Hormone Therapy for Breast Cancer in Men

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Abstract

Breast cancer in men is rare, but its incidence is increasing, in keeping with the aging population. The majority of breast cancers in men are estrogen receptor positive. There is a paucity of clinical trials to inform practice, and much has been extrapolated from breast cancer in women. Hormone therapy represents the mainstay of adjuvant and palliative therapy but may have contraindications or poor tolerability. We review the evidence for choice of hormone therapy in both the adjuvant and palliative setting in breast cancer in men.

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Introduction

Breast cancer in men (MBC) is rare, with a reported frequency of less than 1% in the population overall, but with an increase in incidence in the seventh decade of life.[1] As with all solid tumors, the incidence of MBC is increasing, in keeping with the aging population. Historically, the disease often presented at a later stage than breast cancer in women; delays in diagnosis were thought to be due to lack of awareness.[2,3] However, the majority of cancers in men are now stage I or II at presentation (37% and 21%, respectively), with 33% at stage III and only 9% at stage IV.[4-8]

Factors associated with the development of MBC include the following: genetic (*BRCA2*,[9-11] *BRCA1*,[12] Klinefelter syndrome,[13,14] Cowden syndrome,[15] *p53* mutation[16]), lifestyle[17] (obesity,[18] alcohol excess,[19,20] estrogen intake, hormone manipulation[21]), work[22] (high ambient temperatures, exhaust emissions[23]) and other diseases (pituitary adenoma,[24,25] testicular damage,[26] orchiditis,[20,27] liver diseases causing hyperestrogenism,[28] radiation exposure to the chest[29]). A link with gynecomastia has also been established in the Male Breast Cancer Pooling Project; a consortium of 11 case–control and 10 cohort investigations involving 2405 case patients reported statistically significant correlation (odds ratio, 9.78; 95% confidence interval [CI], 7.52-12.7).[30] There have also been reports of MBC in patients treated with hormone manipulation for prostate cancer and in transsexual patients (Table 1).[21]

Up to 90% of MBC are estrogen receptor positive. Hormone therapy therefore plays a major role in both the adjuvant and palliative settings. Because of the rarity of MBC, there is a paucity of clinical trials to inform practice. The main principles of management have thus been extrapolated from the wealth of literature available about breast cancer in women. It has been reported that breast cancers in both sexes are biologically similar.[31] Given the increasing incidence of MBC, we aimed to collate and review the published data on the use of hormone therapy in MBC.

Biology

Because the majority of MBC are estrogen receptor positive,[32] hormone therapy is the mainstay of both adjuvant and palliative management.[32] Ductal carcinoma is the most common subtype,[33,34] with lobular carcinoma reported less frequently.[35] Less common subtypes, including inflammatory, medullary, papillary, and trabecular duct, have also been reported.[36]

Luminal A subtype has been reported to be the most common subtype in MBC (83%), followed by luminal B subtype (17%). Fifteen percent of MBC are human epidermal growth factor receptor 2 (HER2) positive, similar to breast cancer in women (15% to 20%).[37] The incidence of basal-type disease has not yet been reported. The cumulative risk of breast cancer in male *BRCA2* carriers is estimated to be 6.3% (95% CI, 1.4-25.6) by 70 years.

Endocrine Therapy

In a similar manner to postmenopausal women, a significant proportion of male estrogen is generated by the conversion of circulating androgens via the aromatase enzyme. Estradiol (E2) levels are significantly higher in older men than in postmenopausal women,[38] and an age-associated increase in aromatase activity is well documented in men.[39] Approximately 20% of circulating estrogen in men is directly secreted by the testicles,[40] while the rest is from peripheral conversion, thus providing a direct source of oncogenic stimuli.

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Table 1 Risk Factors for Breast Cancer in Men

Genetic
• *BRCA1* and *BRAC2* mutations.
• Klinefelter syndrome.
• Cowden disease.
• *P53* and *PTEN* mutations.
Lifestyle
• Obesity.
• Alcohol.
• Estrogen intake.
• Hormone manipulation.
Work
• High ambient temperature.
• Exhaust emissions.
Disease
• Pituitary adenoma.
• Testicular damage.
• Liver cirrhosis.
• Radiation exposure to chest.

