Impact of Molecular Subtype on Inflammatory Breast Cancer-Specific Mortality in Adult Women

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Abstract

Background:

Methods:

Results:

Conclusions:

Introduction

Inflammatory breast cancer (IBC) is a rare but aggressive subtype of breast cancer, accounting for 2% to 6% of all breast cancer cases in the United States (Devi et al. 2019; Hance et al. 2005). IBC presents differently than other types of breast cancer. It often lacks a breast lump and may not appear on a mammogram, making accurate diagnosis challenging and potentially delaying treatment. IBC causes symptoms of breast inflammation, such as swelling and redness, due to cancer cells blocking lymphatic vessels in the skin, giving the breast an "inflamed" appearance (Menta et al. 2018).

Clinically, IBC is categorized as T4d in the TNM classification for its aggressive biological behavior. In spite of multimodal therapy, IBC has a local recurrence rate of up to 50% and survival rates of only 35% to 40%, significantly lower than those of other types of breast cancer (Robertson et al. 2010). Despite its rarity, IBC disproportionately accounts for up to 10% of all breast cancer-related deaths (Devi et al. 2019; Hance et al. 2005).

Because IBC is rare, the biological characteristics of IBC are not commonly reported and the molecular alterations that result in poor prognosis are not well understood. However, hormone receptors (HR) and human epidermal growth factor receptor-2 (HER2), which define the molecular status of IBC through immunohistochemistry (IHC), are fundamental markers used to demonstrate molecular features, predict prognosis, and optimize therapeutic regimens (Li et al. 2017). IBC tumors are characterized by combinations of hormone receptors and oncogenes, allowing the majority to be characterized as Luminal A (HR+/HER2-), Luminal B (HR+/HER+), HER2 Positive (HR-/HER2+), and Triple Negative by IHC.(Bonito, Cantile, and Botti 2019). Studies have shown that these four molecular subtypes reveal the prognostic discrepancies in both common breast cancers and IBC (Robertson et al. 2010; Le Du et al. 2015; Tolaney et al. 2015; Iwamoto et al. 2011). A previous study examined the association between molecular subtypes and survival outcomes in IBC patients from 2010 to 2013 (Li et al. 2017). However, no updated population-based studies have investigated this relationship.

Therefore, using the most recent Surveillance, Epidemiology, and End Results (SEER) data, this study aims to assess the effect of molecular subtype on IBC-specific mortality in adult females with IBC.

Methods

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database is an authoritative source of information on cancer incidence and survival in the United States (https://seer.cancer.gov/). SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48% of the U.S. population. This study utilized SEER incidence data from 2010 to 2021.

Study Population

The study population focuses on adult females diagnosed with IBC. Data was extracted from the SEER 17 Registries (2000-2021) using the SEER*Stat software (version 8.4.4; Surveillance Research Program, NCI, Bethesda, MD). The specific criteria used to identify patients with IBC were as follows: (1) Site and Morphology (TNM 7/CS v0204 Schema recode) was limited to "Breast"; (2) Derived TNM classification, AJCC 7th edition (2010-2015) was limited to "T4d", SEER Combined T (2016-2017) was limited to "c2D" and "p4D", and EOD 8th edition (2018+) was limited to "T4D"; and (3) Histology type (ICD-O-3) ranged from 8500 to 8549. Year of diagnosis was limited to 2010 to 2021 because SEER started collecting breast cancer molecular subtype in 2010. To limit our data to adult females, age at diagnosis was limited to patents 20 years and older and sex was limited to "Female".

Variables

For each case, the following information from SEER was obtained: age at diagnosis (20-49, 50-69, and >=70), race (white, black, other), marital status (unmarried, married), N (node) stage (N0, N1, N2, N3), M (metastasis) stage (M0, M1), grade (I/II, III/IV), radiation (no/unknown, yes), chemotherapy (no/unknown, yes), surgery (no/unknown, yes), survival months, cause-specific death classification (Alive or dead of other cause, Dead (attributable to this cancer), Dead (missing/unknown COD)), and other cause of death classification (Alive or dead due to cancer, Dead (attributable to causes other than this cancer), Dead (missing/unknown COD)). Breast cancer subtypes were classified as Luminal A (HR+/HER2-), Luminal B (HR+/HER+), HER2 positive (HR-/HER2+), and Triple Negative. In addition, cases with incomplete information on any of these characteristics and patients who survived less than one month were excluded from the study. To focus on IBC-specific mortality, patients with an unknown cause of death or whose death was attributed to other causes were excluded.

Statistical Analysis

Clinicopathological characteristics were compared between IBC subtype using Pearson's Chi-squared test. Median, 1-year, 5-year, and 10-year survival for IBC is estimated for each variable in using the Kaplain-Meier method and compared using the log-rank test in the subgroups. The proportional hazards assumption was assessed visually with log-log plots and statistically by calculating Schoenfeld residuals and the Pearson's product moment correlation coefficient of the Schoenfeld residuals and ranked survival times. After determining the assumption of proportional hazard was met, univariate and multivariate Cox proportional hazards regressions were used to model the relationship between potential covariates and IBC-specific survival. We obtained hazard ratios (HR) and 95% confidence intervals for each covariate. All statistical analyses were performed using the survival package in R version 4.3.3.