Treatment of Prostate cancer – and why I refuse to know my PSA

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Princess Margaret Hospital and University of Toronto

Outline of Presentation

1. Requirements for screening to be effective in reducing mortality from a disease
2. Potential for screening to be harmful
3. Screening for prostate cancer; results of the screening trials
4. What did we gain from discovering PSA?
5. Advances in management of metastatic prostate cancer – hormonal therapy
6. Advances in management of metastatic prostate cancer – chemotherapy and other approaches
Potential conflicts of interest

I have advised multiple companies about design of trials for prostate cancer for which I have received contributions to my research fund.

I have chaired international company-sponsored trials for hormone-refractory prostate cancer (TAX-327, VENICE)

I do not accept personal remuneration from companies

Requirements for screening to be effective in reducing mortality from a disease

• A test that increases the probability of detecting cancer in an asymptomatic individual
  ➢ Ideally the test should be simple, non-invasive, have high specificity, and be inexpensive

• Available treatment that leads to better outcome than treatment applied at onset of symptoms
  ➢ Survival from diagnosis will be improved by screening (lead time bias) but may not lead to improvement in overall mortality

• The disease must be common

• Benefits of screening must outweigh the harms
Various types of bias can influence the interpretation of screening

- **Selection bias:**
  - Individuals who present for screening may be more likely to have the disease (motivated, and often better general health)

- **Lead-time bias**
  - Screening will advance the date of diagnosis, and survival from diagnosis, even if it has no effect on course of disease

- **Length bias**
  - Screening is more likely to detect disease in those with a long pre-clinical history (i.e., those with indolent disease who might not need treatment) than in those with a short preclinical phase

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**Lead-time and length bias**


A. Comparison of date marks

<table>
<thead>
<tr>
<th></th>
<th>Inception</th>
<th>Escape from cure</th>
<th>Date of diagnosis</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Not screened</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Difference in dates is lead time

B. Comparison of survival

- Screened
- Not screened

Population alive vs. Time (years)

Point of application of screening test

Horizontal lines represent the length of time that disease is present prior to the death of the patient.
Rigorous trials to evaluate potential benefits of screening

- Rigorous evaluation requires a large randomised controlled trial comparing screened and unscreened populations
- The primary endpoint is usually cause-specific mortality (i.e. deaths due to the cancer which is being screened)
- Ideally the endpoint should be overall mortality
  - It is not a successful strategy to save lives due to a cancer but to have an equal (or possibly greater) mortality as a result of investigations prompted by screening

Potential for screening to be harmful

- Complications of the test itself (including induced anxiety)
- Harms from investigations stimulated by positive tests (both false and true positives).
  - e.g. Complications from biopsy of breast, prostate, lung etc
- Detection and unnecessary treatment of cancers that would never have caused medical problems

N.B. Giving a diagnosis of cancer to someone who would never become aware of it, and the toxicity of treatment applied to produce a “pseudo-cure”, are major potential harms due to screening.
**Slippery linkage bias in screening trials**

- **Screen**
  - More subjects tested for disease
  - Less deaths from cancer balanced by those resulting from screening

- **Control**
  - Reported cancer-specific mortality
  - Overall mortality

Adapted from Black et al, JNCI 2002; 94:167-73

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**An example of slippery linkage**

- **Mr Jawal** has PSA screening for prostate cancer. His PSA is 5ng/ml
- He undergoes trans-rectal biopsies which show normal prostatic epithelium
- He develops a pelvic abscess after the procedure which requires drainage and i.v. antibiotics
- Six months later he dies suddenly
- Autopsy shows a pulmonary embolus, a large clot in his internal iliac vein, and no evidence of prostate cancer
- **Classification**: Death unrelated to prostate cancer
Particular problems with screening for prostate cancer

- Many men have occult prostate cancer but die of other causes
  - detecting and treating their disease is a disservice
- Investigation is invasive
  - complications are rare, but so also is extending life through treatment
- Slippery linkage will occur
  - death from pulmonary embolus 6 mos after biopsy will be called "unrelated"
- Treatment is not very effective
  - and has considerable side-effects

How good is PSA as a screening test?

