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Discerning Clinical Relevance of Biomarkers in Early Stage Breast Cancer

Mary Lou Smith[1], Elda Railey[1]; Carol B. White[2], Bryan P. Schneider[3]
[1]Research Advocacy Network, Plano, TX; [2]Carol B. White & Associates, Evanston, IL; [3]Indiana University Simon Cancer Center, Indianapolis, IN

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Abstract

Background: Patients face complex treatment choices with a range of benefits/risks. Researchers seek new biomarkers to predict individualized risks/benefits. It is essential that biomarkers yield information useful to patients. Our prior research in metastatic breast cancer showed choice-based conjoint (CBC) allowed patients to express risk-benefit preferences. This study focused on patients with early stage breast cancer who received chemotherapy and quantified relative influence of benefit and specific toxicities on predicted treatment choice for common therapies.

Methods: A CBC survey was developed and sent to patients. The survey showed 12 pairs of hypothetical treatment choices based on benefit/risk profiles similar to those of TC, AC, AC→T, and TAC to allow assessment of what drove selections. Choices included benefit (relative risk reduction range: 20%-50%) and likelihood of toxicities including: peripheral neuropathy (PN range: 0%-60% with degrees of severity/duration); congestive heart failure (CHF range: 0%-10%); and clinically relevant infection (CRI range: 5%-25%). Analysis (N=417) allowed treatment choice prediction for any benefit/toxicity combination. Hypothetical biomarkers were modeled to determine shifts in toxicity/efficacy necessary to change treatment selection.

Results: Severity of PN experience had significant influence in decisions. When simply asking patients for perceived impact of previous PN experience on a future decision, the majority who had mild/moderate PN felt a future decision would not be impacted by a similar experience. Conversely, a plurality (47%) who had prior severe PN would be less likely to take similar future treatment. With CBC, we examined the derived influence of risks/benefits on treatment decisions. Based on estimated benefit/risk profiles, 50% selected a regimen similar to TC > AC (22%) > AC→T (16%) > TAC (10%). Incremental benefit had substantial impact on selected regimen. The desire for a given regimen decreased with incremental increase for each toxicity; most dramatically for CHF. Patients with a perception of low recurrence risk had higher preference for a non-anthracycline based profile, while those with higher perceived recurrence risk had higher preference for a combined anthracycline/taxane based profile. Interestingly, PN-naïve patients had higher preference for non-taxane based profile, whereas those who had prior PN had higher preference for some taxane-based profiles. With moderate/limited PN, substantially more PN-naïve patients avoided a taxane profile (31%) vs. those who had experienced PN (18%). When focusing on likelihood of severe/irreversible PN, there was dramatic shift toward non-taxane based regimens: AC (53%) > TC (23%) > AC→T (20%) > TAC (3%). When modeling impact of biomarkers on therapy selection, as likelihood of PN in taxane profiles increased, the fraction that chose a non-taxane profile increased. As likelihood of CHF in anthracycline-based profile increased, the fraction that chose such a regimen decreased.

Conclusion: Patients considered all information about benefit and risks when making treatment choices. The information effective hypothetical biomarkers could add impacted these choices. Personal experience with a given toxicity appeared to impact decision for future therapies.

Background

- Data regarding how patients' feelings or perceptions weigh into treatment decisions are lacking
- The impact of type, risk, severity, & duration of toxicity on choice of regimen is unclear
- The additional impact of toxicity biomarkers (that shift likelihood of toxicity) on patient treatment decisions is not established
- Key Aims:
  - Describe how important variables might impact patient decisions about therapy in the curative setting
  - Quantify relative influence of benefit & specific toxicities on predicted treatment choice
  - Predict influence of predictive biomarkers on treatment selection

