Evolution of Chemotherapy for Hormone Refractory Prostate Cancer

Ian F Tannock MD, PhD
Daniel E Bergsagel Professor of Medical Oncology
Princess Margaret Hospital and University of Toronto
In 1985, two articles were published in *JCO* suggesting that there was no role for chemotherapy for men with prostate cancer, outside of a well designed clinical trial.

**A Reevaluation of Nonhormonal Cytotoxic Chemotherapy in the Treatment of Prostatic Carcinoma**

By Mario A. Eisenberger, Richard Simon, Peter J. O’Dwyer, Robert F. Wittes, and Michael A. Friedman

**Is There Evidence That Chemotherapy Is of Benefit to Patients With Carcinoma of the Prostate?**

By Ian F. Tannock
With that background, we and others began trials of non-hormonal systemic therapy for men with prostate cancer.

**Principles of treatment:**

- Patients are often old and frail - use gentle drugs
- The aim is to palliate patients - i.e. to improve their duration and quality of survival
- Improvement in symptoms and quality of life should be measured directly
- Doctors are poor judges of patients' quality of life - This must be assessed by the patients themselves
Using those principles the Canadian group undertook a RCT comparing mitoxantrone and prednisone to prednisone alone for men with HRPC and pain (Tannock et al JCO 1996;14:1756-64).

The trial showed improved pain control with chemotherapy – but no difference in survival (it was not powered to show a survival difference).

The FDA approved mitoxantrone and prednisone as palliative treatment for men with symptomatic HRPC – the first time a chemo drug had been approved based on a symptom control endpoint.
# Phase 3 Trials of Mitoxantrone + Corticosteroid

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patients</th>
<th>Pain response</th>
<th>PSA Response</th>
<th>Diff in arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>M+ P vs P (Canadian)</td>
<td>161</td>
<td>Symptomatic</td>
<td>38%</td>
<td>34%</td>
<td>M+P &gt; P</td>
</tr>
<tr>
<td>M+H vs H (CALGB)</td>
<td>242</td>
<td>Mixed</td>
<td>Better than H</td>
<td>37.5%</td>
<td>M+H &gt; H</td>
</tr>
<tr>
<td>M+P vs P (Berry et al, 2002)</td>
<td>120</td>
<td>Asymptomatic</td>
<td>N/A</td>
<td>48%</td>
<td>M+P &gt; P</td>
</tr>
<tr>
<td>M+P+clodronate vs M+P+placebo (Canadian)</td>
<td>209</td>
<td>Symptomatic</td>
<td>39%</td>
<td>29%</td>
<td>No diff</td>
</tr>
</tbody>
</table>
These trials showed that elderly men could tolerate chemotherapy and derive palliative benefit from it.

The next generation of chemotherapy trials sought to improve survival.
TAX 327 Study

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

1006 patients with HRPC

- 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

All patients received prednisone 10mg/day

11/11/2008
PMH Anniversary Meeting
TAX 327: Endpoints

- **Primary endpoint:**
  Overall survival (OS)

- **Secondary endpoints:**
  - Pain response (if Pain Intensity $\geq 2$ or Analgesic Score $\geq 10$)
  - PSA response (if PSA $\geq 20$)
  - Measurable tumour response
  - QOL (10% improvement in FACT-P)
  - Safety
Overall Survival

- Docetaxel 3wkly
- Docetaxel wkly
- Mitox 3 wkly

Probability of Surviving

Months

0 6 12 18 24 30

11/11/2008 PMH Anniversary Meeting
TAX 327: Updated survival
(Berthold et al, JCO 2008;26:242-5)

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel q 3wks</th>
<th>Docetaxel weekly</th>
<th>Mitoxantrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>% dead</td>
<td>85.1%</td>
<td>85.3%</td>
<td>88.1%</td>
</tr>
<tr>
<td>Median survival</td>
<td>19.2 mos</td>
<td>17.8 mos</td>
<td>16.3 mos</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.79, P=0.004</td>
<td>0.87, P=0.09</td>
<td></td>
</tr>
<tr>
<td>3-year survivors</td>
<td>18.6%</td>
<td>16.8%</td>
<td>13.5%</td>
</tr>
</tbody>
</table>
# TAX 327: Secondary Endpoints

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

Rates are underestimates because they exclude patients who had worsening before improvement.

