Biodiversity and Health Care Quality: The 21st Century Challenge

Patient Differences: Biologic and Non-Biologic Factors

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- The views expressed in this presentation are solely those of the speaker and do not necessarily represent the views of the University of Maryland or NPC.

- The findings and conclusions in this presentation have been published as:

Heterogeneity of Treatment-Effect (HTE) for Stage 4 Prostate Cancer (s4PC) Therapies

• HTE factors and patient response to s4PC therapies
  – Biological
  – Non-biological

• Applications & lessons learned for other diseases

• Implications
  – Patients
  – Healthcare Providers
  – Payers
  – Policy Makers
Conceptual Framework for Interactions and Implications of Biologic and Non-Biologic factors in Heterogeneity of Treatment Effect
Systematic Review of HTE in s4PC

• **Study Objectives**
  – To perform a systematic review of the available published evidence on biologic and non-biologic factors contributing to HTE and s4PC outcomes
  – To discuss the implications of the results on health-care practice and policies
Systematic Review of HTE in s4PC

• Methodology
  – MEDLINE and the PubMed electronic databases were searched for English language, human studies published between January 1946 and March 2012
  – Of the final 92 Journal articles selected
    • 87 articles studied the role of biologic factors in HTE
      – genetic factors, age, race, co-morbidities, prior treatment, clinical signs and symptoms, laboratory data and measures of s4PC disease severity
    • 5 articles studied the role of non-biologic factors in HTE
      – social, geographic and dietary factors
Systematic Review of HTE in s4PC

• Characteristics of the 92 studies
  – Conducted in the USA, Canada, or Europe
  – 16 multi-regional studies and half were multi-center studies
  – Included subgroup analyses, cohort studies, and registry data
  – Two studies were pre-specified RCTs that studied the impact of different factors on s4PC treatment-outcomes
  – Post-hoc analyses of RCTs (46%) and comparative observational studies (50%) comprise the majority of the studies
Systematic Review of HTE in s4PC

- AHRQ quality guidelines
  - Quality of the articles was rated as good, fair or poor
    - Majority were of fair quality
    - 15% were of good quality
    - 16% were of poor quality
Systematic Review Findings

- Clinical characteristics of the 92 articles
  - Most common (74%) treatment protocol was hormonal therapy
    - Androgen deprivation therapy, peripheral androgen blockade, orchiectomy and estrogen therapy
  - Main outcome in 53 (58%) was Overall Survival
    - Of these, 25 articles (27%) articles studied OS only
  - Seven percent examined HRQOL
  - Two percent examined adverse events
Factors

Biologic

Biomarkers

RACE

Age

Race

Comorbidities

Prior treatment

Clinical signs/symptoms

Disease severity

Medications

Biologic

HER2 expression
AR-CAG repeat length
Prostatic AR content
AR binding activity
Nuclear AR immunostaining intensity
Tumor growth fraction/Ki67
immunostaining
CXCR4 expression
PDGFR phosphorylation
UPAR forms
TMPRSS2-ERG expression
Growth fraction/Ki67
immunostaining
Tumor cellular proliferation fraction
Ploidy of metastases
RACE

Radiation therapy
ADT
Orchiectomy
Flutamide
Estrogen therapy
Chemotherapy

PAIN

Bone pain
Performance status
General health status
Global QOL
Fatigue
Urologic symptoms
Days of motor deficit in MSCC
Ambulatory status before RT in MSCC
BMI

Grade

Stage
Gleason score
Visceral metastases
Bone scan (progression, index)
Extent of disease
Soloway score
Months fracture free
History of skeletal fracture
Risk group
Duration of disease, time to CRPC
Pattern of disease progression
Malignant pleural effusion
Tumor growth/regression constant
Liver scan
BM biopsy

PSA (Baseline, 4wk, 2m, 3m, 6m)
PSA velocity, rate of decrease (4wk, 12wk)
PSA nadir
Time to PSA nadir, normalization
PSADT (pre treatment, post nadir)
Time to halving time
PSA Response (decline, progression, % decrease)
Log PSA, log PSA velocity
Testosterone level (baseline, 3m, 6m)
PAP (baseline, 1m, 3m, 6m, flare)
ALP (baseline, 1m, 3m, 6m, flare)

LDH
CTC
SGOT
BAP
PRL
Albumin
ESR
CRP
BUN
Creatinine
LH
FSH
SHBG
CEA

PINP
TKL-40
NSE
CgA
TPS
Plasminogen
Fibrinogen
proGRP
Erythrocyte polyamine
CTX-1
YKL-40

* Number of good quality articles on overall survival
^ Number of good quality articles on outcomes other than overall survival
Factor explored in 3 or more articles with overall survival as the outcome
### Results for HTE Factors in s4PC Patient, Outcome = OS

