CHEMOTHERAPY IN PROSTATE CANCER

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Important Specific Issues for Prostate Cancer

- Potentially long natural history – 10+ years
- Elderly patients
  - intercurrent disease
  - deaths from competing risks
- Variable clinical manifestations – the “states” model
  - Advanced “conventional” disease – clinical metastases
  - Hormone treated – relapsed, resistant, refractory
  - New imaging techniques used more actively → earlier stage
  - PSA-only disease after treatment
- Stage migration
  - Changes in imaging
  - PSA and other tumor markers
  - Quality of life measurement – new indices
- Changing surrogate measures of outcome
OBJECTIVES BY CLINICAL STATE

INITIAL EVALUATION: NO CANCER DIAGNOSIS

LOCALIZED DISEASE

RISING PSA

CLINICAL METASTASES: NON-CASTRATE

CLINICAL METASTASES: CASTRATE

PREVENTION

MINIMIZE MORBIDITY/ MAXIMIZE CURE

PREVENT METASTASES

ELIMINATE / PREVENT SYMPTOMS

DEATH OF DISEASE
EARLY CHEMOTHERAPY ERA

HORMONE REFRACTORY PROSTATE CANCER
PRIOR TO MAY 2004

MITOXANTRONE - advanced PC (FDA approved in 1996)

- no evidence of a survival benefit

- one-third of symptomatic patients experienced improvement in pain (QOL)
Mitoxantrone Phase III Canadian Trial: Study Design

Symptomatic HRPC

Mitoxantrone + Prednisone

Primary Endpoint: Palliation

Prednisone*

N=80

N=81

*Crossover on progression (N=50)

Mitoxantrone for Advanced Prostate Cancer: Overall Survival

Mitoxantrone for Advanced Prostate Cancer: Quality of Life

2003, FDA approved ZOLENDRONIC ACID for metastatic HRPC with bone metastasis

QOL – pain relief
October 2004, the New England Journal of Medicine reported on two studies using docetaxel in advanced PC

‘DOCETAXEL ERA’
- **TAX 327**

- **1006 PATIENTS**

- **RCT**: docetaxel plus prednisone vs. mitoxantrone plus prednisone.

- **MEDIAN SURVIVAL**: 18.2 months compared with 16.4 months
- **SWOG 9916**
- 770 men
- docetaxel and *estramustine* compared with mitoxantrone and prednisone
- overall survival favored docetaxel (18.9 months compared with 16 months for mitoxantrone).
THUS CAME FDA APPROVAL TO DOCETAXEL IN 2004

‘DEFINITE SURVIVAL BENEFIT’
Chemotherapy for Prostate Cancer: "Why Bother?"

DIFFERENCE IN SURVIVAL ONLY 2-21/2 MONTHS
MARK TWAIN:

FAMOUS QUIB ABOUT PRACTICE OF LYING:- 3 TYPES:

“lies”, “damned lies”, and “statistics”
Several points should be made about the survival analysis in these studies:

1. Both studies crossed over (to docetaxel) men who initially received mitoxantrone and did not respond.

2. Median survival: analysis includes all patients, not only those who respond, but also those that do not respond.

3. Median survival analysis says little about patients on the right side of the survival curve (the men who respond to treatment, despite a poor prognosis).
The existence of a small group of survivors far past the “median” point, even in cancers with a dire prognosis such as advanced PC, should provide real hope even when the prognosis is bleak.
Summarize effects of Docetaxel

- Survival improved
- Pain relief much superior
- greatest benefit was in “quality of life” issues (area of weight loss, appetite, pain, physical comfort, and bowel and genitourinary function)
What About Chemotherapy in Earlier Stages of PC?
SUBSET OF "high-risk" PC (> 50% chances of disease recurrence):

- **PSA** > 20
- **Gleason score** of 8 or higher
- **Clinical Stage** of T3 or higher determined by a digital rectal exam (tumor is already extending outside of the prostate gland).
- **PSA doubling time** (< 6 months)
COMBINING CHEMOTHERAPY WITH NOVEL AGENTS IN ADVANCED PROSTATE CANCER
metastatic HRPC is the ‘HETEROGENEOUS’ disease

means that there are several or multiple forms or clones of PC cells existing within one patient

