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The Use of Real-World Data to Examine Comparative Effectiveness Research and Treatment Patterns in HER2-Negative and Triple-Negative Metastatic Breast Cancer: A Systematic Literature Review

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BACKGROUND

- About 66% of women with breast cancer have human epidermal growth factor receptor 2 negative (HER2-) and 10-17% have triple negative (TN) breast cancer. Both subtypes are especially difficult to treat.[1]
- Metastatic breast cancer (mBC) is associated with poor outcomes: 5-year survival is only 26.3%.[2]
- With the accumulation of real world data (RWD) in healthcare, opportunities to conduct research in oncology, such as comparative effectiveness research (CER), continue to expand.[3]
- Conducting real world studies in oncology may be challenging, as many RWD sources do not capture clinical response, and may be missing information on progression and survival.

OBJECTIVES

- To better understand real-world evidence in mBC, we examined common endpoints reported in RWD studies on CER and treatment patterns (TxP) in mBC, focusing on HER2- and TN mBC.

METHODS

Data Sources

- PubMed and 4 online conference databases:
  - American Society of Clinical Oncology (ASCO) Annual Meeting
  - ASCO Breast Cancer Symposium (BCS)
  - ASCO Quality Care Symposium (QCS)
  - San Antonio Breast Cancer (SABC) Symposium
- Bibliographies of included articles

Search Strategy

- Searches conducted in January 2016.
- MeSH terms, subheadings, and key words used included: metastatic breast cancer, triple negative, ER negative, estrogen receptor negative, PR negative, progesterone receptor negative, HER2 negative, treatment, comparative effectiveness, unmet need, patient reported outcomes, self-report, and pain.

Screening Criteria

- Included studies were published after 2006 or presented from 2013-2015 and in English, reported data on treated human patients with HER2-negative or TN mBC on topics of interest (CER and TxP).Clinical trials were excluded.

Outcomes

- Common outcomes across studies were examined.

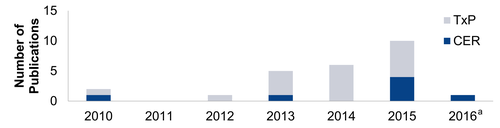
RESULTS

- Of 1,782 total references (1,070 articles; 712 conference abstracts), 25 were screened in:
  - 7 CER studies (6 articles and 1 abstract)
  - 18 TxP studies (10 articles and 8 abstracts).
- Studies that reported data in non-human subjects, were not specific to HER2- or TN mBC, were not in US patients, or were not on research topics of interest were excluded.

RESULTS

- All included studies were retrospective; the majority were chart reviews (6 CER, N ranging from 90 to 1,782; 10 TxP, N=17-699), others were retrospective secondary database analyses (1 CER; 6 TxP) and physician surveys (2 TxP).
- Secondary data sources included commercial insurance claims (used in 2 studies, N ranging from 3,298 to 19,120), SEER-Medicare (2 studies, N=4,364-13,170), and the California Cancer Registry data (1 study, N=6,268).
- 18 studies reported results in HER2-negative mBC patients, 6 in patients with TN disease, and 1 in both HER2-negative mBC and TNBC patients.
- Common primary endpoints included OS, PFS, and treatment duration.
- 71% of the CER studies reported endpoints of treatment duration and 86% reported at least one survival measure (e.g., OS, PFS).
- 61% of TxP studies examined survival outcomes in addition to treatment patterns.
- Overall, the studies had diverse methods and objectives. Results were consistent with the observation that HER2-negative and TNBC have generally worse outcomes than HER2-positive/ER-positive disease.
  - Studies using RWD increased over time.

Figure 1. Number of RWD Studies per Year



[a] Only searched until January 2016.

