Received: 26 February 2020 | Revised: 16 May 2020 | Accepted: 2 June 2020

DOI: 10.1111/cen.14263

LETTER TO THE EDITOR

WILEY

Testosterone therapy considerations in oestrogen, progesterone and androgen receptor–positive breast cancer in a transgender man

1 | INTRODUCTION

A 44-year-old premenopausal individual assigned female at birth but with a male gender identity presented requesting masculinizing hormone therapy for long-standing gender dysphoria. His past medical history was unremarkable, and being adopted, his family history was unknown. Baseline blood tests and hormonal panel were within female reference ranges (Table 1).

He was commenced on intramuscular testosterone undecanoate 1000 mg 12 weekly in August 2018. Four months after commencement, he sought chest reconstructive surgery (bilateral mastectomy) due to significant dysphoria towards his breasts. A 3-cm breast lump in the lower outer quadrant of the left breast was detected on examination, and subsequent mammography, ultrasound and core biopsy demonstrated an invasive ductal breast carcinoma. Histology from a left mastectomy and axillary node clearance revealed a 25 mm grade 2 invasive ductal carcinoma that was oestrogen receptor (ER)–positive (>95%), progesterone receptor–positive (>95%), human epidermal growth factor receptor 2 (Her2)–negative on immunohistochemistry and Ki-67 <10%. Three of 10 axillary lymph nodes had foci of metastatic disease. Staging CT chest, abdomen and pelvis and bone scans did not show distant metastases.

Given his treatment with exogenous testosterone, subsequent androgen receptor (AR) staining was performed on the tumour, which was strongly positive in >95% of tumour cells. Serum total testosterone concentrations were within the male reference range (Table 1). Testosterone therapy was ceased in December 2018 due to theoretical risk of agonistic activity on the AR or the ER via aromatization.

Completion right mastectomy (for gender dysphoria) was followed by adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) and radiotherapy which was poorly tolerated due to frequent misgendering in a traditional female breast cancer treatment environment at his multiple hospital visits. Depression and anxiety which initially increased following cessation of testosterone therapy worsened to the point of suicidal ideation. He persistently expressed a strong desire to restart testosterone therapy and accepted the theoretical risk of tumour progression. An informed decision was made to recommence low-dose transdermal testosterone gel at 25 mg daily in March 2019.

Given that his tumour was ER-positive, considerations were made regarding oestradiol deprivation therapy, which was complicated by concurrent testosterone therapy. He elected to have a total abdominal hysterectomy and bilateral salpingo-oophorectomy, and aromatase inhibitor (AI) therapy with anastrazole. Due to arthralgias, myalgias, low mood, insomnia due to hot flushes and flashbacks about his time during chemotherapy, he ceased anastrazole after 3 weeks. Symptoms resolved. Aware of the lower long-term survival data, he elected not to trial tamoxifen or alternative AI therapy. The patient declined genetic testing.

2 | BREAST CANCER IN TRANSGENDER MALES

There have been fewer than 20 cases published of breast cancer occurring in transgender men (female-to-male) on testosterone therapy, and the majority are ER-positive.[1] AR is not routinely reported in breast cancer due to uncertain clinical implications. Retrospective cohort studies have suggested that the incidence in transgender men overall is similar to that of the expected population incidence, if not lower than the general female population. However, breast cancer appears to be diagnosed earlier in transgender men (median of 44.5 years) compared with the cisgender female median age of diagnosis of 62 years. Diagnoses occurred after a relatively short duration of testosterone therapy 5-10 years which may potentially suggest that affected individuals may have a genetic predisposition to breast cancer.[2]

3 | ROLE OF ANDROGENS IN BREAST CANCER RECURRENCE

This case sparked much debate regarding the implications of testosterone therapy on breast cancer development and recurrence risk. The 4-month time course between initiation of testosterone therapy and breast cancer diagnosis was considered too short to implicate testosterone in carcinogenesis. The association between higher oestradiol levels and ER-positive breast cancer development is well established, but the role of androgens is less clear. Proposed