The estrogen receptor belongs to a family of hormone-activated transcription factors that can initiate or enhance the transcription of genes containing specific hormone response elements. The estrogen (ER) protein consists of 595 amino acids with a molecular weight of 66 kDa,[41] on chromosome 6q sub band 25.1.[42] In late 1970s, the triphenylethylene compound, now known as tamoxifen, became an established option for the treatment of breast cancer of all stages.[43,44] Tamoxifen is an antiestrogen in the breast but has estrogen-like properties in other target tissues, such as bone and endometrium. Tamoxifen is a prodrug that is metabolized in the liver into its active metabolites, 4-hydroxytamoxifen (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifen).[45] Tamoxifen acts as a selective estrogen receptor modulator, with its active metabolite, hydroxy tamoxifen, binding to estrogen receptors competitively in tissues producing a nuclear complex that reduces DNA formation and inhibits estrogen effects. It causes cells to remain in G0 and G1 phases of cell cycle. Tamoxifen has also been used in infertility,[46] gynecomastia, and bipolar disorder.[47] It has also been reported to have antiangiogenic properties.[48]

Aromatase inhibitors (AI) suppress the main source of estrogen in men by inhibiting the aromatase enzyme; they do not affect testicular production of estrogen. AI create a feedback loop with significant decrease in E2 levels, coupled with increasing levels of follicle-stimulating hormone, luteinizing hormone, and testosterone, which provide increased substrate for aromatization. Gonadotrophin-releasing hormone (GNRH) analogues are thought to be able to overcome the increase in substrate issue and therefore increase the biologic efficacy of AI.

Methods

A literature search of PubMed, Embase, Cochrane Library, Web of Science, and Google Scholar databases was performed using the terms "male" and "breast cancer." Trials or case reports were included if they were published in English and included details of hormone therapy administered to male patients diagnosed with breast cancer in either the adjuvant or palliative setting.

Adjuvant Hormone Treatment

Surgical Hormone Ablative Techniques. The first reported hormone manipulation in MBC was orchidectomy in 1942.[49] Adrenalectomy and pituitary surgery have been cited as providing response rates of 45%, but these invasive techniques are seldom used compared to medical options. The adrenal gland secretes less than 1% of circulating sex steroids, and these precursors undergo peripheral conversion, which results in less than 5% of all testosterone, 80% of all dihydrotestosterone and E2, and estrone (98%).[50] The levels of E2 have been found to be 3 to 4 times higher in older men compared to postmenopausal women.[51]

Antiandrogens, Steroids, Estrogens, and Progestins. Medical hormone treatment options include antiandrogens, steroids, estrogens, progestins, AI, and tamoxifen. These options are generally more preferable to men than orchidectomy.[52] Table 2 summarizes the published literature.

Adjuvant Tamoxifen. Adjuvant tamoxifen is commonly used in MBC because of its efficacy in both the adjuvant and palliative

Table 2 Published Literature Regarding Adjuvant Hormone Therapy in Breast Cancer in Men

Study	Year	First Author	No. of Study Subjects	Hormone Therapy	Reported Toxicity	Outcome
53	1992	Ribeiro	39	Tamoxifen, stage II and III	—	Actuarial survival 61%; DFS 56%
36	1999	Goss	229	Tamoxifen, diethylstilbestrol, or medroxyprogesterone; ablative hormone therapy; orchiectomy	—	5-year DFS 47%; 5-year OS 53%; 5-year LC 91%
54	2005	Giordano	38	Tamoxifen 92%, other 8%	—	Hazard ratio 0.45; $P = .01$
55	2013	Eggemann	257	Tamoxifen 207 (80.5%), AI 50 (19.5%)	—	OS 60%; median 114 months' OS (32%)
56	2014	Bradley	125	Tamoxifen 109 (compliance at 1 year = 89%, at 3.5 years = 70%); AI (11 anastrozole, 4 letrozole, 2 exemestane); no patient received GNRH in conjunction	12% discontinued tamoxifen due to toxicity; 19% discontinued AI due to toxicity (arthropathy, skin peeling, headaches, dizziness)	5-year OS 72%; 5-year BCSS 86%; 5-year PFS 62%

Abbreviations: AI = aromatase inhibitor; BCSS = breast cancer–specific survival; CR = complete response; DFS = disease-free survival; GNRH = gonadotrophin-releasing hormone; LC = local control; MS = median survival; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.