It is difficult to define a reliable PSA cut off to separate those with and without disease.

CONCLUSIONS
Biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to be in the normal range.
"Is cure necessary in those in whom it may be possible?"

"Is cure possible in those in whom it may be necessary"

W.F. Whitmore Jr, 1990

N.B. The commonest cause of death in men with prostate cancer is..... Cardiovascular disease

The disparity between reported incidence and mortality rates leads to the probable conclusion that only a small proportion of diagnosed low-risk prostate cancers will progress to life-threatening disease during the lifetime of the patient.
Moreover, because of length bias, PSA screening is more likely to detect men with slowly-progressive cancer rather than the small proportion of men who are destined to die as a result of their cancer.

And how effective is radical treatment in preventing death due to prostate cancer?

Scandinavian RCT of 695 men (with clinical diagnosis)

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer  

Anna Bill-Axelson, M.D., Lars Holmberg, M.D., Ph.D., Mirja Rustu, M.D., Ph.D.

J Natl Cancer Inst 2008;100:1144–1154
## The Scandinavian Trial...

*J Natl Cancer Inst* 2008;100:1144–1154

<table>
<thead>
<tr>
<th>Median F/U = 10.8 years</th>
<th>Radical prostatectomy (N=347)</th>
<th>Watchful waiting (N=348)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths</td>
<td>137 (33%)</td>
<td>156 (40%)</td>
<td>0.82 (0.65-1.03) p=0.09</td>
</tr>
<tr>
<td>Deaths due to prostate cancer</td>
<td>47 (13.5%)</td>
<td>68 (19.5%)</td>
<td>0.65 (0.45-0.94) p=0.03</td>
</tr>
<tr>
<td>Deaths of men &gt;65 yrs</td>
<td>42%</td>
<td>39%</td>
<td>1.04 (0.77-1.40) P=0.81</td>
</tr>
</tbody>
</table>

- Number needed to treat (NNT) to save one life is 19
- Benefit appears restricted to men with age<65
- NNT will be much greater for screen-detected cancer
- You don’t buy immortality!

City-wide Rounds, Toronto

## Current results of the prostate cancer screening trials

**Mortality Results from a Randomized Prostate Cancer Screening Trial Screening and Prostate-Cancer Mortality in a Randomized European Study**


Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lijia, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määtänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators

City-wide Rounds, Toronto
The American (PLCO) trial

• 76,693 men (aged 55-74) randomised to screening or not between 1993 & 2001
• Screening: Annual PSA testing for 6 years and digital rectal exams for 4 years
• Follow-up determined by practitioners
• Primary analysis: Intent to screen comparison of prostate-specific mortality
• Analysis after 7 years of follow-up

... is unfortunately not interpretable due to adoption of PSA screening in the control group ("Contamination")

Compliance with screening:

In those assigned to screening: 85%
In the control group: 40% after 1 year
52% after 6 years

Not surprisingly there were no differences in low rates of death due to prostate cancer in the "screened" (N=50) and "control" (N=44) groups
The European trial

- 162,243 men in core age group of 55-69 randomised to screening or not
- Screening: PSA testing at an average interval of 4 years
- Most centres used a PSA threshold of 3ng/ml for bx
- Primary analysis: Intent to screen comparison of prostate-specific mortality
- 82% compliance in screened group
  Low contamination in control group
- First analysis after median 9 years of follow-up

Main results of the European trial

382,160 Subjects 50-74 yr old
162,387 Were in the core aged 55-69
82,836 Were assigned to the screening group
72,890 Were 55–69 yr old
6830 Had prostate cancer
5990 Were 55–69 yr old

Figure 1. Enrollment and Outcomes, Accrual
The predefined core age group for the years 55 and 69 years.

Figure 2. Cumulative Risk of Death from Prostate Cancer.
As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The Nielsen–Aalen method was used for the calculation of cumulative hazard.
What do these results mean?

• Relative risk of dying of prostate cancer in the screened as compared to control group = 0.80 (0.65-0.98); p=0.04
• Absolute difference in risk of death from prostate cancer = 0.71 per 1000 men

1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer.