11/11/2008  PMH Anniversary Meeting
SWOG 99-16 Study
(Petrylak et al: NEJM 2004;351:1513-20)

770 pts with HRPC

Docetaxel + estramustine

Mitoxantrone + prednisone

Study shows:
1. Small difference in survival in favour of docetaxel arm
2. Greater toxicity with estramustine
TAX-327 and SWOG 9916

- The studies confirm the palliative benefit of Mitoxantrone + Prednisone, and this remains appropriate treatment for patients who are averse to side effects of Docetaxel.
- Estramustine adds only toxicity and should not be used.
- On the basis of its survival advantage, Docetaxel + Prednisone is appropriate treatment for many patients with HRPC.
Principles of Management for castrate-resistant prostate cancer

• For those with slowly rising PSA and minimal symptoms:
  - Consider further hormonal manipulations (e.g. DES, ketoconazole) or clinical trials of targeted agents

• For those with symptoms or rapidly-rising PSA
  - Optimize pain control with regular dosing of narcotic medication, such as morphine
  - Give regular laxatives to control the constipation that will be caused by morphine
  - Consider local radiotherapy if there is a dominant site of pain
  - Consider chemotherapy or bone-seeking radioisotopes
New agents, new targets, new trials
Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group

Howard I. Scher, Susan Halabi, Ian Tannock, Michael Morris, Cora N. Sternberg, Michael A. Carducci, Mario A. Eisenberger, Celestia Higano, Glenn J. Bubley, Robert Driecer, Daniel Petrylak, Philip Kantoff, Ethan Basch, Wm. Kevin Kelly, William D. Figg, Eric J. Small, Tomasz M. Beer, George Wilding, Alison Martin, and Maha Hussain

From the Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY.
Submitted May 4, 2007; accepted November 19, 2007.

ABSTRACT

Purpose
To update eligibility and outcome measures in trials that evaluate systemic treatment for patients with progressive prostate cancer and castrate levels of testosterone.
Selected new criteria for prostate cancer trials

• 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
Several phase 3 trials are comparing docetaxel + prednisone +/- a biological agent, including:

- Antiangiogenic agents (bevacizumab, VEGF-TRAP)
- OGX-011 (anti-clusterin - to stimulate apoptosis)
- Atrasentan and ZD4054 (endothelin receptor antagonists)
- Vaccines (GVAX: GM-CSF transduced irradiated prostate cancer cells)

Many additional agents are being evaluated in phase 2 trials.
Cautionary tales: docetaxel is not an easy partner

- In a large phase 2 study (N=250) weekly docetaxel + DN-101 appeared to give better survival (not the primary endpoint) than weekly docetaxel alone (Beer et al, JCO 2007;25:669-74)

- A phase 3 trial with projected sample of >1000pts was initiated to compare weekly docetaxel + DN-101 vs 3-weekly docetaxel (with prednisone)

- Small Pharma (Novacea) sold rights to DN-101 to Big Pharma (Schering-Plough) for $$$$$$$$

- Phase 3 trial halted by DSMC because of excess deaths in DN-101 arm after recruitment of >900 pts

- Recently a large trial of docetaxel +/- GVAX also stopped because of increased toxicity in combination arm
Second-Line Therapy
**Mitoxantrone after docetaxel and vice versa**  

<table>
<thead>
<tr>
<th>Investigator</th>
<th>M → D</th>
<th>D → M</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michels et al</td>
<td>N=33</td>
<td>N=35</td>
<td>Results favour initial docetaxel.</td>
</tr>
<tr>
<td></td>
<td>RR=44%</td>
<td>RR=15%</td>
<td></td>
</tr>
<tr>
<td>Saad et al</td>
<td>N=20</td>
<td>N=35</td>
<td>Docetaxel active independent of sequence.</td>
</tr>
<tr>
<td></td>
<td>eval</td>
<td>RR=85%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR=85%</td>
<td>RR=6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFS 16.3 wks</td>
<td>PFS 6.1 wks</td>
<td></td>
</tr>
<tr>
<td>Oh et al</td>
<td>N=33</td>
<td>N=35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR=60%</td>
<td>RR=6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFS 16.3 wks</td>
<td>PFS 6.1 wks</td>
<td></td>
</tr>
<tr>
<td>Joshua et al</td>
<td>N=20</td>
<td></td>
<td>Weekly docetaxel.</td>
</tr>
<tr>
<td></td>
<td>RR=45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenberg et al</td>
<td></td>
<td>N=41</td>
<td>Part of rand. Phase 2 study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR=20%</td>
<td></td>
</tr>
<tr>
<td>Berthold et al (TAX 327)</td>
<td>N=25</td>
<td>N=71</td>
<td>D weekly and 3-weekly combined</td>
</tr>
<tr>
<td></td>
<td>RR=28%</td>
<td>RR=15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFS 16.3 wks</td>
<td>PFS 6.1 wks</td>
<td></td>
</tr>
</tbody>
</table>

11/11/2008  
PMH Anniversary Meeting
Dendritic cells are leukapheresed from patients with prostate cancer, exposed to PAP (prostatic acid phosphatase) linked to GM-CSF and re-infused x3

- A small RCT (N=127) did not show significantly improved TTP (primary endpoint) but suggested improved survival

  The FDA denied approval on the basis of this trial. Prostate cancer experts on the FDA advisory committee were offered police protection after receiving death threats following this decision.

