Contemporary Systemic Therapy for Male Breast Cancer

Katherine L. Bradley,[1] Scott Tyldesley,[1] Caroline H. Speers,[2,3] Ryan Woods,[2,3] Diego Villa[4]

Abstract

The management of male breast cancer remains complex and undefined because it occurs infrequently. Male breast cancers almost always express hormone receptors, and although endocrine therapy is an important treatment cornerstone, men often encounter challenges with toxicity and adherence. The outcomes of men with breast cancer appear to be similar to those of women matched by prognostic and treatment factors.

Background: The use, effectiveness, and tolerability of tamoxifen, aromatase inhibitors, and trastuzumab in early and advanced male breast cancer were examined at a population level. **Patients and Methods:** A total of 158 consecutively referred men with invasive breast cancer diagnosed between 2000 and 2010 were identified. Stage and prognostic factors were compared with a random sample of contemporary female patients. Survival outcomes were compared with a separate female cohort matched 2:1 by prognostic and treatment factors. **Results:** Men were older (median 69.5 years) than women (median 60 years) and presented with more advanced stage disease. Estrogen receptor was positive in 96% (n = 152) of cases. Tamoxifen was more commonly used than aromatase inhibitors in the curative and metastatic settings. Adherence to adjuvant tamoxifen therapy was generally adequate with estimated actuarial rates of persistence at 1 year and 3.5 years of 89% and 70%, respectively. For the 146 men treated with curative intent, 5-year overall survival, breast cancer-specific survival and progression-free survival were 72%, 86%, and 62%, respectively. Outcomes were similar to matched female patients in univariate and multivariate analyses. **Conclusions:** In this large population-based study, outcomes appear similar between male and risk-matched female patients with breast cancer. Side effect profiles, tolerance, adherence, and outcomes after tamoxifen, aromatase inhibitors, and trastuzumab in men appear comparable with those described in the literature for women.

Clinical Breast Cancer, Vol. 14, No. 1, 31-9
Keywords: Adherence, Aromatase inhibitors, Tamoxifen, Toxicity, Trastuzumab

Introduction

There are limited data informing the management of male breast cancer (MBC) because it occurs infrequently. Recommendations, including those for hormonal therapy, generally follow those for female patients in whom the hormonal milieu differs. MBC tends to present at a later age, at a higher stage, is more often estrogen receptor (ER)- and progesterone receptor (PR)-positive, and less often HER2 receptor-positive.[1-5]

[1]Department of Radiation Oncology
[2]Breast Cancer Outcomes Unit
[3]Cancer Surveillance and Outcomes
[4]Department of Medical Oncology
British Columbia Cancer Agency, Vancouver, British Columbia, Canada

Submitted: Mar 31, 2013; Revised: Sep 10, 2013; Accepted: Sep 24, 2013; Epub: Oct 1, 2013

Address for correspondence: Diego Villa, MD, British Columbia Cancer Agency, 600 West 10th Ave, Vancouver, British Columbia V5Z 4E6, Canada
Fax: 604-877-0585; e-mail contact: dvilla@bccancer.bc.ca

Adjuvant tamoxifen is widely used in MBC[6-8] on the basis of its effectiveness in the curative[9-15] and palliative[16-19] management of female breast cancer. However, men often tolerate tamoxifen poorly, resulting in lower adherence rates than women.[20,21]

Similar to postmenopausal women, a significant proportion of male estrogen is generated by conversion of circulating androgens via the aromatase enzyme.[22,23] Thus, in the presence of progressive disease on tamoxifen, or when tamoxifen is contraindicated, treatment with aromatase inhibitors (AIs), with or without a gonadotropin-releasing hormone analogue, is an alternative option. There is a paucity of literature describing the effectiveness of this approach in men, although responses have been documented in small series and case reports.[24-28]

Overexpression of HER2 is much less prevalent in men than women with breast cancer.[1,5,29] Although trastuzumab is very effective in the management of early and advanced female breast cancer,[30-36] there are no data describing the benefit of trastuzumab in MBC. Again, usage follows the practice in female breast cancer.

1526-8209/$ - see frontmatter
http://dx.doi.org/10.1016/j.clbc.2013.09.001

The purpose of the current study is to describe the use, effectiveness, and tolerability of tamoxifen, AIs, and trastuzumab in the treatment of MBC, and to compare the presentation, management, and outcomes of MBC with female breast cancer at a population-based level.