Here is a man of a certain age who refuses to know his PSA

... and I will not change my mind even if the difference in prostate cancer-specific mortality increases with further follow-up of the European trial
Reasons for not screening

- It leads to massive over-treatment with radical prostatectomy (RP) or radiotherapy in men who would never develop clinical prostate cancer
- Even for clinically diagnosed prostate cancer, the Scandinavian trial shows only small benefits for RP over watchful waiting, and only in younger men
- I do not believe that the toxicity of radical treatment (surgery or radiotherapy) warrant the small benefits for most men in this trial.
- And benefits will be less in screen-detected cancers

So what have we gained from discovery of PSA?

Different scenarios where PSA is often measured

- Screening of healthy men to detect occult prostate cancer
- To detect recurrence after primary treatment of localised prostate cancer
- As a marker of response or progression during treatment of advanced disease
All we are doing by measuring PSA and then not acting on the information is causing anxiety.

We are converting healthy men into PSA cripples.

Management of Advanced Prostate Cancer
A hypothetical patient

- Mr Eriksson is a 68 year old man with a 3-month history of pain in several bones
- On rectal examination his prostate is enlarged and hard
- A needle biopsy shows prostate cancer, Gleason grade 8/10
- His bone scan is “positive” and his serum level of PSA is 245ng/ml

How should Mr Eriksson be treated?

Which option for hormonal therapy would you recommend?

A. Orchiectomy
B. LHRH agonist (e.g. goserelin; leuprolide) with short course of antiandrogen to prevent flare
C. Antiandrogen alone (e.g. bicalutamide)
D. Combined androgen blockade (LHRH agonist + antiandrogen)
E. Intermittent hormonal therapy
The patient-based meta-analysis showed no significant benefit of MAB after 8000+ pts and 27 trials.

MAB is expensive, has increased toxicity and should not be used.
German study: Miller et al: ASCO 2007

Prostate cancer M+ and/or N+

Goserelin/Bicalutamide x 24 weeks

PSA < 4 mg/dl
Decrease > 90%

Intermittent

N=335

PSA < 4 mg/dl
stop therapy

PSA > 10 mg/dl
resume therapy

Continuous

PSA Progression
3 x rise

Second line treatment

PSA Progression
3 x rise

Second line treatment

Intermittent: median 16.6 months
Continous: median 11.5 months

P = 0.17

Time to Progression
### Randomized trials of intermittent vs continuous hormonal therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Setting</th>
<th>Treatment</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Leval Clin Prost Cancer 2002</td>
<td>68</td>
<td>T3-4, N+, M+</td>
<td>goserelin+ flutamide</td>
<td>↓progression rate to androgen independence (AI)</td>
</tr>
<tr>
<td>Calais da Silva Europ Urol 2009</td>
<td>626</td>
<td>T3-4, N+, M+</td>
<td>triptorelin + cyproterone</td>
<td>similar time to AI &amp; survival improved QoL</td>
</tr>
<tr>
<td>Miller ASCO 2007</td>
<td>335</td>
<td>N+, M+</td>
<td>goserelin + bicalutamide</td>
<td>similar time to AI improved QoL</td>
</tr>
<tr>
<td>Thun AUA 2007</td>
<td>167</td>
<td>rising PSA after RP</td>
<td>leuprolide</td>
<td>similar time to AI improved QoL</td>
</tr>
</tbody>
</table>

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**Should intermittent androgen blockade now be regarded as standard therapy?**

**In answer to the question:**

“What would you do doctor if you were me?”

**My response would be “Yes”**

**Advantages:**

- Less time on a potentially toxic therapy
- Marked decrease in cost

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**City-wide Rounds, Toronto**
Mr Eriksson’s Treatment

- Mr Eriksson is treated with an LHRH agonist with short term bicalutamide to prevent flare
- He becomes pain free within 2 weeks, and one year later his PSA is 0.1
- However, he does have one or two side effects of treatment........

Which of the following is NOT a known side effect of hormonal therapy?