Methods

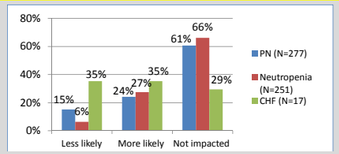
- Data collection: Online survey
  - Patients with early-stage disease who received chemotherapy
  - Living Beyond Breast Cancer (N=362) & consumer panel (N=55)
- Measured how variables may impact patient decisions
  - ***Stated Influence***: Posed direct questions about influences
  - ***Derived Importance using Choice-Based Conjoint (CBC)***:
    - Examined pattern of preferences exhibited in respondents' choices
    - Allowed calculation of utilities to determine relative influence of each risk & benefit
- Quantified relative influence of benefit/toxicities on predicted treatment choice
  - ***Simulation model*** used utilities and set of treatment/regimen profiles to predict preference shares
    - *Biomarker:* Compared hypothetical biomarkers to observe change in preference shares to indicate influence of each biomarker
    - *Diversification of regimens*: Saw how preference shares were spread across broader choice sets

Demographics

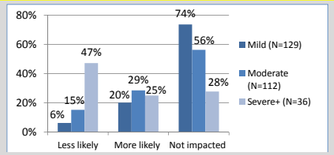
- 35% under age 50; 36% 50-59; 29% 60 or over
- 89% Caucasian; 5% African American; 6% other
- Majority self-classified college-educated, in higher income ranges
- 71% diagnosed < 5 yrs ago; 29% diagnosed 5-8 yrs ago
- 100% received chemotherapy for breast cancer
  - 100% experienced at least one side effect
  - Most common (>50%): alopecia, fatigue, cognitive problems, neuropathy, joint pain, low WBC, anxiety/depression
- Treatment site: 68% community/private & 32% academic medical center

Results

STATED INFLUENCE OF EXPERIENCED TOXICITIES



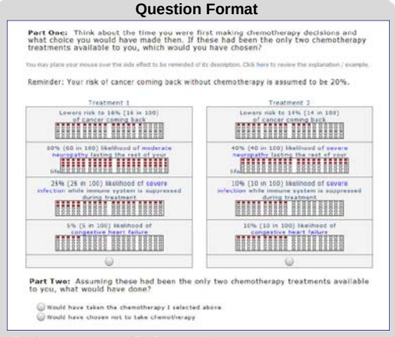
Impact of type of prior toxicity experience on hypothetical future decision to use same regimen



Impact of severity of prior PN toxicity experience on hypothetical future decision to use same regimen

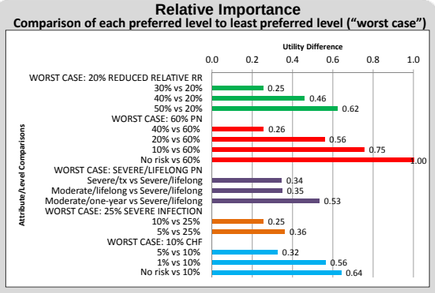
DERIVED IMPORTANCE OF TOXICITIES AND BENEFIT

Question Format



Benefit conveyed in terms of Risk Reduction. Absolute risk was computed and presented based on each respondent's perception of her own absolute starting risk of recurrence without chemo (10, 20, 30, or 40). Those who perceived "greater than 40" used 40 as a starting point.

Relative Importance
Comparison of each preferred level to least preferred level ("worst case")



- Each category compared relative importance of incremental changes against worst case
- Allowed cross-comparison of risks, as well as risk v benefit. Examples:
  - 20% absolute PN reduction had same impact as 10% relative improvement in efficacy
  - PN that is moderate/lifelong had same impact as severe during treatment (each compared to severe/lifelong)

Simulation Results: taxane-based v doxorubicin-based profiles

	AC profile	TC profile
Benefit	27%	35%
PN	No chance	**15%**
PN severity/ duration	N/A	**Moderate 1 yr**
Severe Infection	5%	5%
CHF	1.5%	No chance
Share of Preference	27%	**73%**