TABLE 1 Hormonal assay results pre- and postcommencement of gender-affirming testosterone therapy

	Baseline (midcycle) August 2018	4 mo after commencing testosterone undecanoate December 2018	Postoophorectomy on testosterone undecanoate and anastrazole July 2019	Reference range (adult premenopausal female)	Reference range (adult male)
Total testosterone (nmol/L)	1.3	12.5	15.6	0.3-1.9	10.0-31.0
FSH (IU/L)	37			1-20	1-10
LH (IU/L)	82			1-100	1-10
Oestradiol (pmol/L)	820	587	<70	70-1300	50-150

mechanisms of excess androgen-related breast cancer development include the aromatization of testosterone to oestradiol, or direct activation of ARs leading to cellular proliferation.[3] Whilst administered testosterone is partially aromatized to oestradiol, serum oestradiol levels in general do not increase substantially in testosterone-treated transgender males.

Higher plasma androgen levels per se have been associated with breast cancer risk in postmenopausal women.[4] However, there are limited data on premenopausal women and transgender individuals. In fact historically, testosterone therapy has been used as a breast cancer treatment with a response rate of about 25% and up to 50% in endocrine-resistant ER+ breast cancer.[4]

4 | AR + ER+ BREAST CANCER

The AR is expressed in normal mammary tissue and >70% of breast cancers. Its expression varies with breast cancer subtype, with the highest frequency of expression in ER+ breast tumours.[5] AR seems to be, in general, a positive prognostic factor. Its predictive role for treatment benefit is unclear. The effect of AR targeting is likely to be different across breast cancer subtypes, and particularly important is its interaction with ER signaling.[5]

5 | ENDOCRINE THERAPY FOR BREAST CANCER IN TRANSGENDER MALES

Oestradiol deprivation in the setting of ER-positive breast cancer has survival benefits; however, the effects of testosterone therapy on AR-positive breast cancer are unclear. Standard treatment for women after bilateral oophorectomy is either tamoxifen or AI; however, its efficacy in the setting of exogenous testosterone therapy is unknown.

6 | SUMMARY

Well-informed of potential risks on cancer progression, our patient continues on testosterone therapy without AI or tamoxifen. As of May 2020, the patient is cancer-free and has stable emotional functioning. Whilst there is a lack of long-term data, preliminary reports suggest that testosterone therapy does not appear to adversely affect AR-positive breast cancer recurrence risk regardless of sex. Questions remain regarding the significance of AR expression and the optimal endocrine therapy in the presence of exogenous testosterone. Our case highlights the need to balance treatment choices with quality of life. Until further data are available, individualized treatment decisions need to be made to balance potential harms to not only cancer but also on an individual's well-being.

KEYWORDS
breast cancer, testosterone, transgender

ACKNOWLEDGEMENTS
The patient has given his consent for publication of this case report.

CONFLICT OF INTEREST
We declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analysed in this study.

Melanie Light[1]
Thomas McFarlane[2]
Andrew Ives[3]
Bhaumik Shah[4]
Elgene Lim[5,6]
Mathis Grossmann[1,2]
Jeffrey D. Zajac[1,2]
Ada S. Cheung[1,2]

[1]*Endocrinology Department, Austin Health, Heidelberg, Vic., Australia*
[2]*Department of Medicine (Austin Health), The University of Melbourne, Heidelberg, Vic., Australia*
[3]*Masada Private Hospital, St Kilda East, Vic., Australia*
[4]*Aurora Specialists Care, Fitzroy, Vic., Australia*

[5]Garvan Institute of Medical Research, Darlinghurst, NSW, Australia
[6]St Vincent's Clinical School, University of New South Wales, Darlinghurst, NSW, Australia

Correspondence
Ada S. Cheung, Endocrinology Department, Austin Health, Heidelberg, Vic., Australia.
Email: adac@unimelb.edu.au

ORCID

Thomas McFarlane https://orcid.org/0000-0002-1213-6410
Mathis Grossmann https://orcid.org/0000-0001-8261-3457
Ada S. Cheung https://orcid.org/0000-0001-5257-5525

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