A. Impotence
B. Gynecomastia
C. Hot flashes (“male menopause”)
D. Loss of muscle and bone
E. Anemia
F. Thrombocytopenia
G. Increased risk of cardiovascular events
Prevention of Bone Loss for men on hormonal therapy

Exercise is probably the best protection against loss of bone and muscle.

All men receiving ADT should be taking calcium and vitamin D.

Several randomized trials have shown that bisphosphonates can prevent bone loss due to hormone treatment.

A recent trial showed that Zoledronate given annually is effective in preventing bone loss.

Role of Bisphosphonates in Preventing Bone Loss

- **106 men starting ADT**
  - Zoledronate 4mg every 3 mos
  - 5.6% increase
  - Smith et al: J Urol 2003;169:2008-12

- **40 men starting ADT**
  - Placebo
  - 2.2% decrease

- **40 men starting ADT**
  - Zoledronate 4mg every 12 mos
  - 4.0% increase

City-wide Rounds, Toronto
Androgen Deprivation Therapy (ADT) and Metabolic Syndrome

There is increasing evidence that ADT raises insulin levels and may increase diabetes and cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>CHF</th>
<th>MI</th>
<th>Sudden death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No treatment</strong></td>
<td>20.9</td>
<td>61.3</td>
<td>10.9</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>LHRH agonist</strong></td>
<td>29.0</td>
<td>72.3</td>
<td>13.6</td>
<td>12.9</td>
</tr>
<tr>
<td><strong>Orchiectomy</strong></td>
<td>24.5</td>
<td>63.3</td>
<td>13.2</td>
<td>12.5</td>
</tr>
</tbody>
</table>

>73,000 men age >65 treated for localized Ca prostate 1992-1999, observed through 2001
>1 in 3 received ADT

Other recent series have confirmed these effects
Castration Resistance

- 18 months after starting ADT, Mr Eriksson’s PSA has increased to 5
- At 24 months the PSA is 50 and he is beginning to have some aching pain

He has a transient response of 6 months to adding bicalutamide.
He does not have further response to bicalutamide withdrawal

Subsequent hormonal therapy

Multiple small series indicate that Mr Eriksson, who has progressed after primary ADT, followed by addition and withdrawal of bicalutamide has a low but definite chance of responding to:

- Other anti-androgens (e.g. nilutamide, flutamide)
- Inhibitors of steroid synthesis (e.g. ketoconazole)
- Estrogens such as DES
- Glucocorticoids such as dexamethasone

For this reason the term “Castration-resistance” is more appropriate than “Hormone-refractory.”
Androgen-dependent pathways remain important targets

Several studies have shown substantial androgen levels within prostatic tissue (including cancer) which can stimulate androgen pathways in the face of very low levels of circulating androgens.

Intraprostatic Androgens and Androgen-Regulated Gene Expression Persist after Testosterone Suppression: Therapeutic Implications for Castration-Resistant Prostate Cancer

Habib A. Mostaghel,1,2 Stephanie T. Pugs,2,3 Daniel W. Lin,3,4 Ladan Fazli,5 Ilia M. Coleman,1 Lawrence D. True,1 Beatrice Knausen,1 David L. Hess,2 Colleen C. Nelson,1 Alvin M. Matsumoto,5 William J. Benz,6 Martin E. Gleave,5 and Peter S. Nelson1

1Weill Cornell Medical College, New York, New York, 2Department of Translational Science and Molecular Medicine, Michigan State University, East Lansing, Michigan, 3Department of Medicine, University of Washington, Seattle, Washington, 4Vancouver General Hospital, Vancouver, British Columbia, Canada, and 5Prostate Cancer Research Center, Ontario, Canada, and Virginia

Abstract

Androgen deprivation therapy (ADT) remains the primary treatment for advanced prostate cancer. The efficacy of ADT has not been rigorously evaluated by demonstrating suppres-

Two promising new agents for hormonal treatment of CRPC

Abiraterone acetate, an inhibitor of androgen synthesis

MDV-3100, an irreversible inhibitor of the androgen receptor

Both drugs have shown high rates of PSA response in phase II trials for men with CRPC, both pre- and post-chemotherapy

Both drugs are being evaluated in large RCTs:

Abiraterone + prednisone vs prednisone, MDV-3100 vs placebo, in both pre and post-chemotherapy settings.
Increased emphasis on “time to event” endpoints as compared to “response” endpoints

Early changes in PSA or pain to be ignored (unless overwhelming evidence of clinical progression) and treatment to be continued for at least 12 weeks

No need to wait for anti-androgen withdrawal if there was no response to adding the anti-androgen

Decreased emphasis on bone scans and rigorous requirements for defining progression by bone scan

Abiraterone: a promising new drug
(from Attard et al, JCO 2008;26:4563-71)
Derived from screen of anti-androgens that retain activity in face of increased expression of the AR

\[ \uparrow \text{binding affinity to AR compared to bicalutamide} \]

\[ \downarrow \text{nuclear translocation of AR} \]

\[ \downarrow \text{binding of DNA to androgen response elements} \]

\[ \downarrow \text{recruitment of c-activators} \]

**Phase II results (PSA response rates in men with CRPC) for Abiraterone and MDV3100**

**Abiraterone, Chemotherapy-naïve**


**Abiraterone, Post-chemotherapy**

36% (22/57) (Danila et al: JCO 2010;28:1496-501)

51% (24/47) (Attard et al: JCO 2010;28:1489-95)

**MDV3100, Phase I/II (54% post-choemo)**

56% (78/140) (Scher et al: Lancet 2010;375:1437-46)
How should Mr Eriksson be managed for castration-resistant prostate cancer (CRPC)

- Recognize that he has incurable cancer and Quality of life is important
- Optimize Mr Eriksson’s pain control with regular dosing of narcotic medication, such as morphine
- Give regular laxatives to control the constipation that will be caused by morphine
- Give local radiotherapy to the right hip, his dominant site of pain
- Consider chemotherapy for men with diffuse symptoms or rapid PSA progression

Chemotherapy for castration-resistant prostate cancer

- Earlier trials showed that mitoxantrone + prednisone gave superior pain control and QoL compared to prednisone alone. There was no improvement in survival but the trials were too small to detect small differences (Tannock et al, JCO 1996;14:1756-64)
- Mitoxantrone remains a reasonable option and is very well tolerated.
- More recent trials have shown higher response rate (PSA and pain) and improved survival with docetaxel and prednisone, albeit with increased toxicity (Tannock et al, NEJM 2004;351:1502-12 Petrylak et al, NEJM 2004;351:1513-20)
**TAX 327 Study**

(Tannock et al, NEJM, 2004;351:1502-12)

- **Docetaxel 75 mg/m²**
  - q3wks x 10 cycles

- **Docetaxel 30 mg/m² weekly**
  - for 5 of 6 weeks x 5 cycles

- **Mitoxantrone 12 mg/m² q3 wks x 10 cycles**

1006 patients with HRPC

All patients received prednisone 10mg/day

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**Overall Survival**

- **Docetaxel 3wkly**
- **Docetaxel wkly**
- **Mitox 3 wkly**

Probability of Surviving vs. Months
**TAX 327: Secondary Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel q 3wk</th>
<th>Docetaxel weekly</th>
<th>Mitoxantrone q 3wk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain Response Rate</strong></td>
<td>34.6% p=0.01</td>
<td>31.2% p=0.08</td>
<td>21.7%</td>
</tr>
<tr>
<td><strong>PSA Response Rate</strong></td>
<td>45.4% p=0.0005</td>
<td>47.9% p&lt;0.0001</td>
<td>31.7%</td>
</tr>
<tr>
<td><strong>QOL Response rate</strong></td>
<td>21.9% p=0.009</td>
<td>22.6% p=0.005</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

**Mr Eriksson is treated with docetaxel every three weeks and prednisone**

- He has relief of pain and by the 3rd course of treatment he is able to stop taking morphine.
- His PSA declines steadily from 150 to 25 with the first 6 courses of treatment, but then begins to rise again to 70 after 8 courses.
- He develops numbness in his hands and feet. His docetaxel is stopped because of this progression and to avoid further side effects.

