THE MYTH OF AVERAGE: WHY INDIVIDUAL DIFFERENCES MATTER:

Patient Differences: Biologic and Non-Biologic Factors?

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

- HTE factors and patient response to s4PC therapies
  - Biologic
  - Non-biologic
- Applications & lessons learned for other diseases
- Implications
  - Patients
  - Healthcare Providers
  - Payers
  - Policy Makers
Complexity of HTE in s4PC

• Why is s4PC and HTE so complex?
  – Complexity due to multiple biologic, socioeconomic, and sociocultural determinants
    • Disease severity
    • Age
    • Race
    • Comorbidities
    • Cultural practices
    • Socioeconomic status
    • Diet and exercise practices
  – Complexity due to treatment effects
Complexity of HTE in s4PC

• **Treatment practice patterns**
  – Geographic
  – Healthcare systems
  – Physician specialty

• **Lifestyle**
  – Lifestyle and behavioral factors have been shown to influence the prognosis of PC
    • Obesity and smoking are associated with an increased risk of dying from PC
• Race
  – African American men have the highest incidence rate for PC in the US and are more than twice as likely as Caucasian men to die of the disease
    – PC mortality rates for PC in 2003-2007 in the US
      » 22.8 per 100,000 men among Caucasians
      » 54.2 per 100,000 men among African Americans
    – The lowest death rates for PC were found in Asian/Pacific Islander men
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, orchietomy 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
Biomarkers

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

Comorbidities

- Age
- Prior treatment
- Ischemic cerebral disease
- Ischemic heart disease
- Intermittent claudication
- Decompensated heart disease
- Venous thrombosis
- All CV diseases
- Concomitant diseases

Disease severity

- Clinical signs/symptoms
- 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

Medications

- 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)
- 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)

Laboratory data

- LDH
- CTC *
- SGOT *
- BAP *
- PRL *
- Albumin *
- ESR *
- CRP *
- BUN *
- Creatinine *
- LH *
- FSH *
- SHBG
- CEA *
- PINP
- TKL-40
- NSE
- CgA
- TPS *
- Plasminogen
- Fibrinogen
- proGRP *

Geographic

- Country of residence
- PC-SPES

Social/Behavioral

- Social life
- Professional life
- Sexual life
- Partner status
- Partner status

* 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>
</tr>
</thead>
<tbody>
<tr>
<td>Association with outcomes, direction of correlation and quality of evidence*</td>
<td>Significant association + OR – correlation** (Good, Fair, Poor)</td>
</tr>
<tr>
<td>Age (older age at study entry or diagnosis)</td>
<td>-2 (1,1,0)</td>
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<tr>
<td>Race (AA vs. non-AA)</td>
<td>-2 (0,2,0)</td>
</tr>
<tr>
<td>Clinical signs/symptoms</td>
<td>-28 (9,16,3); +2 (1,1,0)</td>
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<tr>
<td>Disease severity</td>
<td>-58 (11,43,4)</td>
</tr>
<tr>
<td>Gene/Biomarker expression</td>
<td>+2 (0,1,1); -2 (0,1,1)</td>
</tr>
<tr>
<td>Laboratory data***</td>
<td>-96 (20,67,9); +33 (9,22,2)</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>+3 (3,0,0); -1 (1,0,0)</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>0 (0,0,0)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>0 (0,0,0)</td>
</tr>
<tr>
<td>Social</td>
<td>+2 (0,2,0)</td>
</tr>
<tr>
<td>Social life****</td>
<td>+1 (0,1,0)</td>
</tr>
<tr>
<td>Partner status (married vs. single)</td>
<td>+1 (0,1,0)</td>
</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


9 http://www.cdc.gov/cancer/prostate/

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