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Alignment Between Commonly Measured and Patient-Elicited Toxicities and Impacts of Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer Therapies

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Introduction

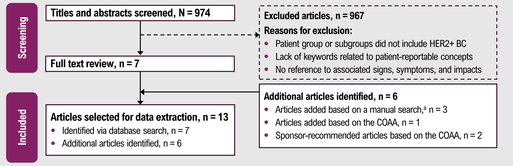
- Successful development of oncology treatments relies on optimizing drug dosing by maximizing both efficacy and tolerability, thereby enhancing patients' health-related quality of life (HRQoL)[1-5]
- Patient-reported tolerability outcomes, including side-effect bother and symptomatic adverse events (AEs), remain undercharacterized in low- and high-risk stage II/III human epidermal growth factor receptor 2–positive (HER2+) breast cancer (BC)

Objective

- To assess the alignment between symptomatic toxicities and impacts evaluated in clinical studies and those elicited as important by patients receiving neoadjuvant and adjuvant therapies for high- and low-risk stage II/III HER2+ BC

Methods

Figure 1. PRISMA Flow Diagram of the Study Selection Process



[a]Manual search describes articles identified through previous project work.
BC, breast cancer; COAA, Clinical Outcome Assessment Accelerator; HER2, human epidermal growth factor receptor 2; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- A targeted literature review was conducted using Ovid and the IQVIA Clinical Outcome Assessment Accelerator—a platform that facilitates the identification of patient-reported concepts, instruments, and endpoints to use in clinical studies by leveraging findings from previously conducted literature reviews and patient interviews
- Search strings were used for English language publications (published from January 2013 to August 2024) that captured patient-reported outcome (PRO) data and patient-elicited experiences with BC per the described inclusion and exclusion criteria

Table 1. Article Eligibility Criteria

PICOS	Inclusion Criteria	Exclusion Criteria
Patients	• Adults (≥18 years) with high- and low-risk stage II/III HER2+ BC who received neoadjuvant or adjuvant systemic therapy (ie, chemotherapy, targeted therapy, immunotherapy)	• Stages 0, I, or IV HER2+ BC or other diseases • Aged <18 years • Nonhuman studies
Intervention and Comparison	• Interventions for high- and low-risk stage II/III HER2+ BC, including—but not limited to—chemotherapy, targeted therapy, hormonal therapy, and immunotherapy • Any intervention or comparator (ie, alternative treatment regimens, no treatment, or placebo)	• Surgery and radiation interventions
Outcomes	• Patient-reported concepts, such as treatment-related symptoms, side-effect burden, and sensitive functional outcomes, and those related to tolerability, symptomatic toxicity and burden, treatment de-escalation or interruption, and adherence • PRO measures • Outcomes in patients receiving systemic therapy vs no treatment	• Literature without an outcome of interest or that focuses on only pathogenesis, genetics, molecular biology, or biomarkers
Study Design	• Clinical trials • Observational studies, including relevant qualitative interviews, registries, and real-world studies focusing on PRO assessments • Expert guidelines • Instrument development and validation studies • Epidemiology studies that report relevant PROs • Intervention studies • Systematic or targeted reviews	• Editorials • Case reports

BC, breast cancer; HER2, human epidermal growth factor receptor 2; PICOS, patients, intervention, comparison, outcome, study design; PRO, patient-reported outcome.

- Symptomatic toxicities and impacts were extracted from the publications and are referred to here as "concepts"
- The number of clinical studies measuring concept use (ie, frequency) and the prevalence of those concepts, as experienced and reported by patients in ≥1 qualitative study, were evaluated
- Concepts were grouped post hoc by frequency and patient-reported prevalence according to the following scheme:



Results

Table 2. Overview of Articles Included in the Literature Review

Author (Date)	Study Design	Study Population	Treatment Arms	PRO Instruments
Yang C, et al (2024)[6]	RCT	HER2+ stage II/IIIC and stage II/III BC (N = 210), low- and high-risk, neoadjuvant	• Arm 1: TCb + platinum-based regimen • Arm 2: TCbH + platinum-based regimen	• EORTC QLQ-C30 • EORTC QLQ-BR23
Fernandes R, et al (2023)[7]	RCT	HER2+ early-stage BC, low-risk (N = 44), neoadjuvant or adjuvant	• Arm 1: P-H • Arm 2: TC-H	• FACT-Taxane • FACIT-F • ESAS
Pohlmann PR, et al (2022)[8]	RCT	HER2+ any-stage BC (N = 51), neoadjuvant or adjuvant	• Arm 1: Crofelemer for patients receiving trastuzumab, pertuzumab, and a taxane • Arm 2: No crofelemer for patients receiving trastuzumab, pertuzumab, and a taxane	• FACIT-D • BSFS
Sawaki M, et al (2022)[9]	RCT	HER2+ early-stage BC in elderly patients (N = 120), adjuvant	• Arm 1: Trastuzumab monotherapy • Arm 2: Trastuzumab and chemotherapy • Arm 3: Non-trastuzumab treatment	• FACT-G
Trial Registry Record (2022)[10]	RCT	HER2+ BC (N = 330), neoadjuvant	• Arm 1: Pertuzumab IV and trastuzumab IV + investigator's choice of chemotherapy • Arm 2: Pertuzumab and trastuzumab FDC SC + investigator's choice of chemotherapy	• EORTC QLQ-C30
O'Shaughnessy J, et al (2021)[11]	RCT	HER2+ BC (N = 160), neoadjuvant	• Arm 1: Pertuzumab and trastuzumab IV followed by pertuzumab and trastuzumab FDC SC • Arm 2: Pertuzumab and trastuzumab FDC SC followed by pertuzumab and trastuzumab IV	• EORTC QLQ-C30* • TASQ IV • TASQ SC • PPQ
O'Sullivan CC, et al (2021)[12]	RCT	HER2+ BC (N = 981), high-risk, adjuvant	• Arm 1: T-DM1 IV + oral placebo BID • Arm 2: T-DM1 IV + tucatinib by mouth BID	• PRO-CTCAE • FACT-B
Pérez-Garcia JM, et al (2021)[13]	RCT	HER2+ stage I–IIIA, invasive, operable BC (N = 319), neoadjuvant and adjuvant	• Arm 1: Docetaxel, carboplatin, trastuzumab, and pertuzumab • Arm 2: Trastuzumab, pertuzumab, letrozole, or tamoxifen	• EORTC QLQ-C30 • EORTC QLQ-BR23
Conte P, et al (2020)[14]	RCT	HER2+ BC with residual tumor present in the breast or axillary lymph nodes following preoperative therapy (N = 1252), adjuvant	• Arm 1: T-DM1 • Arm 2: Trastuzumab	• EORTC QLQ-C30 • EORTC QLQ-BR23
Hurvitz SA, et al (2019)[15]	RCT	Clinical stage II/III HER2+ BC (N = 444), neoadjuvant and adjuvant	• Arm 1: T-DM1 + pertuzumab • Arm 2: Trastuzumab + pertuzumab	• EORTC QLQ-C30 • EORTC QLQ-BR23
Mang'are MV, (2020)[16]	Survey, interviews	HER2+ BC (n = 14 interview participants; n = 44 survey participants), neoadjuvant	Not reported	RSCL-M
Petersen JA, et al (2016)[17]	Qualitative, semistructured interviews	Early-stage and locally advanced HER2+ BC (N = 56), neoadjuvant	Not reported	Not reported
Sodergren SC, et al (2015)[18]	Systematic review	HER2+ BC; 18 trials included in review (samples vary for each trial), adjuvant	Not reported	Not applicable

BC, breast cancer; BID, twice daily; BSFS, Bristol Stool Form Scale; EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Breast Cancer Module (23 items); EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ESAS, Edmonton Symptom Assessment System; FACIT-D, Functional Assessment of Chronic Illness Therapy–Diarrhea; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-Taxane, Functional Assessment of Cancer Therapy–Taxane; FDC, fixed-dose combination; HER2, human epidermal growth factor receptor 2; IV, intravenously; P-H, paclitaxel plus trastuzumab; PPQ, Patient Preference Questionnaire; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RCT, randomized controlled trial; RSCL-M, Modified Rotterdam Symptom Checklist; SC, subcutaneously; T-DM1, trastuzumab emtansine; TASQ, Therapy Administration Satisfaction Questionnaire; TCb, docetaxel and carboplatin; TCbH, docetaxel, carboplatin, and trastuzumab; TC-H, docetaxel-cyclophosphamide plus trastuzumab.

- The literature search identified 980 articles: 974 from Ovid, 5 from a manual search, and 1 from the IQVIA Clinical Outcomes Assessment Accelerator
- Of these, 13 articles were eligible for inclusion and consisted of 10 randomized controlled trials (RCTs),[6-15] 2 qualitative studies,[16-17] and 1 systematic literature review[18]

Table 3. Frequency and Prevalence of and Patient-Elicited Concepts Measured in at Least 5 RCTs