**Should Mr Eriksson also receive a bisphosphonate?**
Zoledronate Study
(Saad et al, JNCI 2002;94:1458-68 and 2004;96:879-82)

643 pts with HRPC

Zoledronte 8mg q3wks

Zoledronte 4mg q3wks

Placebo q3wks

1. 8mg dose caused renal insufficiency and dropped

2. Less bone events with 4mg dose (44%) compared to placebo (33%, p=0.02) but no difference in QL

3. More low-grade toxicity with zoledronate

Use of Zoledronate with Chemotherapy

- Zoledronate is a useful drug to decrease bone events in selected patients.
- Some cases of osteonecrosis of the jaw
- Annual zoledronate is sufficient to prevent osteopenia in patients on long-term anti-androgen therapy
- I know of no evidence to support use of this expensive drug at 3-weekly intervals with chemotherapy
- We are conducting a trial to evaluate duration of suppression of bone turnover after zoledronate
Is the RANK-ligand inhibitor Denosomab superior to Zoledronate?

Denosomab is a fully humanized monoclonal antibody against RANK-L

A RCT of 1901 patients compared denosomab with zoledronate (Fizazi et al, ASCO, 2010)

Time to first Skeletal Related Event (SRE) was longer with denosomab – but there was no difference in survival or time to tumour progression.

Adverse events were similar in both arms.

Little to recommend this (undoubtedly) expensive drug.

Might Mr Eriksson have greater benefit if treated with a molecular targeted agent in combination with docetaxel?

Completed RCTs evaluating docetaxel plus:
- High-dose calcitriol (DN-101)
- Bevacizumab
- GVAX (vaccine against common prostate cancer antigens)

…. have all been negative

Other RCTs are evaluating docetaxel plus:
- Aflibercept (VEGF-Trap)
- Lenolidamide (Thalidomide analogue)
- Atrasentan or Zibentan (Endothelin A antagonists)
- Dasatanib (src/SFK inhibitor)
- Custirsen (OGX-011, anti-clusterin, pro-apoptotic)
The ASCENT2 study: Docetaxel plus high-dose calcitriol versus docetaxel (plus prednisone) for patients with progressive CRPC (Scher et al, ASCO 2010)

Men with metastatic CRPC without prior chemotherapy (N=953)  

\[
\text{Docetaxel 75 mg/m}^2 \text{ q 3 wk + prednisone (Control, n=476)}
\]

\[
\text{Docetaxel 36 mg/m}^2 \text{ weekly 3/4 + 45 µg DN-101 + prednisone (ASCENT, n=477)}
\]

Study was based on a placebo-controlled phase II study suggesting that docetaxel with DN-101 may increase survival compared to docetaxel alone.

Results of ASCENT 2

<table>
<thead>
<tr>
<th></th>
<th>DN-101</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (months)</td>
<td>16.8</td>
<td>19.9</td>
<td>0.019 (0.002 by logrank)</td>
</tr>
<tr>
<td>Deaths due to prostate cancer</td>
<td>142</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Deaths due to other cause</td>
<td>32</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Dose modifications for docetaxel</td>
<td>229</td>
<td>160</td>
<td></td>
</tr>
</tbody>
</table>

Trial was stopped early after an interim analysis showed more deaths in the DN-101 arm.

9/23/10  
City-wide Rounds, Toronto
What can we learn from this negative experience?

1. Docetaxel is a difficult partner – as yet, no drug has augmented its benefit for men with CRPC
2. Even large randomized phase 2 trials may be poor predictors of results in phase III
3. The role of dexamethasone

Some authors have suggested that the superior results of docetaxel compared to mitoxantrone in TAX327 and SWOG 99-16 might be due partly to dexamethasone

In ASCENT2 the experimental arm received greater exposure to dexamethasone (24mg weekly 3/4) compared to the control arm (24mg q 3 weeks) but had poorer survival

Docetaxel + prednisone +/- bevacizumab for CRPC (Kelly et al, ASCO, 2010)

Primary endpoint = Survival (OS)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>DP + B (N=524)</th>
<th>DP (N=526)</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (mos)</td>
<td>22.6</td>
<td>21.5</td>
<td>0.91</td>
<td>0.18</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>9.9</td>
<td>7.5</td>
<td>0.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA-RR</td>
<td>69.5%</td>
<td>57.9%</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>††</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increase in OS and PFS are virtually identical to overview of 3 breast cancer trials – considered positive because primary endpoint was PFS.
Three months after stopping docetaxel, Mr Eriksson is beginning to experience new pain in several areas and is back on morphine.