Patients and Methods

Patient Population

The British Columbia Cancer Agency (BCCA) coordinates cancer care for the entire province of British Columbia (BC). Every resident of BC is assigned a unique health care identification number, allowing linkage of health-related data sets. The BC Cancer Registry captures diagnosis, histology, and demographic characteristics of every new cancer diagnosis in the province. All radiotherapy is delivered at a BCCA cancer center. The BCCA central pharmacy dispenses all approved anticancer drugs, and this information is stored in a linkable electronic database. Approximately 85% of all incident breast cancer patients are referred to a BCCA clinic at diagnosis.

We identified all new cases of MBC (early and advanced stage) diagnosed between January 1, 2000 and March 31, 2010 in the BC Cancer Registry. Records were cross-referenced with the BC central pharmacy electronic database to identify drug usage. Data were then linked to the Breast Cancer Outcomes Unit database to obtain baseline, treatment, and outcome data. Additional information was collected from the Cancer Agency Information System whenever necessary. This study was approved by the University of British Columbia BCCA Research Ethics Board.

Persistence and Compliance Analyses

Persistence and compliance with adjuvant tamoxifen therapy were analyzed to describe adherence to this medication. Persistence indicates a patient's ability to follow a recommended duration of therapy (5 years being the standard recommendation for adjuvant tamoxifen).[13,37] Patients continuing to fill adjuvant tamoxifen prescriptions were deemed persistent. Crude proportions of patients continuing to take tamoxifen at 1 and 3.5 years were calculated. An actuarial analysis of persistence was also performed, in which patients were censored if they relapsed or died, completed 5 years of therapy, or if they continued to take tamoxifen at their last contact.

Compliance indicates the consistency with which patients take medication. Compliance with prescribed adjuvant tamoxifen was defined as having filled sufficient prescriptions to take this medication on at least 80% of days. The total number of tablets provided (excluding the final prescription) was divided by the number of days between the dates of each patient's first and final prescriptions.

There were too few cases treated with AIs or trastuzumab to perform a meaningful analysis of persistence or adherence to these medications.

Statistical Methods

Summary statistics were used to describe baseline and treatment characteristics for the entire MBC cohort. These were then compared with a random sample of 1000 women from the same population who were diagnosed with breast cancer during the same time period, to compare the age, stage, and prognostic factor distribution between male and female patients at presentation. Discrete variables were compared with the χ^2 or Fisher exact test, and continuous variables were compared using Student t test.

Overall survival (OS) was calculated from the date of initial diagnosis to the date of last follow-up or death from any cause. Breast cancer-specific survival (BCSS) was calculated from the date of diagnosis to the date of death from breast cancer or treatment-related complications; patients who died from unrelated causes were censored at the time of death. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of first disease progression or death from any cause.

To compare outcomes for comparable presentations of men and women, each early MBC case was also randomly matched to 2 women diagnosed with breast cancer during the same time period. Matches were made on the basis of the following factors: age within 4 years, year of diagnosis within 2 years, stage, ER status, and HER2 status. Characteristics were compared between both groups using the Fisher exact test.

Outcomes (OS, BCSS, PFS) were estimated using the Kaplan-Meier method. Sexes were first compared in univariate analysis using the log-rank test, and then adjusted for nonmatching factors in multivariate analyses using Cox proportional hazards regression with a backward likelihood ratio approach. Hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) were calculated. The following variables were included in the multivariate analyses: tumor grade, tumor size, nodal status, presence of lymphovascular invasion, adjuvant chemotherapy, and adjuvant hormonal therapy.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 14.0 for Windows; SPSS Inc, Chicago, IL).

Results

Patient Characteristics

As shown on Figure 1, a total of 32,657 cases of breast cancer were diagnosed between 2000 and 2010, of which 205 (0.6%) were men and 184 had invasive MBC. Of these, 158 (0.5%) were referred to BCCA and comprise the cohort for this analysis. Figure 1 shows how the study cohort was identified, and the reasons for exclusion of other cases.

Patient characteristics at presentation for men and a random sample of 1000 contemporary women are summarized in Table 1. The median age was 69.5 years (range, 33-93 years) for men, and 60 years (range, 26-95 years) for women ($P < .001$). The most common histology was infiltrating ductal carcinoma, present either alone or with other histological subtypes, in 154 (97%) men and 812 (86%) women ($P < .001$). Most of the MBC cases were hormone receptor-positive (ER-positive, 96%; PR-positive, 91%), and 9 (6%) were HER2-positive, although complete biomarker (ER, PR, and HER2) data were available for 97 patients. ER positivity was less common in women (n = 805, 81%; $P < .001$). There were no triple negative male cases. Men presented with more advanced clinical stages ($P < .001$).

Treatment Characteristics in Men

Table 2 shows the treatments received by all male patients. Initially, 146 (92%) men were treated with curative intent. However, 24 of these 146 patients (16%) subsequently developed metastatic