Session VI A: Prostate Cancer
Multidisciplinary Approach: a key to success

Joaquim Bellmunt
Multidisciplinary Approach: a key to success

Clinical Stages in Prostate Cancer

- Asymptomatic
- Organ confined
- Locally advanced
- Metastatic
  - Hormone sensitive
  - HRPC
- Terminally ill
- Death

Urologist
Radiotherapist
Medical oncologist
Research

HRPC
Terminally ill
Death
Example of a Successful Multidisciplinary approach
TAX 327

- 1006 men with metastatic HRPC randomized 1:1:1 to docetaxel prednisone weekly (5/6 weeks) vs docetaxel prednisone every 3 weeks vs mitoxantrone prednisone every 3 weeks

- Primary endpoint: overall survival

- Treatment period: 30 weeks

- Dose reductions for grade IV neutropenia > 7 days or grade III non-heme toxicity

Tannock et al. NEJM 2004
At the time of the initial report 557 of 1006 participants in the trial had died.

Report an updated survival analysis of the TAX 327 study.

Survival of all patients and subgroups according to age, PSA baseline, Karnofsky PS and QoL will be shown.

By January 2007, 276 additional deaths were recorded resulting in a total of 883 deaths.
<table>
<thead>
<tr>
<th></th>
<th>Docetaxel Q3W (n=335)</th>
<th>Docetaxel Weekly (n=334)</th>
<th>Mitoxantrone (n=337)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Original Data 2003</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) dead</td>
<td>166 (50%)</td>
<td>190 (57%)</td>
<td>201 (60%)</td>
</tr>
<tr>
<td>Median Survival*</td>
<td>18.9 (17.0-21.2)</td>
<td>17.4 (15.7-19.0)</td>
<td>16.5 (14.4-18.6)</td>
</tr>
<tr>
<td>Hazard Ratio*</td>
<td>0.76 (0.62-0.94)</td>
<td>0.91 (0.75-1.11)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.009</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td><strong>Updated Data 2006</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) dead</td>
<td>273 (81.5%)</td>
<td>269 (80.5%)</td>
<td>291 (86.4%)</td>
</tr>
<tr>
<td>Median Survival*</td>
<td>19.3 (17.6-21.3)</td>
<td>17.8 (16.2-19.2)</td>
<td>16.3 (14.4-18.2)</td>
</tr>
<tr>
<td>Hazard Ratio*</td>
<td>0.79 (0.67-0.93)</td>
<td>0.87 (0.74-1.03)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.005</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

* 95% confidence interval indicated

Berthold et al. JCO in press
TAX 327: improved survival in asymptomatic and symptomatic patients with mHRPC

- Phase III study
- Docetaxel produced a more favourable survival hazard ratio than mitoxantrone:
  - Symptomatic
  - Asymptomatic

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio in favour of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Docetaxel 3qw</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>ITT</td>
<td></td>
</tr>
<tr>
<td>Age &lt;65</td>
<td></td>
</tr>
<tr>
<td>Age ≥65</td>
<td></td>
</tr>
<tr>
<td>Age ≥75</td>
<td></td>
</tr>
<tr>
<td>Pain no</td>
<td></td>
</tr>
<tr>
<td>Pain yes</td>
<td></td>
</tr>
<tr>
<td>KPS ≥80</td>
<td></td>
</tr>
<tr>
<td>KPS ≤70</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio values:
- 0.2
- 0.4
- 0.6
- 0.8
- 1
- 1.2
- 1.4
What is the optimal management for metastatic HRPC patients?

- If both derive benefit…: Do I treat asymptomatic patients or wait for symptomatic progression?
  - Symptomatic response is less common than PSA response. Higher percent of pain-free patients tolerate 10 cycles than those with pain.
## Survival by Pain

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel Q3W (n=335)</th>
<th>Docetaxel Weekly (n=334)</th>
<th>Mitoxantrone (n=337)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>183</td>
<td>183</td>
<td>184</td>
</tr>
<tr>
<td>Median Survival</td>
<td>23.0</td>
<td>21.1</td>
<td>19.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.73</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.009</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>152</td>
<td>151</td>
<td>153</td>
</tr>
<tr>
<td>Median Survival</td>
<td>14.9</td>
<td>15.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.85</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.17</td>
<td>0.068</td>
<td></td>
</tr>
</tbody>
</table>
## Survival by PSA baseline