Table 1. Comparative Effectiveness Literature

Reference	Design	Data Source	Primary Outcomes	Patients	Treatments
Dawood et al. J Clin Oncol 2010.	Chart review	MD Anderson Cancer Center (N=1,782)	1-year, 2-year, 5-year OS	HER2/neu-negative mBC	Breast conserving surgery, mastectomy
Dranitsaris *et al.* ASCO BCS. 2013.	Chart review	8 community oncology practices (N=90)	TTF; toxicity; treatment intensity and duration	TN mBC	Eribulin; prior anthracycline
Dranitsaris et al. Clin Ther. 2015.	Chart review	19 community oncology practices, part of the Cancer Clinics of Excellence network (N=225)	TTF, HCRU, treatment related toxicities, factors related to treatment choice, treatment duration, treatment discontinuation, morbidity, death	TN mBC	Eribulin, capecitabine, gemcitabine, or vinorelbine and targeted agents
Li et al. Curr Med Res Opin. 2016.	Secondary data analysis	MarketScan, PharMetrics commercial health insurance databases (2002Q1-2014Q2) (N=3,298)	TOT	HR+/HER2- mBC	Everolimus-based therapy, chemotherapy, capecitabine monotherapy
Li. et al. Int J Breast Cancer. 2015.	Chart review	Community oncology practice (N=371)	OS; PFS; TOT	Postmenopausal women with HR+/HER2- stage IV mBC	Everolimus-based therapy, chemotherapy
Lin et al. Expert Opin Pharmacother. 2015.	Chart review	98 physicians from community-based practices, recruited from a nationwide online panel, contributed data (N=202)	TOT; PFS	Stage IV HR+/HER2- mBC with liver metastasis	Everolimus-based therapy, endocrine monotherapy, or chemotherapy
Xie et al. Curr Med Res Opin. 2015.	Chart review	Sample collected from a panel of community-based oncologists and hematologists registered with the American Medical Association (N=513)	TOT; PFS; TTC	Postmenopausal, stage IV, HR+/HER2- mBC women	Everolimus-based therapy, endocrine monotherapy

Table 2. Treatment Patterns Literature

Reference	Design	Data Source	Primary Outcomes	Patients	Treatments
Clarke. SABC Symposium. 2014.	Secondary data analysis	California Cancer Registry (N=6,268)	OS	De-novo mBC (included TNBC)	Breast surgery; full or partial mastectomy; lumpectomy; bilateral mastectomy; chemotherapy; radiation
Engel-Nitz. SABC Symposium. 2013.	Secondary data analysis	Linked medical and pharmacy claims from a large national US health plan with a proprietary clinical cancer database containing physician-reported data (N=317)	Mortality; length of survival; treatment patterns	HR+/HER2- advanced breast cancer	Endocrine therapy; chemotherapy
Faria. ASCO Annual Meeting. 2014.	Chart review	21 US community oncology practices (N=173)	TTP; TTF	TN mBC; HER2- mBC	Eribulin mesylate
Hao. SABC Symposium. 2013.	Secondary data analysis	Physician reports linked to medical and pharmacy claims database from a large national US health plan (N=317)	Treatment sequencing, patterns, and duration; mortality	HR+/HER2- advanced breast cancer	Endocrine therapy; chemotherapy
Karve. ASCO Annual Meeting. 2013.	Secondary data analysis	Surveillance, Epidemiology and End Results-Medicare (SEER-Medicare) data (N=13,170)	Treatment patterns; survival	HR+/HER2- mBC women ≥65 years old	Surgery; radiation; hormone therapy (megestrol; anastrazole; fulvestrant); chemotherapy (cyclophosphamide; doxorubicin; paclitaxel).
Koshy et al. Breast. 2010.	Chart review	Louisiana State University Health Sciences Center (N=17)	PFS, OS	mBC (including TNBC)	Cisplatin-gemcitabine chemotherapy
Krook. ASCO Annual Meeting. 2013.	Chart review	Community oncologists in southeast USA (N=205)	Treatment patterns	HR+/HER2- stage IV mBC	Anthracyclines
Li et al. Curr Med Res Opin. 2015.	Chart review	Community-based oncologists and hematologists (N=699)	Everolimus treatment patterns; reasons for prescribing everolimus	Postmenopausal HR+/HER2- mBC; failed non-steroidal aromatase inhibitor	Everolimus; endocrine therapy; chemotherapy
Lin et al. Cancer Med. 2015.	Physician survey	213 community-based oncologists/ hematologists from a nationwide online panel (N=1,323)	Treatment patterns; survival	Postmenopausal, stage IV, HR+/ HER2- mBC women	Endocrine therapy or chemotherapy
Macalad et al. Curr Med Res Opin. 2015.	Chart review	Network of community-based oncology practices (N=144)	Treatment patterns and durations by lines of treatment	HR+/HER2- mBC	Endocrine therapy or chemotherapy
Morris et al. Breast J. 2012.	Chart review	Memorial Sloan-Kettering Cancer Center (N=298)	OS; treatment patterns; incidence of brain metastases	TN mBC	Radiotherapy, surgery, systemic chemotherapy
Pahuja. SABC Symposium. 2014.	Chart review	Magee Women's Breast Cancer Program at University of Pittsburgh (N=86)	TTR; TTP	TNBC pts. that did not receive pCR after neo-adjuvant chemotherapy	Anthracycline and taxane based NAC
Patt. ASCO Annual Meeting. 2014.	Physician survey	US oncology network physicians (N=104 physicians)	nab-Paclitaxel utilization, toxicity, frequency, management, duration	HER2- mBC	Nab-Paclitaxel
Seah et al. J Natl Compr Canc Netw. 2014.	Chart review	Dana-Farber Cancer Institute (N=318)	Treatment patterns; duration of chemotherapy; OS	HR+/HER2- mBC	Adjuvant/ neoadjuvant chemotherapy, endocrine therapy, or anti-HER2 therapy
Swallow et al. Curr Med Res Opin. 2014.	Secondary data analysis	Truven Health MarketScan Commercial and Medicare Supplemental health insurance claims databases (N=19,120)	Treatment patterns and durations by lines of treatment	HR+/HER2- mBC	Endocrine therapy or chemotherapy
Vaz-Luis et al. Breast Cancer Res Treat. 2015.	Secondary data analysis	SEER-Medicare data (N=4,364)	OS; treatment utilization; time to treatment initiation	≥66 year old women with mBC with first invasive breast cancer diagnosed 1998-2009, by HER2 (included HER2-)	Received vs. did not receive trastuzumab
Xie et al. Exp Hematol Oncol. 2015.	Chart review	188 physicians from community-based oncology practices contributed data (N=699)	PFS; TOT; OS	Postmenopausal women, HR+/HER2- mBC	Endocrine therapy or chemotherapy
Zeichner et al. Breast Cancer Res Treat. 2015.	Chart review	Large breast cancer oncology private practice and the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC) tumor database (N=153)	OS	mBC by HER2 status (included HER2-)	Chemotherapy, hormone therapy reported as observed

