Rationale for Multimodality Therapy for High Risk Localized Prostate Cancer

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Localized Prostate Cancer is Sometimes a Systemic Disease
- High risk of failure of local therapy alone:
  - Clinical stage T3, T4
  - PSA ≥ 20 ng/ml
  - Gleason 8-10
  - High volume Gleason 7 cancer
  - PSA velocity > 2 ng/ml/yr

Cancer Specific Survival Is Poor In High Risk Disease
Why Consider Neoadjuvant Therapy For Patients?

- Well characterized high risk groups
- Cytoreduction prior to surgery or RT
- Control local residual disease
- Early treatment of micrometastases

Additional Benefits With Neoadjuvant Rx Prior To RP

- Ability to assess in vivo chemosensitivity
- Ability to assess molecular determinants of response in pathologic specimens
- Rapid ability to assess effect of new agents compared with adjuvant trials

What Are Appropriate Endpoints For Neoadjuvant Trials?

- Randomized trials
  - PFS
  - OS
- Non-randomized trials
  - pCR?
  - PSA declines?
  - Radiologic response?
  - Molecular endpoints?
Paradigm: Locally Advanced Breast Cancer

- Over 6000 patients accrued to 14 phase II and 6 phase III trials (1989-2002)
- Clinical response rates 60-90%
- Clinical CRs 15-30%
- Pathologic CRs 5-15% (doxorubicin-based) to 25-30% (docetaxel-based)

Shannon Crit Rev Oncol Hemat 2003

pCR Predicts Enhanced Survival In Breast Cancer

Kuerer JCO 1999

Radiation +/- ADT In Locally Advanced Prostate Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Exper</th>
<th>Better DFS?</th>
<th>Better OS?</th>
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<td>RTOG 8610</td>
<td>None</td>
<td>4 mo</td>
<td>Yes</td>
<td>No</td>
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<td>RTOG 8531</td>
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<td>RTOG 9202</td>
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<td>2 yrs</td>
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<td>EORTC</td>
<td>None</td>
<td>3 yrs</td>
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Better OS? Better DFS?
Neoadjuvant Chemotherapy + RT Trials
• 2 studies in 65 and 23 patients
• Broad definitions of high risk disease
• RT dose from 65-70 Gy to 75.6 Gy
• Estramustine + vinblastine prior to and during RT
• Increased GI/GU toxicity
• 5 year freedom from PSA recurrence dependent on clinical stage: 17-49%

Phase III Trial RT +/- ADT for Intermediate Risk Disease
• 205 patients with PSA > 10 or Gleason >6
• Randomized to RT or RT+ 6 months of ADT
• Median followup 4.5 years
• PFS and OS survival benefit with ADT

Overall Survival

Neoadjuvant And Concurrent Chemotherapy With ADT/RT

Primary Endpoint: 5 yr OS
Radical Prostatectomy

Neoadjuvant Leuprolide Does Not Improve 5-Year DFS With RP

Neoadjuvant Docetaxel Prior To Radical Prostatectomy
- Phase II trial at DFCI
- Up to 6 months of weekly docetaxel prior to RP in high risk localized prostate cancer
- Monthly PSA, DRE assessments
- Endorectal coil MRI at 0, 2, and 6 months
- Primary endpoint: Pathologic CR

Preoperative Chemotherapy → Radical Prostatectomy
- 6 months of Taxotere before surgery
- Monthly PSA, DRE assessments
- Prostate MRI at 0, 2, and 6 months
- Primary endpoint: Complete eradication of cancer from surgical specimen
Treatment Response

- PSA decline ≥ 50%
  - 11/19 patients (58%)
- Tumor shrinkage ≥ 25% on MRI
  - 13/19 (68%)
- Complete eradication of cancer
  - 0/16 (0%)

Conclusions

- Neoadjuvant docetaxel is well-tolerated
- PSA declines >50% are seen in the 2/3 of patients, independent of testosterone
- Radiographic reduction of tumor seen in 2/3 of patients
- No evidence of pathologic CRs
Next Steps For Neoadjuvant Therapy?

- Randomized trials*
- Novel therapeutics
  - Immune therapy (GM- VSF, anti-CTLA4)
  - Angiogenesis inhibitor (sunitinib +/- LHRH-A)
  - Growth factor receptor inhibitor (imatinib, bortezomib, enzastaurin, temsirolimus)
- Novel hormonal therapies
- Chemotherapy combinations

CALGB 90203: Neoadjuvant Chemotherapy In High Risk Cancer

- High Risk ≤60% PFS
- ADT x 6 months Docetaxel x 6 cycles
- RP

n = 750
PI: Eastham

Primary Endpoint: 3 yr PFS

RTOG 0521
Adjuvant Chemotherapy

- High Risk
- ADT x 2 yrs + RT
- 6 cycles docetaxel (75 mg/m²) and prednisone starting 1 mo after RT

N=600
Primary Endpoint: Overall Survival

Neoadjuvant GM-CSF + Thalidomide

- 24 high risk localized RP patients evaluable
- GMCSF 250 mg/m² SQ TIW
- Thalidomide escalated over 10 days from 100 to 200 mg daily
- Max 8 weeks therapy prior to RP
- Grade ½ fatigue 46%, constipation 67%, skin reactions 67% parathesias/dizzy 54%.
- One DVT

Garcia Proc ASCO Prostate 2007
PSA Decline After GM-CSF and Thalidomide

Persistent Prostatic Androgen Activity Despite Systemic Castration

Clinical trial of neoadjuvant ADT in men with clinically localized prostate cancer (M. Gleave, Vancouver)
- LHRH agonist + anti-androgen
- Patients treated for up to 9 months prior to prostatectomy
- Tissues collected for IHC (TMA) and gene expression analyses (LCM)

Mostaghel Cancer Res 2007

Suppression of Prostatic Androgen Activity Is Heterogeneous After Prolonged ADT

Preoperative Taxotere + Bevacizumab in High Risk Cancer

High Risk Prostate Cancer → Taxotere x 18 wks Avastin x 15 wks → Surgery (RP)

n = 42
PI: Oh

Prostate MRI response →
Neoadjuvant Docetaxel/Bevacizumab Followed by RP

- 42 high risk localized cancer
  - Median age 55, PSA 10.5, Gleason 8
- Docetaxel 75 mg/m2 x 6 cycles
- Bevacizumab 15 mg/kg x 5
- 9/23 (39%) evaluable pt had PR by erMRI
- 65% had PSA declines
- Well tolerated

Oh ASCO 2009
Summary: High Risk Localized Prostate Cancer

• Multi-modality therapy is the key to improving outcome
• Better systemic agents and combinations
• Improved understanding of biology and heterogeneity
  – Chemoresistance
  – New targets