- A Phase 3 double-blind RCT (N=500) of has completed accrual
Satraplatin and Prednisone Against Refractory Cancer (Sternberg et al, ASCO 2007; N=950)

Metastatic HRPC after 1 prior chemo (~50% prior docetaxel)

RANDOMIZE

2:1

Satraplatin 80mg/m² po daily 1-5 q35d + Prednisone 5mg po BID

Placebo po daily 1-5 q35d + Prednisone 5mg po BID

Primary endpoints were progression-free and overall survival

11/11/2008

PMH Anniversary Meeting
Progression Free Survival

Survival Probability (%)

- Satraplatin + Prednisone
- Placebo + Prednisone

There was no difference in overall survival

Median (wks)  S  11.1  P  9.7
HR: 0.67 (95% CI: 0.57 - 0.77)
Log-Rank P = 0.0000003

11/11/2008  PMH Anniversary Meeting

Princess Margaret Hospital
University Health Network
A question for future trials of second line chemotherapy

The basic tenet of a phase 3 trial is that it should compare experimental therapy with the current standard of care.

Should the control arm be:

A. Therapy that has been approved by regulatory bodies such as the FDA? (or minimal treatment if there are no approved therapies)? or

B. Therapy that is most commonly applied in the oncologic community?
Androgen-dependent pathway remains an important target

- 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**


Fred Hutchinson Cancer Research Center, Departments of Medicine, Urology, and Pathology, University of Washington School of Medicine, Veterans Affairs Puget Sound Health Care System, Seattle, WA, Vancouver General Hospital, Vancouver, British Columbia, Canada, and Oregon National Primate Research Center, Beaverton, OR

**Abstract**

Androgen deprivation therapy (ADT) remains the primary treatment for advanced prostate cancer. The efficacy of ADT has not been rigorously evaluated by demonstrating suppression efficacy will require testing of novel approaches targeting complete suppression of systemic and intracellular contributions to the prostatic androgen microenvironment. [Cancer Res 2007;67(10):5033–41]
Abiraterone
(e.g. Attard et al, JCO [Oct 1] 2008)
Recent results for abiraterone acetate

De Bono (#5005, ASCO 2008): 72 evaluable pts with castration-resistant prostate cancer
>60% PSA response in chemo-naive pts
>40% PSA response in taxane-treated pts

Similar results in other trials from: UCSF, MD Anderson and Memorial (#5017-5019)

A Phase III (2:1) double-blind, placebo-controlled trial (N=1160) of abiraterone plus prednisone has been initiated in patients with metastatic HRPC who have failed docetaxel-based chemotherapy

11/11/2008
PMH Anniversary Meeting
Targeting of receptor tyrosine kinases

- Prostate cancer cells express a variety of growth factor receptors
- Phase 2 trials of gefitinib (targeting erbB1) and of trastuzumab (targeting erbB2) had disappointing results
- Trial of sunitinib underway

As yet, no agent targeting receptor tyrosine kinases has shown promising activity in prostate cancer
Some hot-spots of translational research in prostate cancer

• Circulating Tumour Cells (CTC) as a strong predictor of survival in men with castration-resistant prostate cancer

• Gene expression patterns (e.g. ETS fusion genes) that are associated with disease progression and are potential targets for therapy

• Strategies to restore androgen sensitivity after castration-resistance

• Markers for putative prostate cancer stem cells (CD133+/α2β1 integrin/CD44+ phenotype)
Acknowledgements

• The many investigators who collaborated in the trials that I have described.

• The patients who participated in the trials and thereby contributed to knowledge about how to best treat this disease.

• The international fellows who stimulate my ideas (but are not responsible for them)
ASCO 2007

Spain    Switzerland    Australia (2)

Germany

Singapore

New Zealand

(Brazil)
(China)
(France)
(Slovenia)

11/11/2008    PMH Anniversary Meeting