QOL-Adjusted Clinical Efficacy: A Pilot Study Integrating Treatment Efficacy and Quality of Life in Oncology Clinical Trials

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Background

- The majority of women diagnosed with breast cancer will experience some form of drug-related toxicity, psychosocial distress, and subsequent impairments in their quality of life (QoL) during their cancer trajectory.
- Impairments in QoL can interfere with treatment adherence, engagement in health-promoting behaviors and effective management of symptoms.
- The utilization of QoL or other Patient-Reported Outcome (PRO) measures in clinical trials remains inconsistent, and no uniformly accepted measure exists to integrate QoL data with clinical efficacy in the assessment of therapeutic agents.

I-SPY 2 TRIAL

I-SPY 2: A multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents as neoadjuvant therapy for high-risk breast cancer

Inclusion criteria: Tumor Size ≥ 2.5cm; hormone-receptor (HR)+HER2-MammaPrint (MP) high risk, HR-HER2- or HER2+

Primary Endpoint: Pathologic complete response (pCR)

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by HR and HER2 status, and MP

Regimens may leave the trial for one of four reasons: Futility (< 10% probability of success) ; Maximum sample size accrual (with probability of success ≥ 10% and < 85%) ; Graduation (≥ 85% predictive probability of success) ; or as recommended by the independent DSMB

To date: 11 experimental regimens have been evaluated for efficacy

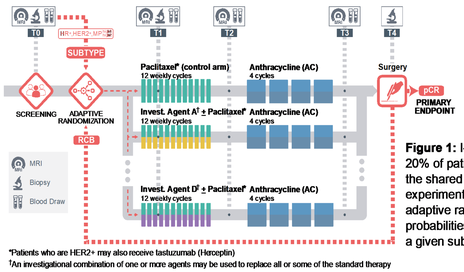

Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

Methods

- Study participants were part of the I-SPY 2 TRIAL assessing novel neoadjuvant therapies added to standard chemotherapy in the treatment of Stage 2/3 breast cancer.
- Patients in the study were randomized to the control arm or seven experimental drug arms, with patients in the control arm treated with Paclitaxel followed by anthracycline (AC).
- Participants completed a validated QoL measure at baseline, prior to surgery, and 1-month post-surgery. PROs were assessed using the NIH Patient-Reported Outcomes Measurement Information System (PROMIS®) measure and results at each time point used to calculate the PROPr score, a single utility-based index score to assess overall health-related QoL.
- PROPr is a preference-based summary score of health-related QoL that is constructed from 7 PROMIS® domains. In the current pilot study, the PROPr utility score was calculated at three time points and used to generate a single longitudinal QoL score or estimate of quality-adjusted life years (QALYs) lost during treatment. For each patient, baseline QoL scores were used to calculate the QALYs that would be experienced if they had not undergone treatment.
- Nearly twenty percent (n=102, 18.5%) of patients had complete data across the three study timepoints and were included in our analyses, and thus our data represent a proof of concept study.

Figure 1: Example of QALY calculation using PROPr scores.

Quality Adjusted Life Year – conceptually

Example:

No treatment QALY = .5 * (6.5/12) = .27

Baseline = .5 (PROPr), Pre-surgery =.4 (PROPr), Post-surgery = .3 (PROPr), 5.5 months btw baseline and pre-surgery, 1 month between pre and post surgery

Baseline to Pre-surgery : (.5+.4)/2 * (5.5/12) = .20 QALYs

Pre-surgery to post-surgery : (.4+.3)/2 * (1/12) = .05 QALYs

Total QALYs = .25 during treatment

Lost QALY = .02 during treatment - had they maintained baseline, they would have enjoyed .02 QALYs more, which equates to 7.3 days at full health.

RESULTS

- We are reporting the development of a novel, standardized assessment that could form a routine part of clinical trials in oncology (Figure 2).

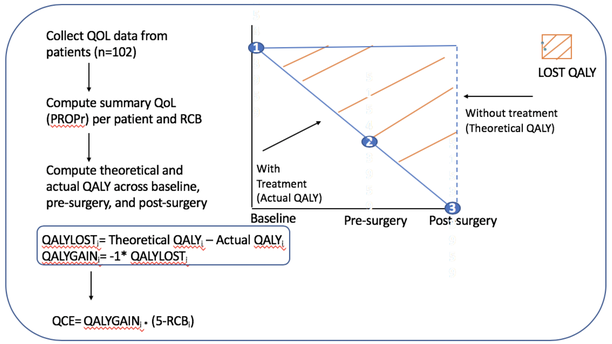

Figure 2: Workflow describing calculation of clinical benefit index.

- The QALY Lost index demonstrated a range of outcomes, with some arms clearly more challenging to tolerate, and others much better, with values ranging from -.186 to 0.25. The RCB index of the seven study arms ranged from 0.37 to 1.93 (Figure 3).
- The QCE, an integration of the longitudinal QoL and RCB indexes, demonstrated a range from -2.53 (individual treated with Drug 4) to 1.86 (individual treated with Drug 3)(Figure 3).
- For example, Drug 3 and 4 both possess similar distribution and mean values on the RCB index (0.87 vs. 0.85), suggesting similar clinical efficacy, however, examination of the QoL scores and integrated QCE suggest that Drug 3 is less toxic and better tolerated by patients.

RESULTS

Figure 3: RCB Index, Quality of Life Lost, and Clinical Benefit Index Across Eight Agents in the I-SPY Trial

CONCLUSIONS

- The QCE represents a novel approach to providing summary data that can be easily interpreted as part of clinical trial outcome data.
- Ideally, these integrated assessments would provide a more comprehensive evaluation of investigational therapies, and ultimately help inform treatment decisions and discussions between patients and providers.
- The collection of QoL data may also help motivate more timely interventions to abrogate side effects in cancer care.
- Moving forward, electronic PRO data should be collected as part of routine care in clinical trials, thus enabling a longitudinal QoL and QCE scores to be generated for every agent evaluated.

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