the combination of chemotherapy with a novel or innovative agent takes advantage of our evolving understanding of advanced PC biology.
<table>
<thead>
<tr>
<th>Target</th>
<th>Agent(s)</th>
<th>(many in combination with chemotherapy) for Metastatic Hormone Refractory Prostate Cancer</th>
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<tbody>
<tr>
<td>Microtubule</td>
<td>Epothilones, halichondrin, B, analog, SB 715992</td>
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<tr>
<td>VEGF, VEGFR, Integrine</td>
<td>Bevacizumab, EMD121974, PTK787, SU11248</td>
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<td>Histone deacetylase</td>
<td>SAHA, aplidine</td>
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<tr>
<td>EGFR, PDGF, HER-2</td>
<td>Sorefamib, imatinib, trastuzumab</td>
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<tr>
<td>AKT, mTOR</td>
<td>CCI779, RAD001</td>
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<tr>
<td>Endothelin receptor</td>
<td>Atrasentan</td>
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<tr>
<td></td>
<td>Vaccines (GVAX, APC8105), lenalidomide,</td>
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<td></td>
<td>Revlimid, Prostavac-VE, Provenge</td>
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<tr>
<td>Immune modulation</td>
<td>Gossypol, Bcl-2 antisense, anti-clusterin</td>
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<tr>
<td>Apoptotic pathway</td>
<td>Proteasome Inhibition</td>
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<td>Antiangiogenic</td>
<td>thalidomide</td>
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RECENT TRIALS

......HORMONE REFRACTORY STATES
GM-CSF and Anti-CTLA4 in Hormone-Refractory P Ca

- CTLA4 transmits an inhibitory signal to activated T cells
  - Anti-CTLA4 augments T-cell responses and antitumor immunity in animal models

- Phase I study of GM-CSF 250 μg/m²/day SC on Days 1-14 every 28 days with escalating doses of anti-CTLA4 Abipilimumab (0.5-3.0 mg/kg)

Oblimersen + Docetaxel in Hormone-Refractory P Ca

- Bcl-2 regulates apoptosis, contributes to docetaxel resistance
- Oblimersen sodium: DNA antisense oligonucleotide that prevents Bcl-2 protein production
- Phase II study evaluated benefit of adding oblimersen to docetaxel

Patients with first-line metastatic hormone-refractory prostate cancer
(N = 111)

**Oblimersen** 7 mg/kg/day Days 1-7 + **Docetaxel** 75 mg/m² Day 5 Q3W (n = 54)

**Stratified by institution, M0 vs M1, prior estramustine, prior bisphosphonates**

**Docetaxel** 75 mg/m² Day 1 Q3W (n = 57)

Satraplatin + Prednisone in Hormone-Refractory PCa

- Satraplatin: novel oral platinum compound
  - Associated with significant PFS improvements in chemotherapy-naive patients with hormone-refractory PCa[1]
- SPARC: phase III, randomized, placebo-controlled trial[2]

Patients with progressive metastatic hormone-refractory PCa with objective or PSA progression after ≥ 2 courses chemotherapy
(N = 950)

- **Satraplatin** 80 mg/m² Days 1-5 Q 35 days
- **Antiemetic** 1 mg BID Day 1-5 Q 35 days
- **Prednisone** 5 mg BID
  (n = 635)

- **Placebo** 80 mg/m² Days 1-5 Q 35 days
- **Placebo** 1 mg BID Days 1-5 Q 35 days
- **Prednisone** 5 mg BID
  (n = 315)

Treatment until progression, intolerable toxicity, or death

*Placebo antiemetic.

Efficacy of Satraplatin + Prednisone in Hormone-Refractory PCa

- PFS significantly longer with satraplatin + prednisone vs prednisone
- Median PFS: 11.1 vs 9.7 weeks
- Median PFS among patients with prior docetaxel (n = 487): 10.1 vs 9.1 weeks
- Greater proportion of satraplatin-treated patients received ≥5 treatment cycles (40% vs 20%)

Atrasentan in Nonmetastatic, Hormone-Refractory PCa

- **Atrasentan**: oral selective endothelin A receptor antagonist

- Phase III randomized, controlled study of 941 patients with nonmetastatic, hormone-refractory PCa and rising PSA

- Trend toward higher rate of new skeletal lesions with placebo vs. atrasentan (44.3% vs. 36.2%)

Isotope Therapy + Docetaxel for Castrate Metastatic PCa

- Phase I study of docetaxel + $^{153}\text{Sm-lexidronam}$ (Samarium-153) in patients with progressive CMPC (N = 15)

- Escalating trial of docetaxel (65-75 mg/m$^2$) and Samarium-153 (0.5-1.0 mCi/kg) every 6 weeks

- Dose-limiting toxicity not reached at 75 mg/m$^2$ docetaxel and 0.75 mCi/kg Samarium-153

NITI RAIZADA, CHEMOTHERAPY CA PROSTATE
SUMMARY

- Survival has been the standard
- Surrogates under evaluation
  - Quality of Life and Patient Reporting
  - PSA response
  - PSA time dependent kinetics
  - Markers of bone turnover
- New agents that cause cytostatic effects
  - Need for new parameters?
  - Are they really useful?
THANK YOU.....