His PSA is fairly stable in the range of 60-80

Does this mean that his pain is due to causes other than progression of his disease?

NO - prostate cancer can evolve to a more aggressive form which produces less (or no) PSA during treatment

Should Mr Eriksson receive second-line chemotherapy?

- Mitoxantrone is often used second line, and is associated with ~15% PSA RR after docetaxel
- Some patients may respond to retreatment with docetaxel after an interval off-treatment
- Satraplatin was shown in a randomized trial to increase time to progression (but not survival) compared with prednisone alone – it was not approved by the FDA
- Cabazitaxel was shown recently to improve survival in an RCT compared to mitoxantrone
The TROPIC study: cabazitaxel or mitoxantrone with prednisone for metastatic CRPC previously treated with docetaxel (De Bono et al, ASCO 2010)

Primary objective: Overall survival (To detect or R/O a HR<0.75)

Secondary objectives: PFS (tumor progression, pain progression, PSA progression, or death from any cause), response rate, safety

Men with metastatic CRPC progressing during and after docetaxel (N=755)

- Cabazitaxel 25 mg/m² q 3 wk + prednisone for 10 courses (CBZP, n=378)
- Mitoxantrone 12 mg/m² q 3 wk + prednisone for 10 courses (MP, n=377)

The study met its primary objective

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>12.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.61–0.84</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

Combined median follow-up: 13.7 months

Proportion of OS (%) vs Time (months)
### Important secondary results

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>MP</th>
<th>CBZP</th>
<th>p-value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor response (%)</td>
<td>4.4</td>
<td>14.4</td>
<td>0.0005</td>
<td>MP consistent with other studies</td>
</tr>
<tr>
<td>PSA response (%)</td>
<td>17.8</td>
<td>39.2</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Pain response (%)</td>
<td>7.8</td>
<td>9.2</td>
<td>0.63</td>
<td>Disappointing !</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>MP</th>
<th>CBZP</th>
<th>p-value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic death</td>
<td>7</td>
<td>18</td>
<td>(4.9%)</td>
<td>Concerning!</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>1.3%</td>
<td>7.5%</td>
<td></td>
<td>Major impairment to quality of life</td>
</tr>
<tr>
<td>Diarrhea (≥ grade III)</td>
<td>0.3%</td>
<td>6.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>????</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Other trials are evaluating various molecular targeted agents

Ongoing or completed phase III trials are evaluating:
- Atrasentan and Zibotentan (Endothelin A antagonists)
- Ipilumumab (anti-CTL4)
- Sunitinib (multiple tyrosine kinase inhibitor)
- Alpharadin (bone-seeking radioisotope)

Multiple targeted agents are in phase II evaluation
Mr Eriksson has treatment with mitoxantrone

He improves for about 4 months but then starts to have pain again and is tired.

His treatment is stopped, and he accepts that treatment will now be designed to minimize his symptoms.

On his next visit to clinic, Mr Eriksson is clearly failing, but his wife brings a newspaper clipping about a new type of immunotherapy for prostate cancer

Couldn't this treatment be used to save my husband's life, she asks?
Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Premo, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators


The estimated cost is $93,000.

The median survival was 4.1 months longer in the sipuleucel-T group (25.8 months) than in the placebo group (21.7 months) (Fig. 2A).

No. at Risk

Sipuleucel-T 341 274 129 49 34 1
Placebo 171 123 55 19 4 1

Estimated cost = $93,000

Thank you for your attention—and also to our international fellows who stimulate my ideas (but are not responsible for them)

ASCO 2007

Spain (2) Switzerland Australia (2)

Germany

New Zealand

(Brazil)

(France)

(Slovenia)

(Nepal)

City-wide Rounds, Toronto