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Inhibition of the phosphoinositide 3-kinase pathway for the treatment of patients with metastatic metaplastic breast cancer.

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Abstract

BACKGROUND: Mesenchymal/metaplastic breast cancers (MpBCs) are often triple-negative (TNBC), and chemo-refractory, and can harbor phosphoinositide 3-kinase (PI3kinase) alterations; thus, therapy with mTor inhibitors may demonstrate activity.

PATIENTS AND METHODS: Patients with mesenchymal/MpBC treated with temsirolimus-based regimens were evaluated. Mutational analyses [polymerase chain reaction (PCR)-based DNA sequencing method, mass spectrometric detection (Sequenom MassARRAY), or next-generation sequencing] as well as loss of phosphatase and tensin homolog (PTEN) (immunohistochemistry) were performed (archived tissue when available).

RESULTS: Twenty-three patients (one of whom was on two separate trials) were treated using temsirolimus-containing regimens: temsirolimus alone (n = 1 patient) or combined with the following: liposomal doxorubicin and bevacizumab (DAT, n = 18); liposomal doxorubicin (DT, n = 1); paclitaxel and bevacizumab (TAT, n = 2); paclitaxel (TT, n = 1); carboplatin and bevacizumab (CAT, n = 1). Response rate [complete response (CR) + partial response (PR)]

was 25% across all regimens; 32% in the anthracycline-based regimens [DAT and DT (CR = 2, PR = 4; N = 19)]. An additional two patients achieved stable disease (SD) ≥6 months [total SD ≥6 months/CR/PR = 8 (33%)]. Molecular aberrations in the PI3K pathway were common: PIK3CA mutation = 6/15 (40%), PTEN mutation = 3/11 (27%), and PTEN loss = 2/11 (18%). A point mutation in the NF2 gene (K159fs*16; NF2 alterations can activate mTor) was found in one patient who attained CR (3+ years). Of the eight patients who achieved SD ≥6 months/CR/PR, all 4 patients with available tissue had a molecular aberration that activate the PIK3CA/Akt/mTOR axis: PIK3CA mutation = 2; PTEN loss = 1; NF2 aberration = 1.

CONCLUSIONS: DAT has activity in MpBCs including complete CRs. Molecular aberrations that can activate the PI3 K/Akt/mTOR axis are common in MpBC.

KEYWORDS: bevacizumab; liposomal doxorubicin; metaplastic breast cancer; temsirolimus

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