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel Q3W (n=335)</th>
<th>Docetaxel Weekly (n=334)</th>
<th>Mitoxantrone (n=337)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA &lt;115</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>168</td>
<td>176</td>
<td>163</td>
</tr>
<tr>
<td>n (%) dead</td>
<td>124 (73.8%)</td>
<td>128 (72.7%)</td>
<td>137 (84.0%)</td>
</tr>
<tr>
<td>Median Survival</td>
<td>21.8</td>
<td>21.4</td>
<td>19.2</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.83</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.12</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td><strong>PSA &gt;=115</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>167</td>
<td>158</td>
<td>174</td>
</tr>
<tr>
<td>n (%) dead</td>
<td>149 (89.2%)</td>
<td>141 (89.2%)</td>
<td>154 (88.5%)</td>
</tr>
<tr>
<td>Median Survival</td>
<td>17.5</td>
<td>13.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.73</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.008</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>
In TAX 327 patients aged >75 years experienced the same benefit with docetaxel as younger patients (Tannock et al, 2004)

There is an increased risk of neutropenia in elderly patients receiving docetaxel

Greater caution → closer monitoring of blood counts, and, when appropriate, growth factor support

Age alone should not discount a patient with metastatic AIPC from receiving chemotherapy
Survival by Age

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel Q3W (n=335)</th>
<th>Docetaxel Weekly (n=334)</th>
<th>Mitoxantrone (n=337)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;=68 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>176</td>
<td>158</td>
<td>170</td>
</tr>
<tr>
<td>Median Survival</td>
<td><strong>19.5</strong></td>
<td>17.2</td>
<td>16.4</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.81</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.071</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;=69 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>159</td>
<td>176</td>
<td>167</td>
</tr>
<tr>
<td>Median Survival</td>
<td>18.9</td>
<td>18.6</td>
<td>15.7</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td><strong>0.77</strong></td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td><strong>0.036</strong></td>
<td>0.091</td>
<td></td>
</tr>
</tbody>
</table>
TAX 327: A multivariate prognostic model incorporating PSA kinetics

- 1006 men with HRPC
  - 686 men 3 or more baseline PSA measurements each separated by at least 1 week (univariate analysis)
  - 635 men PSA kinetics + all other data available (multivariate analysis)

- Median PSA 114 mg/ml (n=1006)
- Median PSA-DT 55 days (n=686)

Amstrong et al, Clin Canc Res, in press
Overall Survival by PSA and PSADT

- **PSA <114, PSADT ≥55 days**
  - n=189
  - Median survival: 24.7 months
  - HR 1.0

- **PSA ≥114, PSADT ≥55 days**
  - n=154
  - Median survival: 18.5 months
  - HR 1.52

- **PSA <114, PSADT <55 days**
  - n=127
  - Median survival: 17.8 months
  - HR 1.33

- **PSA ≥114, PSADT <55 days**
  - n=216
  - Median survival: 13.8 months
  - HR 2.02

Logrank p<0.001
TAX 327: A multivariate prognostic model incorporating PSA kinetics in HRPC

AJ Armstrong 222
Chemotherapy for Hormone Refractory Prostate Cancer

- Robust data on “Why”
- New data on “When”
Example of an Unsuccessful Multidisciplinary approach

Other populations?

- Rising PSA post local therapy in hormonosensitive (not truly adjuvant)
- Rising PSA only in HRPC
RTOG 0014-androgen-dependent prostate cancer: PSA relapse after local therapy

- Chemo-hormonal therapy x 4 cycles
- then hormonal therapy alone
  - T/E q 3
  - T/E q w
  - P/E q w
  - KAVE
  - New active regimens

Primary endpoint: Overall survival

Hormonal therapy until failure

PSA relapse (n=1050)

Closed Feb 2005 due to tox
ECOG 1899: AIPC without metastases

AIPC no mets (n=590)

Randomise

Docetaxel + estramustine

Primary endpoint: Objective PFS

Ketoconazole + hydrocortisone

Closed Dec 2004 (no longer recruitment. Lack of accrual)
Study design TAX 3501

Randomization
High risk using Kattan nomogram
After RT

Observation

Progression
HT
HT+CT

2nd Progression
HT
HT+CT

Expected start in 2006/ Closed due to poor accrual in 2007
What Is More Exciting? The Activity of Docetaxel in Early Prostate Cancer or the Successful Collaboration Between Urologists and Medical Oncologists to Complete a Study in Early Prostate Cancer?