ER – estrogen receptor; HCRU – healthcare resource utilization; HER2 – human epidermal growth factor receptor 2; HR – hormone receptor; mBC – metastatic breast cancer; NAC – neoadjuvant chemotherapy; NCCN: National Comprehensive Cancer Network; OS – overall survival; pCR – Pathological complete response rate; PFS – progression-free survival; TNBC – Triple-negative breast cancer; TN mBC- Triple-negative metastatic breast cancer; TOT – Time on treatment; TTC – time to chemotherapy; TTF – time to treatment failure; TTP – time to progression.

CONCLUSIONS

- Real-world literature on patients with HER2-negative mBC in the US is limited, particularly for patients with TN mBC; though this type of research is becoming more prevalent, especially as examined over the last 5 years.
- Due to the nature of retrospective research, which is a commonly employed study methodology for using RWD, clinical data and corresponding endpoints traditionally published in clinical trials may be unavailable.
- As such, studies examining RWD will use surrogate endpoints including treatment duration or progression free survival when comparing treatment options. Understanding the clinical utility of these endpoints and how they resonate with various stakeholders will be important as more RWD is published.
- Given the diversity of topics examined in the included studies, it is difficult to draw summary conclusions about the clinical findings.

LIMITATIONS

- Given the increase in RWD publications, an update to the current review may be necessary in the near future.
- Although this was a rigorous review on broad RWD research topics in mBC, a search of different databases or with a different search strategy may have yielded somewhat different results.
- The study only focused on recently published US literature.

CORRESPONDENCE

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DISCLOSURES

- Monika Parisi and Corey Pelletier are employees of the Celgene Corporation. Nadia Noormohamed is a student at the Massachusetts College of Pharmacy and was a rotational student at the Celgene Corporation.
- Dasha Cherepanov and Michael Broder are employees of Partnership for Health Analytic Research, LLC a health services research company paid by the Celgene Corporation to conduct this research.

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