Concepts (Toxicities and Impacts)	PRO Instruments Measuring the Concept	No. of RCTs Measuring the Concept, (n = 10)[6-15]	Concept Prevalence[a] Reported in Qualitative Studies and Systematic Literature Review[16-18]
High prevalence outcomes (reported by ≥25% of patients) measured in ≥5 studies			
Social impacts[b,c]	EORTC QLQ-C30; FACT-B; FACIT-D; FACIT-F	9	21%–28%[16]
Diarrhea[c]	EORTC QLQ-C30; BSFS	7	29%[18]
Fatigue (tiredness)[c]	EORTC QLQ-C30; ESAS	7	7%,[18] 13%,[16] 35%–71%[17]
Difficulty sleeping, insomnia[b]	EORTC QLQ-C30	6	27%[16]
Financial difficulties[c]	EORTC QLQ-C30; FACT-G; FACIT-F	6	31%[16]
Low prevalence outcomes (reported by <25% of patients) measured in ≥5 studies			
Physical impacts[b,c]	EORTC QLQ-C30; FACT-B; FACIT-D; FACIT-F	9	NPDI
Role functioning[b,c]	EORTC QLQ-C30; FACT-B; FACIT-D; FACIT-F; FACT-G	9	NPDI
Emotional impacts[b,c]	EORTC QLQ-C30; FACT-B; FACIT-D; FACIT-F	8	NPDI
Cognitive functioning[b,c]	EORTC QLQ-C30; FACT-G	7	NPDI
Breathing abnormality[c]	EORTC QLQ-C30; ESAS	7	NPDI
Loss of appetite[c]	EORTC QLQ-C30; ESAS	7	1%,[18] 10%[16]
Nausea[c]	EORTC QLQ-C30; ESAS	7	8%,[18] 10%[16]
Pain (general)[c]	EORTC QLQ-C30; ESAS	7	NPDI
Constipation	EORTC QLQ-C30	6	1%[18]
Vomiting	EORTC QLQ-C30	6	4%[18]

[a]Reported in ≥1 qualitative study, where mentioned.
[b]Reported as bothersome.[c]
[c]Redundantly measured by >1 PRO instrument in ≥5 RCTs.
BSFS, Bristol Stool Form Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; ESAS, Edmonton Symptom Assessment System; FACIT-D, Functional Assessment of Chronic Illness Therapy–Diarrhea; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; NPDI, no prevalence data identified; PRO, patient-reported outcome; RCT, randomized controlled trial.

Table 4. Frequency and Prevalence of and Patient-Elicited Concepts Measured in Fewer Than 5 RCTs

Concepts (Toxicities and Impacts)	PRO Instruments Measuring the Concept	No. of RCTs Measuring the Concept, (n = 10)[6-15]	Concept Prevalence[a] Reported in Qualitative Studies and Systematic Literature Review[16-18]
High prevalence outcomes (reported by ≥25% of patients) measured in <5 studies			
Anxiety	FACIT-F	1	26%[16]
Hair loss	EORTC QLQ-BR23	1	0%,[18] 87%[17]
Distortion of taste	NII	0	73%[17]
Hot flashes	NII	0	<1%,[18] 50%[17]
Joint pain	NII	0	2%,[18] 14%,[16] 38%[17]
Memory loss	NII	0	64%[17]
Runny nose	NII	0	26%[17]
Tingling sensation	NII	0	64%[17]
Low prevalence outcomes (reported by <25% of patients) measured in <5 studies			
Sexual intimacy[b]	EORTC QLQ-BR23	4	20%[16]
Oral issue	NII	0	2%,[18] 9%[16]
Skin rash	NII	0	22%[18]
Weight gain	EORTC QLQ-BR23	0	20%[17]

[a]Reported in ≥1 qualitative study, where mentioned.
[b]Reported as bothersome.
EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Breast Cancer Module (23 items); FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; NII, no instrument identified; PRO, patient-reported outcome; RCT, randomized controlled trial.

- From these 13 eligible publications, 27 total concepts were extracted and grouped
- Thirteen concepts were reported as ≥25% prevalent in the qualitative literature
  - Of these concepts, 5 were assessed in ≥5 RCTs and 8 were measured in <5 RCTs
  - Of the 8 concepts measured in <5 RCTs, 6 (distortion of taste, hot flashes, joint pain, memory loss, runny nose, and tingling sensation) were not measured by any PRO instrument
- Fourteen concepts were not reported as ≥25% prevalent in the qualitative literature
  - Of these concepts, 10 were assessed in ≥5 RCTs
- Across groups, 12 concepts were redundantly measured by >1 PRO instrument in 6 or more RCTs
- Seven concepts were identified as bothersome to patients, defined as a rating of >6 on an 11-point scale (0 = none; 10 = extremely bothersome)[17]
- Insufficient data were available to assess differences in concepts in the neoadjuvant vs adjuvant setting or between high- and low-risk populations

Conclusions

- Results were based only on 10 RCTs, 2 qualitative studies, and 1 systematic literature review; therefore, data regarding tolerability-related concept frequency and prevalence in patients with stage II/III HER2+ BC were limited
- Many of the most frequently elicited symptoms and impacts by patients in the qualitative literature, including known symptomatic AEs such as distortion of taste, hot flashes, and memory loss, were not assessed by any measures in any of the identified RCTs
- Conversely, many symptoms that were infrequently or never identified by patients, were redundantly measured by multiple instruments in several RCTs, including breathing abnormalities, appetite loss, and nausea
- Concept mapping against PRO item libraries, such as the PRO version of the CTCAE, should be utilized to ensure the most relevant symptomatic AEs are assessed in RCTs and reduce patient burden by minimizing the number of symptoms that are assessed multiple times across multiple instruments
- Further qualitative research is needed to identify the most sensitive symptoms and outcomes for assessment

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