ESMO Open
Cancer Horizons

Male breast cancer: finding the way in this uncommon path

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To cite: Maurer C, Martel S, Azambuja Ede. Male breast cancer: finding the way in this uncommon path. *ESMO Open* 2017;**0**:e000169. doi:10.1136/esmoopen-2017-000169

Received 26 January 2017
Accepted 26 January 2017

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Male breast cancer (BC) is a rare disease and accounts for less than 1% of all BCs. Knowledge of this disease is limited and mainly derives from small single-institution retrospective studies with contradictory results. The management of male patients with BC is generalised from the management of BC in women.

However, evidence is growing that the biology of male BC differs at least partly from female patients with BC. An analysis of the Surveillance, Epidemiology, and End Results (SEER) registry containing a total of 5494 men and 8 35 000 women diagnosed with BC between 1973 and 2005 showed that advanced stage-related tumour characteristics (eg, tumour size >2 cm and positive axillary lymph nodes) were more common in men compared with women. In contrast, negative biology-related prognostic factors like hormone receptor (HR) negativity and high tumour grade were more often found among women. While 23% of the female breast tumours were oestrogen receptor negative, this was only the case for 7.6% of the male tumours.[1] Inconsistencies have also been reported regarding the HER2 status of male BC. A combined analysis of nearly 60 studies on male BC in 2010 reported a higher rate of HER2 positivity in men compared with women with BC (34% and 25%, respectively),[2] which is in contrast to the SEER data and other recent studies.[3 4] However, the combination of data from different studies with different methodologies and cut-offs for HER2 positivity must be interpreted with caution.

In this edition, Xing-Fei Yu *et al* report the results of a retrospective study of 134 cases of male BC treated at Zhejiang Hospital in China between 1990 and 2008. Based on the latest 2013 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for ER/progesterone receptor (PR) and HER2 testing, their results were consistent with the SEER data and other recent studies showing that most male tumours are ER+ and that HER2 positivity seems to be less common in men than in women with BC. The authors also evaluated the effect of adjuvant chemotherapy in male BC. The majority of patients (58.21%) received adjuvant chemotherapy. Even if the disease-free survival and overall survival rates were the same for patients with and without adjuvant chemotherapy, the authors suggest that chemotherapy might have a positive impact on OS as patients undergoing chemotherapy had a more advanced disease and displayed more aggressive biology-related characteristics like HR negativity and HER2 positivity. This article opens the door for a current and important discussion in BC: Is male BC similar to female BC and if so, can the current available treatments used to treat women with BC be safely extrapolated to men with BC?

Trying to address these questions, an international consortium, coordinated by the European Organisation for Research and Treatment of Cancer and Translational Breast Cancer Research Consortium under the Breast International Group and the North American Breast Cancer Group network, was created to better characterise and manage male BC. First results of part 1, a retrospective analysis of clinical data including a central pathology review of tumour specimens in order to overcome difficulties seen in individual studies with different methodologies, were presented at the San Antonio Breast Cancer Symposium in 2014 and highlighted important differences between male and female BC. Among 1473 male patients with BC, more than half of the cases were ER positive, PR positive, androgen receptor positive and were classified as luminal A-like subtype (58%). Interestingly, only 5% was HER2 positive and 1% was triple negative, which is far less common than the reported rates in female BC.[5] Furthermore, the association between different histological features and outcomes seems to differ between men and women: unlike in female BC where the histological grade is associated with poorer survival, this association was not found in a retrospective analysis in male BC.[6]

In terms of genetic landscape, little is known about male BC. A recent study reported that, despite similarities between male and female BC, male BC less frequently harboured *PIK3CA* and *TP53* mutations and losses of 16q, suggesting that at least a subset might be driven by a different repertoire of somatic aberrations.[4]

Taking into consideration the growing evidence of important biological differences between female and male patients with BC, it is not clear if treatment recommendations for female BC can simply be extrapolated to men. Besides chemotherapy, the optimal management of endocrine treatment in the adjuvant and in the metastatic settings for male patients with BC remains an open question, particularly the role of aromatase inhibitors (AIs) needs to be defined. There is concern that monotherapy with AIs is less effective because of an increase in follicular stimulating hormone and testosterone that could lead to an increase in the AIs' substrate via a feedback loop.[7 8] According to the Third ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer, treatment with an AI for metastatic BC in men should be combined with an LHRH agonist.[9] The role of fulvestrant in male BC is not clear either, despite its well-established role in female BC. A retrospective pooled analysis from five articles of 23 male patients with advanced BC showed that fulvestrant could be of potential therapeutic value. In that study, the clinical benefit rate was 73.9%.[10] Unfortunately, in many countries, AIs, LHRH agonists and fulvestrant are not reimbursed for the treatment of male BC. Consequently, drugs with a clear benefit for the treatment of (female) BC are denied to men. Once more, this situation illustrates the discrimination against a minority—in this case male patients with BC—in different healthcare systems. To address the issue of adequate treatments, the inclusion of male patients with BC should be allowed in clinical trials testing new drugs in BC or, ideally, all efforts should be done to run clinical trials for male patients with BC only.

In 2014, the second part of the International Program of Breast Cancer in Men, a prospective registry for male patients with BC, was activated and whenever possible, all male patients with BC should be given the opportunity to participate in such programme. To move research forward and ultimately to improve treatment and outcome of male patients with BC, a fully committed global effort is required. The collaboration among researchers should be envisaged, and joint efforts to better understand this uncommon and important disease are crucial. The first important steps are already done, and there is still a long way to go to really address the need of male patients with BC.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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