men, 52% had metastatic disease, the average age was 67, and the median pre-hormone therapy PSA was 53. 96% of men with non-metastatic disease that had not spread to the nodes were planned for adjuvant radiotherapy, as were 62% of men with non-metastatic node positive disease.
Common severe side-effects:

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Group A</th>
<th>Group G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes and / or impotence</td>
<td>14 in 100 men</td>
<td>14 in 100 men</td>
</tr>
<tr>
<td>Problems with joints (for example, arthritis)</td>
<td>5 in 100 men</td>
<td>7 in 100 men</td>
</tr>
<tr>
<td>Cardiovascular problems such as hypertension or heart problems</td>
<td>4 in 100 men</td>
<td>10 in 100 men</td>
</tr>
<tr>
<td>Diarrhoea, stomach ache, constipation or sickness</td>
<td>4 in 100 men</td>
<td>5 in 100 men</td>
</tr>
<tr>
<td>Problems with tiredness, fever or weakness</td>
<td>3 in 100 men</td>
<td>5 in 100 men</td>
</tr>
<tr>
<td>Breathlessness or colds or flu</td>
<td>2 in 100 men</td>
<td>5 in 100 men</td>
</tr>
<tr>
<td>Abnormal results from lab tests checking if their livers were working properly</td>
<td>1 in 100 men</td>
<td>7 in 100 men</td>
</tr>
</tbody>
</table>

STAMPEDE found:

After 3 years

- **Standard hormone therapy**
  - Alive without disease coming back
  - Alive with disease come back
  - Dead from any cause

- **Abiraterone + standard hormone therapy**
  - Alive without disease coming back
  - Alive with disease come back
  - Dead from any cause
Abiraterone or docetaxel?
There have not yet been any fully powered trials directly comparing adding abiraterone or docetaxel to long-term hormone therapy for these men. Within STAMPEDE, the reported effect size of abiraterone on overall survival is slightly larger than that reported for docetaxel, but abiraterone has a substantially larger effect on failure free survival than was seen with docetaxel. However, the patient mix was slightly different and it may not be appropriate to make this comparison.

Abiraterone has a lower profile of side-effects and is an easier treatment to administer logistically than docetaxel. Conversely, treatment duration with abiraterone is longer than docetaxel, some patients suffer chronic effects of steroid usage (docetaxel is also given with prednisolone but for less time) and cost is a consideration. In the absence of comparative data, patient choice and healthcare systems’ ability to support the use of these drugs will determine the relative use of docetaxel and abiraterone.

The key question may not be whether to use abiraterone or docetaxel, but whether the benefits could be combined. The two drugs have different mechanisms of action, and abiraterone has been shown to be effective following docetaxel, so there may potentially be an additive effect by giving abiraterone immediately after docetaxel. The PEACE-1 trial, which is currently ongoing, may help to clarify this.

Conclusion
Abiraterone is highly effective at improving both survival and the length of time before treatment fails among men starting long-term hormone therapy for the first time. The effect sizes seen in STAMPEDE are remarkable. However, the cost of this expensive drug is likely to be a barrier to rapid implementation.

Recommendations
1. Adding abiraterone acetate plus prednisolone is a new standard of care for men with metastatic or non-metastatic prostate cancer starting long-term hormone therapy for the first time
2. Given the remarkable size of effect seen, drug regulatory and technology appraisal bodies should consider the evidence as swiftly as possible

Further information
- Briefing paper about the STAMPEDE and meta-analysis docetaxel results http://bit.ly/2p41CKh

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