Scenario One:
taxane-based PN set at 15% moderate/one-year

TC profile, as depicted, was preferred by majority

	AC profile	TC profile
Benefit	27%	35%
PN	No chance	**5%**
PN severity/ duration	N/A	**Severe lifelong**
Severe Infection	5%	5%
CHF	1.5%	No chance
Share of Preference	61%	**39%**

Scenario Two:
taxane-based PN set at 5% severe/lifelong

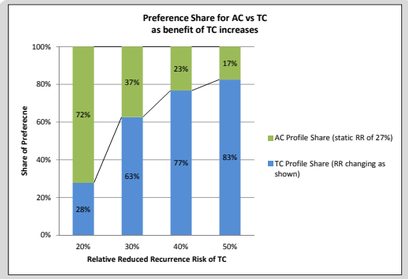
Severity/duration of PN led to dramatic change in preference

	Total Sample		PN Naïve		PN experienced	
	AC profile	TC profile	AC profile	TC profile	AC profile	TC profile
TC profile: 15% chance of Moderate PN 1 yr	27%	**73%**	36%	**64%**	23%	**77%**
TC profile: 5% chance of Severe lifelong PN	61%	**39%**	55%	**45%**	64%	**36%**
Change in TC share		**-34%**		**-19%**		**-41%**

Compare PN subgroup reactions to different PN Severity/Duration levels

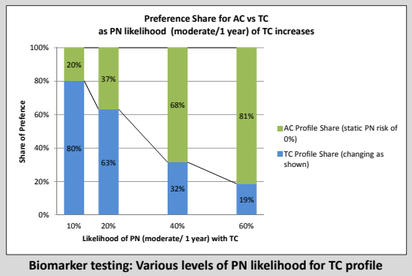
Those who had not had PN showed some change in preference as the severity/duration changed, but those who had had PN showed a dramatic change as severity/duration changed.

BIOMARKER MODELING



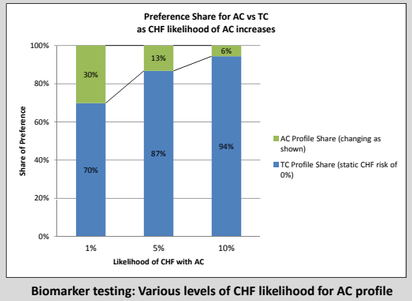
Biomarker testing: Reduced recurrence risk for TC profile

As expected, preference for TC versus AC increased significantly as benefit increased, particularly as TC's benefit exceeded AC's benefit



Biomarker testing: Various levels of PN likelihood for TC profile

Preference for TC v AC decreased significantly as PN likelihood increased



Biomarker testing: Various levels of CHF likelihood for AC profile

Preference for AC v TC decreased as CHF likelihood increased

Discussion

Stated and derived importance showed importance of toxicity, of severity, and influence of experience:

- CHF experience had greater influence on stated future decision than PN or Neutropenia
  - However, severity of PN experienced played a significant role
  - *Severe* PN experience appeared as influential as CHF
- CBC showed benefit & toxicities were influential
  - Using reasonable depiction of actual risk/benefit, majority of fully-informed respondents preferred treatment without severe PN, even with less benefit
  - Reduction in PN (20% absolute) was as important as improvement in efficacy (10% relative reduced RR)
- PN prior experience was important
  - PN-naïve reacted less strongly to PN changes than PN-experienced respondents

Biomarker influence:

- Preference for TC was enhanced as hypothetical biomarkers predicted increased benefit
- Predicted changes in toxicity with biomarkers had significant influence on preference
  - Most prominent for markers of PN

Conclusions

- Biomarkers can influence decision for patients faced with a multi-regimen choice.
- Patients considered both benefit & toxicity likelihoods and severity/duration.
- Prior toxicity experience had substantial influence on preference.

Clinical relevance:

- Consider individual patient preferences when considering therapy choices, particularly in settings in which patients have treatment choices with trade-offs.
- Educate patients regarding nuances and realities of toxicity experience, so patients have a basis to consider and express well-founded preferences.
- Make two-way communication a priority.

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