Advances in Prostate Cancer
Chemotherapy:
The Dawn of a New Era

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Will DRE for food
What patients with HRPC do you refer for consideration of chemotherapy?

- **Group #1**: PSA failure
- **Group #2**: Asymptomatic + Bone scan
- **Group #3**: Symptomatic Dz + Bone scan
Objectives

- Discuss the evolution of chemotherapy for hormone refractory prostate cancer (HRPC)
- Highlight mechanisms of chemoresistance
- Discuss second-line therapies under development for patients failing docetaxel chemotherapy
The evolution of chemotherapy for HRPC

I think we should invest in this PSA company.
Figure 1. Estramustine Phosphate

Mitoguazone

- Overall RR 8.7% (95% CI 6.4-9.0%)
- ‘Promise’ in the vinblastine-estramustine combination
- Pre-PSA era made assessment and documentation of response a significant challenge for clinical trials

Assessment of response: Pre-PSA era

- Minority of patients had measurable disease (10-20%)
- Lack of established criteria for judging response in treatment of a disease that was largely evident by bone scan only
- ? Are patients with visceral mets representative of HRPC pts in general
Assessment of response: Pre-PSA era

‘Chaos will continue to reign when the efficacy of one drug is reported to be 0-85%...when investigators continue to include stable disease findings in the so-called objective response category, thereby intimating that significant prostate cancer cell death has occurred’

Yagoda and Petrylak, 1993

Assessment of response: PSA era

- Response to agents in clinical trials began to be measured and reported in terms of PSA response
- In Phase II trials, a ↓ PSA of 50% appeared to correlate with an increased survival (Smith et al. J Clin Oncol 1998)
Assessment of response: PSA era

- 1999 Consensus conference (Bubley et al. J Clin Oncol 1999) defined a PR as a minimum ↓ PSA of 50% confirmed by a 2nd value 4 weeks later – in the absence of clinical or radiographic disease progression
- Contemporary use...PSA has become the standard method to screen for activity in phase II trials...although not validated in a phase III trial as a surrogate for response or survival

Evolution #1: Mitoxantrone

Well Mr. Osborne, it may not be kidney stones after all
Phase II (161 patients),
- Enrollment: pain a prerequisite
- Primary endpoint – ‘Palliative response’ (questionnaire) – 29% vs. 12%
- Secondary endpoint – no increase in analgesic use
- Most responding patients had an improvement in QOL and decrease in PSA

Duration of palliation was 43 vs. 18 weeks
- No difference in overall survival
- Well tolerated – 5 patients in mtx group possible cardiac toxicity, febrile neutropenia (1%)
- ***Crossover design (if on prednisone and not responding could crossover to mtx group) – study underpowered to assess survival
- Phase III (242 pts), powered to detect a 50% improvement in overall survival (primary endpoint),
- Enrollment: >1/3 had no pain

- Primary outcome – no difference (12.6 mos vs 12.3 mos)
- Difference in TTP 3.7 mos vs. 2.3 mos (p=.0218)
- > 50% decrease in PSA associated with longer survival
- Well tolerated (5% gr ¾ cardiac dysfn)
- Study’s 50% improvement in survival target possibly overly optimistic
Mitoxantrone summary

- Approved by the US FDA for the palliative treatment of *symptomatic* prostate cancer
- No improvement in overall survival demonstrated, possibly due to underpowered studies
- Well tolerated
- May be useful as control arm in future phase III trials

Evolution #2: The Taxanes

"On the Internet, nobody knows you’re a dog."
TAX 327

Phase III, 1006 patients
3 arms
i) Dt q3weeks + prednisone
ii) Dt qweekly + prednisone
iii) Mtx q3weeks + prednisone

Patients @ baseline – 45% had pain, 90% had bony mets, 23% had visceral mets
* Survival q3wk Dt = 18.9 mos., q3wk Mtx = 16.5 mos.

<table>
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<tr>
<th></th>
<th>q3wk Docetaxel</th>
<th>Q3wk Mitoxantrone</th>
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<tr>
<td>PSA response</td>
<td>45%</td>
<td>32%</td>
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<tr>
<td>Pain response rate</td>
<td>35%</td>
<td>22%</td>
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<tr>
<td>AEs: grade 3-4 neutropenia</td>
<td>32%</td>
<td>22%</td>
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<tr>
<td>Serious AEs:</td>
<td>26%</td>
<td>20%</td>
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Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer

Daniel P. Petrylak, M.D., Catherine M. Tangen, Dr.P.H., Maha H.A. Hussain, M.D., Primo N. Lara, Jr., M.D., Jeffrey A. Jones, M.D., Mary Ellen Taplin, M.D., Patrick A. Burch, M.D., Donna Berry, Ph.D., R.N., Carol Molinari, Ph.D., Manish Kohli, M.D., Mitchell C. Benson, M.D., Eric J. Small, M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.