Michael A. Carducci, Division of Medical Oncology, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD

RTOG 0014 (Feb 2005), ECOG 1899 (Dec 2004), TAX 3501 (Sept 2007) failed to meet their accrual goals and have been closed. ...
Multidisciplinary Approach: a key to success

The Future

Genomics
Biomarkers
Better Imaging
Better therapeutics
Expectations

- Genetic profiles predicting individual drug responses
- Prognostic serum/urine markers allowing early patient selection for systemic therapy
- Pilot studies to select compounds for Phase III trials
Oncogene addiction and response to targeted agents

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Gene</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>BCR/ABL</td>
<td>Imatinib</td>
</tr>
<tr>
<td>GIST</td>
<td>C-KIT</td>
<td>Imatinib</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Mutant EGFR</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Breast</td>
<td>Her2</td>
<td>Trastuzumab</td>
</tr>
</tbody>
</table>

Prostate cancer is complex!
PROPOSED GENETIC MODEL FOR PROSTATE CANCER

BENIGN
- 8p, 10q, 16p 50%
- RB gene 13p 25%
- Laminin
- Collagen VII
- Catenin
- E.cadherin
- PTEN

PIA?
- GSTP1

PIN
- AMACR

LOCALIZED PROSTATE CANCER
- Laminin
- Collagen VII
- Catenin
- E.cadherin
- PTEN

METASTATIC CANCER
- Catenin
- E.cadherin
- PTEN

HORMONE REFRactory CANCER

Ch 7, 8, 10
- Bcl 2
- c.erbB2, B3
- PDGF
- Cathepsin
- C-met
- AMACR

p53 17p 25%

Androgen receptors
Mutation or amplification
Changes in Gene Expression After Castration and During AI Progression

Programmatic drift in gene expression upregulation of apoptosis- & progression-related genes

Androgen Dependent

Regressing Tumor

Androgen Independent

+ + PSA
- Bcl-2
- EGFR
- clusterin
- IGFBP 2&5
- TGFβ
+ + IGFBP 3 & 4
- YB-1
+ + survivin

- PSA
+ + Bcl-2
+ + Bclx-L
- EGFR
+ + clusterin
++++ IGFBP 5
IGFBP 3 & 4
+ c-myc
+ YB-1
- survivin

Genasense failed!

+ + PSA
+++ Bcl-2
+++ Bclx-L
+ EGFR
+++ clusterin
++ IGFBP 2 & 5
++ c-myc
++ YB-1
++ survivin

Gleave M, modified
Successful Multidisciplinary collaboration

Translational Research from the Lab to the Clinic and Back

Molecular biology/Gene profiling – a model

- Diagnosis
- Classification
- Prognostic Factor
- Predictive Factor
- Future drug development: complement traditional trials with studies of new agents in molecularly defined populations
Gene-based diagnosis of prostate cancer

Prostate Cancer

Urgent need for:

• More accurate diagnostic tests to reduce the number of unnecessary biopsies

• Biomarkers that distinguish aggressive from more indolent forms of PCa
Concordance analysis

Concordance analysis of TMPRSS2-ERG versus PCA3 in prostate cancer patients

<table>
<thead>
<tr>
<th></th>
<th>PCA3 ⊕</th>
<th>PCA3 ⊘</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMPRSS2-ERG ⊕</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>TMPRSS2-ERG ⊘</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>30</td>
</tr>
</tbody>
</table>

Sensitivity PCA3 test = 62% (48/78)

PCA3-test combined with TMPRSS2-ERG 57 cancers were detected

Sensitivity TMPRSS2-ERG + PCA3 test

= 73% (57/78)
Multidisciplinary Approach: a key to success (golden triangle)

The Future

Genomics

Biomarkers

Better Imaging

Better therapeutics (Rt, Surgery)
Dose escalation:

Use of diagnostic imaging, image guidance, and sharper beams or brachytherapy to focally boost to high doses

Exploiting new imaging techniques (iron nanoparticle MR lymphangiography)

Incorporate Anti-angiogenic therapy to radiation

• The technology can be used creatively to improve tumor targeting
  • Increase dose to all/part prostate
  • Reduce number fractions
  • Reduce morbidity

• But it is seductive, costly, time-consuming and needs collaboration
So what about the future?

Indolent disease
Avoid overtreatment

- The real promise will be in biological markers (blood products and tissue)
- Men with non-indolent disease will be stratified according to the biology of their disease possibly through epigenetic and genetic changes like fusion gene detection (TMPRS2-ERG)

need collaboration !!
Multidisciplinary Approach: a key to success
New therapies need new ways of working

- Urologist
- Medical Oncologist
- Radiotherapist
- PATIENT
We need to improve collaboration …

Multidisciplinary Team:
- What therapy: S, Rt, XT, “surveillance”
- What clinical trials are needed
- Epidemiology
- Prevention, markers & early diagnosis
- New treatment approaches

Solution: Experienced physicians working together (Urologist, Oncologist, Radiotherapist, Pathologist, Basic Researchers….)