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CLINICAL VIGNETTE

Contemporary Issues in Hormone Receptor-Positive Male Breast Cancer Management

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Case Presentation

A 65-year-old male with past medical history significant for hypertension presented to his primary care physician with a palpable painless 2 cm mass in the left breast. Subsequent mammography and ultrasound revealed a solid lesion with atypical calcifications. Biopsy revealed an invasive ductal carcinoma that was estrogen receptor positive and progesterone receptor positive (ER+/PR+) and HER2 was not overexpressed. The Ki67 was elevated at 25%. He underwent a partial breast resection with a sentinel lymph node biopsy. The final pathology revealed a stage I breast cancer- 1.8 cm mass and 0/2 sentinel lymph nodes involved (pT1N0). Genetic work up for a germline mutation was unremarkable. An OncotypeDx assay revealed a low-recurrence risk score of 13 which is associated with a distant recurrent risk of 8% in 10 years when treated with tamoxifen. After a course of external beam radiation therapy the patient was started on adjuvant endocrine-based therapy.

Discussion

Less than 1% of all breast cancers occur in men and has been considered an “orphan disease”. For men, the lifetime risk of breast cancer is about 1 in 1,000, despite a small increase in the incidence over the last decade. Current literature suggests that germline mutations, including BRCA mutations, are rare but well-established risk factors accounting for up to 14% of male breast cancers. Other possible conditions that may increase the risk include conditions with abnormal estrogen-to-androgen ratios. The excessive estrogen exposure may be due to marijuana use, hormone ingestion, hepatic dysfunction and Klinefelter syndrome. However, the majority of male breast cancers are not associated with a causative factor.¹

There is a paucity of data guiding the medical management of male breast cancer. The rarity of the disease has precluded prospective randomized clinical trials. The majority of data have been collected from retrospective studies spanning several decades, and treatment recommendations are extrapolated from results of trials in female patients.²

In the realm of adjuvant therapy for breast cancer, the trend has been to utilize molecular profiles to direct care. Gene expression profile testing is gaining momentum and multianalyte assays with algorithmic analysis (MAAAs) are now commonplace.^{3,4} OncotypeDx 21-gene recurrence score assay is a commercially available (MAA) that predicts the likelihood of disease recurrence and identifies patients who are most and

least likely to derive benefit from adjuvant chemotherapy. Its use has been validated in male breast cancer as prospective data in male breast cancer is available.⁵

Retrospective trials have documented improvement in overall survival for men with hormone receptor-positive disease treated with adjuvant tamoxifen. In several trials the use of adjuvant tamoxifen has been associated with an improved survival. The hazard ratios from these small trials span 0.4-0.50.⁶

Data to support the use of aromatase inhibitors (AI) monotherapy in the adjuvant setting for male breast malignancy is lacking. The most robust data comes from a German retrospective analysis consisting of 257 men that were treated with an AI or tamoxifen. After adjusting for patient's age, tumor size, node status, and tumor grading, the AI treatment was linked to a 1.5-fold increase in risk of mortality compared to tamoxifen (HR 1.55; 95 % CI: 1.13-2.13; p = 0.007). The study concluded that tamoxifen remains the standard of care.⁷

In pre-menopausal woman, the addition of a Gonadotropin Receptor Hormone (GnRH) agonist to an AI has been shown to be superior to tamoxifen in preventing disease recurrence.⁸ Some have extrapolated this data and applied it to male breast cancer. The Male-GBG54 trial is a phase II, prospective randomized study evaluating tamoxifen with or without GnRH versus an AI with GnRH in male breast cancer patients. In preliminary results, AI plus GnRH therapy was associated with a 64 percent suppression in estradiol levels versus 35 percent with an aromatase inhibitor.⁹ It is yet to be determined if the detected hormone level changes will translate to a clinical benefit.

In summary, the management of male breast cancers continue to evolve. Molecular characterization of malignancies should provide a solid foundation for clinical trials.

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