Phase III, 674 patients
2 arms
  i) Dt and estramustine q3wks
  ii) Mtx q3wks + prednisone
Overall survival 17.5 vs. 15.6 months
AEs: 15% of D/E suffered gr3 or higher cardiovascular or clotting events
TAX 327 and SWOG 9916 summary

- US FDA approved the regimen of docetaxel q3weeks in combination with prednisone 5 mg po bid for the treatment of advanced prostate cancer

A suggested paradigm of current practice guidelines...

PSA failures
Asymptomatic + Bone scan
Symptomatic Dz + Bone scan

Treat...
?Who
?How
?When
Mechanisms of chemoresistance
Mechanism of action: cytotoxic chemoRx

Mechanism: spindle inhibitors
Mechanisms of chemoresistance

1. Altered membrane transport (MDR1 gene encoding P-gp, MRP1)
2. Altered target enzyme (e.g. mutated topoisomerase II)
3. Decreased drug activation
4. Increased drug degradation (altered expression of drug-metabolising enzymes)
5. Drug inactivation due to conjugation with increased glutathione

6. Subcellular redistribution
7. Drug interaction
8. Enhanced DNA repair
9. Failure of apoptosis as a result of mutated cell cycle proteins (e.g. p53)
10. Others – upregulation of cell stress survival proteins (clusterin, Hsp27)
Second-line therapies under development for patients failing docetaxel chemotherapy

- Satraplatin
- Epothilones
- OGX-011 (Clusterin antisense)

Satraplatin
**Satraplatin**

- PO 3rd generation platinum-based compound
- Phase III study of satraplatin +/- prednisone suggested increase in PFS 5.2 vs. 2.5 months (trial prematurely closed, 50/380 planned pts assessed), first-line chemotherapy trial

**Satraplatin – SPARC trial**

- Phase III trial evaluating satraplatin +/- prednisone as 2nd-line therapy in pts with HRPC
- Improved median PFS 11 wks. Vs. 9.7 wks.
- Survival data available fall 2007
Satraplatin – unresolved issues

- PFS is the primary endpoint of SPARC trial (bone scans, pain progression)
- PFS controversial as a surrogate for survival in mHRPC
- 9.7 vs. 11 weeks difference although statistically significant is questionable clinically
- Has been submitted for fast track review by FDA, survival data (2007) may determine outcome

Epothilones
Epothilones

- Naturally occurring compounds of the epothilone class
- Have demonstrated pre-clinical activity in a number of taxane resistant prostate cancer cell lines
- Derived from the myxobacterium *Sorangium cellulosum* – isolated in South Africa off the shores of the Zambezi river
Epothilones - Ixabepilone

- Originally identified as antifungals
- Noted to have potent cytotoxicity against multiple cell lines
- Tubulin-polymerizing agents (similar to taxanes)
- Less susceptible to P-gp drug efflux
Epothilones – Ixabepilone – Trials

- Phase II – PSA responses for single agent 33-48%, in combination with estramustine 69%
- Phase II – second-line as a single agent showed only modest activity when compared with M/P (JCO abstracts 2006)

OGX-011 – Clusterin antisense oligonucleotide

Antisense technology
OGX-011 – Clusterin antisense oligonucleotide

Clusterin

- A cytoprotective chaperone protein that regulates the activity of several key apoptosis-regulatory molecules
- Is associated with HRPC and induces a resistant phenotype towards treatment with
  - i) androgen ablation
  - ii) radiotherapy
  - iii) chemotherapy

OGX-011 – Clusterin antisense oligonucleotide

Development of a chemoresistant subline

a) PC-3  b) PC-3R
OGX-011 – Clusterin antisense oligonucleotide

**PC-3R are multidrug resistant**

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<th>Drug</th>
<th>PC-3</th>
<th>PC-3R</th>
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<tr>
<td>Mitoxantrone</td>
<td>335±164</td>
<td>1900±418</td>
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<tr>
<td>Docetaxel</td>
<td>64±38</td>
<td>1350±530</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>13±8</td>
<td>295±140</td>
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OGX-011 – Clusterin antisense oligonucleotide

**Clusterin is elevated in PC-3R cell line**

Clusterin is elevated in PC-3R cell line.
**OGX-011 – Clusterin antisense oligonucleotide**

**Downregulation of clusterin by OGX-011**

**Chemosensitization to Docetaxel in vitro**

Cell proliferation compared to control

Docetaxel concentration (nM)
OGX-011 – Clusterin antisense oligonucleotide

Chemosensitization to mitoxantrone in vitro

Cell proliferation compared to control

Mitoxantrone concentration (nM)

OGX-011 – Clusterin antisense oligonucleotide

Relative growth of PC-3/PC3-R cell lines in vivo after taxane chemotherapy and OGX-011/MM treatments
OGX-011 – Clusterin antisense oligonucleotide

Relative growth of PC-3/PC3-R cell lines in vivo after mitoxantrone chemotherapy and OGX-011/MM treatments.

Conclusions: Pre-clinical data (2nd line)
- Clusterin can confer a chemoresistant phenotype
- OGX-011 may be useful in enhancing the effects of cytotoxic chemotherapy in patients with HRPC progressing after first-line docetaxel chemotherapy
- Clinical trials evaluating the role of OGX-011 in combination with docetaxel or mitoxantrone will soon begin
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