<table>
<thead>
<tr>
<th>HTE Factor</th>
<th>No. of times factor studied, N</th>
<th>Significant association</th>
<th>No significant association</th>
<th>Total number of times factor studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association with outcomes, direction of correlation and quality of evidence*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Significant association</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ OR – correlation**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Good, Fair, Poor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (older age at study entry or diagnosis)</td>
<td>-2</td>
<td>(1,1,0)</td>
<td>12</td>
<td>14 (3,10,1)</td>
</tr>
<tr>
<td>Race (AA vs. non-AA)</td>
<td>-2</td>
<td>(0,2,0)</td>
<td>7</td>
<td>9 (3,6,0)</td>
</tr>
<tr>
<td>Clinical signs/symptoms</td>
<td>-28</td>
<td>(9,16,3); +2 (1,1,0)</td>
<td>9</td>
<td>39 (8,26,5)</td>
</tr>
<tr>
<td>Disease severity</td>
<td>-58</td>
<td>(11,43,4)</td>
<td>29</td>
<td>87 (18,63,6)</td>
</tr>
<tr>
<td>Gene/Biomarker expression</td>
<td>+2</td>
<td>(0,1,1); -2 (0,1,1)</td>
<td>3</td>
<td>7 (1,4,2)</td>
</tr>
<tr>
<td>Laboratory data***</td>
<td>-96</td>
<td>(20,67,9); +33 (9,22,2)</td>
<td>52</td>
<td>181 (41,124,16)</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>+3</td>
<td>(3,0,0); -1 (1,0,0)</td>
<td>5</td>
<td>9 (8,1,0)</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>0</td>
<td>(0,0,0)</td>
<td>1</td>
<td>1 (0,1,0)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>0</td>
<td>(0,0,0)</td>
<td>0</td>
<td>0 (0,0,0)</td>
</tr>
<tr>
<td>Social</td>
<td>+2</td>
<td>(0,2,0)</td>
<td></td>
<td>2 (0,2,0)</td>
</tr>
<tr>
<td>Social life****</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner status (married vs. single)</td>
<td>+1</td>
<td>(0,1,0)</td>
<td></td>
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</tr>
</tbody>
</table>

*Quality of evidence based on AHRQ guidelines

** + is a positive correlation and – is a negative correlation with OS

***Elevated laboratory values

**** Social life assessed by questionnaire including a score for degree of impairment of family/social life due to the medical condition or the treatment
Lessons Learned and Challenges for HTE in Other Diseases

• Searching for HTE requires casting a wide net
  – HTE not a reliable search term
  – HTE goes by many names (some incorrect)

• Pre-specified HTE factors aid literature searches
  – Adds to the number of articles
  – BUT you don’t know what you don’t know

• HTE challenging to detect retrospectively
  – Analytic rigor of empirical analysis
  – Interpretation of study reports
Lessons Learned and Challenges for HTE in Other Diseases

• HTE likely to be a secondary not primary aim
  – Best case is pre-specified secondary aim
  – Post hoc analyses have methodological challenges

• Many studies provide subgroup analyses
  – Not all address HTE
  – Not always clear how to disentangle principal effect from interaction of {HTE factor x treatment}
Lessons Learned and Challenges for HTE in Other Diseases

• As a proportion of the vast literature in s4PC, focus on HTE is small
  – Most s4PC HTE literature on biologic v. non-biologic
  – Existing evidence leaves significant gaps regarding HTE

• Literature that addresses HTE may be less extensive for other disease states than s4PC
  – Need more studies
  – Need appropriate study designs to address HTE
Policy Implications

• Lessons Learned
  – Patients
    • Promote efficient and targeted treatments
    • Awareness of environmental factors association with cancer and its treatment may modify behavior
    • Aid in treatment decision-making
    • Aid in setting expectations of treatment effectiveness and risk of potential adverse effects
Policy Implications

• Lessons Learned
  – Healthcare Providers
    • Promotes greater awareness of HTE factors
    • Address challenges associated with providing treatment to diverse populations
    • Aid in treatment recommendation
    • Aid in communications with patients regarding treatment benefits and risks
Policy Implications

• **Lessons Learned**
  – Policy Makers and Payers
    • **Because of HTE, FDA may perform (or require the drug sponsor to perform) subgroup analysis**
      – Ideally pre-specified
      – Identify subgroups that do not benefit
      – Identify those that suffer severe adverse events
    • **Payers may also demand more HTE evidence**
      – Target the right patient
      – Develop disease management protocols
Related References


10. NCI. http://www.cancer.gov/cancertopics/types/prostate