Letter to the Editor

rare tumors

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TP 53 status and estrogen receptor-beta in triple negative breast cancer management in Africa: Time to rethink regime management of triple negative breast cancer and save more lives in Nigeria

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Although Estrogen receptor alpha (ESR1) is now routinely used in typing breast cancers in most of Eastern Nigeria, where it is used as a major prognostic and predictive factor in treatment outcome.[1,2] ESR1 negative breast cancer remains a significant subtype contributing to (38.4%) and usually the predominant triple negative breast cancers.[1,2] For these patients no further treatment is given after surgery and neoadjuvant chemotherapy and radiotherapy. A comparative study done by Wright et al.[3] shows that comparatively by 50 weeks after diagnosis and management survival probability of triple negative breast cancers in Nigeria; fall from 1 to 0.3, while in UK survival probability only falls from 1.0 to 0.6 (twice as good). By 100 weeks it has flattened to 0.1 in Nigeria and in UK 0.353. Although the differences can be explained in part by our late presentations, poorer health care systems and lack of good health insurance. We note that Adding Transcription factor 53 status as well as the estrogen receptor beta status evaluation only for triple negative breast cancers will make a significant difference in survival. Estrogen receptor beta (ESB2) shares structural homology at DNA and ligand binding domains (98% and 56%, respectively) with (ESR1) the major type of estrogen receptor in breast cancer.[4,5] ESR2 functions and expression patterns are different from ESR1 and is widely expressed in both basal and luminal epithelial cells.[6–8] The precise role of ESR2 in breast cancer is unclear, with both antiproliferative and proliferative roles described.[9,10] The mechanisms for these opposing actions of ESR2 in breast tumorigenesis have not been fully elucidated.[11] Mukhopadhyay et al.[12] provides an explanation for the dual nature of ESR2 function in triple-negative breast cancer (TNBC) related to its interactions with TP53 status (wildtype or mutant). In wild-type TP53-expressing cells, silencing of ESR2 augmented apoptosis, whereas its over expression resulted in increased proliferation. Opposite effects were observed following silencing or overexpression of ESR2 in mutant TP53 cells, suggesting the important role of TP53 status in determining ESR2's function. Mechanistically, ESR2-mutant TP53 interaction mediates sequestration of mutant TP53, leading to the TP73 activation and antiproliferative effects. Treatment with tamoxifen (4-hydroxy tamoxifen) also increases ESR2 expression and reactivates TP73 in mutant TP53 cells, providing an

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explanation for its beneficiary effects. Analysis of the Molecular Taxonomy of Breast Cancer International Consortium TNBC subgroup of basal-like tumors ($n=259$), based on ESR2 levels and TP53 mutation status, confirmed the impact of these interactions on survival, that is, mutant TP53-expressing tumors with high ESR2 levels have better survival.[11] Mukhopadhyay et al.[12] suggest that the company of ESR2 with mutant TP53 can prognosticate TNBC patients and more importantly help select a population for tamoxifen therapy. The beneficial effects of endocrine therapy in unselected ESR1-negative breast cancer and TNBC cohorts have been previously described.[12–14]

whereas it is not standard-of care for TNBC for tamoxifen to be included in management. However, there have been isolated reports on beneficial effects of tamoxifen therapy in certain cohorts of ESR1-negative BC. It has been reported that high levels of ESR2 in ESR1-negative BC[14] and TNBC[13] patient tumors were associated with good clinical outcome in response to tamoxifen therapy. In another study, expression of ESR2 along with its coregulator was found to be predictive for benefit from tamoxifen therapy.[15]

Chemotherapeutic agents for TNBC shows Pathological complete response rates of more than 80% have been observed with four cycles of single agent cisplatin. In fact, two of the patients achieved pathological complete responses with only two cycles of cisplatin BRCA 1 positive cases.[16] Another important development has been identification of poly ADP ribose polymerase (PARP) inhibitors as another group of drugs with significant activity in this group of patients.[17] A study has been reported using a combination of cisplatin and bevacizumab as neoadjuvant therapy. Approximately 37% patients had a complete or near complete pathological response (19/45).[18] Tamoxifen should be given in a sequence if TP 53 is mutated and ER beta is amplified.

The ability to selectively administer endocrine therapy should, in principle, lead to greater response rates. It is unclear what the impact of ESR2-TP53 interactions have in ER-positive breast cancer, particularly because all patients are offered endocrine therapy. In view of the above we suggest a further routine subtyping of all triple negative breast cancers in Nigeria to ascertain their TP 53 status as well as ESR2 receptor status. Those with mutant TP 53 and prominent expression of ESR2 should still have tamoxifen which we believe will prolong their survival and give them a better quality of life.

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