specifically stated that taxane-resistant tumors did not show cross-resistance to ixabepilone. This statement is useful for the situation where a first clinical study uses taxane, and a second clinical study uses ixabepilone. Consistently, Buzdar (92) has stated that breast tumors frequently develop resistance to anthracyclines and taxanes by way of overexpression of the MDR1 gene and MRP gene while, in contrast, ixabepitone does not induce these genes.

3. Tamoxifen

Drug resistance can be acquired by genetic mutations. Chemotherapy of breast cancer with tamoxifen is frequently met with drug resistance by tumors (93). Tamoxifen targets estrogen receptor. Estrogen receptor is part of a cell-signaling pathway that promotes growth of the breast cancer tumor (94). Patients having breast cancer tumors that express estrogen receptor are candidates for treatment with this drug (95). A high percentage of ER-positive breast cancers that respond to initial tamoxifen treatment subsequently develop resistance. Sustained tamoxifen resistance continues to be a major problem in managing advanced breast cancer (96). Miller et al. (97) and Fan et al. (98) describe mechanisms by which estrogen receptor acquires resistance to tamoxifen. These include mutations in the tumor's genome that lead to increased activity of the tumor's phosphatidylinositol 3-kinase (PI3K) can lead to resistance against tamoxifen.

4. Imatinib

c-KIT is a kinase that mediates cell signaling in normal and cancer cells. But in some tumor cells, c-KIT acquires a mutation that is responsible for the transformation of a normal host cell to a tumor cell (99). Imatinib, which inhibits c-KIT, is used to treat patients having tumors where c-KIT is responsible for this transformation. But with imatinib, 50% of patients develop resistance due to additional mutations in c-KIT. Therefore, second-line

[92] Buzdar AU. Preoperative chemotherapy treatment of breast cancer – a review. *Cancer*. 2007;110:2394–2407.

[93] Bernard-Marty C, Cardoso F, Piccart MJ. Facts and controversies in systemic treatment of metastatic breast cancer. *Oncologist*. 2004;9:617–632.

[94] Miller TW, Pérez-Torres M, Narasanna A, et al. Loss of phosphatase and Tensin homologue deleted on chromosome 10 engages ErbB3 and insulin-like growth factor-I receptor signaling to promote antiestrogen resistance in breast cancer. *Cancer Res*. 2009;69:4192–4201.

[95] Higgins MJ, Stearns V. Understanding resistance to tamoxifen in hormone receptor-positive breast cancer. *Clin Chem*. 2009;55:1453–1455.

[96] Kumar R, Zhang H, Holm C, Vadlamudi RK, Landberg G, Rayala SK. Extranuclear coactivator signaling confers insensitivity to tamoxifen. *Clin Cancer Res*. 2009;15:4123–4130.

[97] Miller TW, Pérez-Torres M, Narasanna A, et al. Loss of Phosphatase and Tensin homologue deleted on chromosome 10 engages ErbB3 and insulin-like growth factor-I receptor signaling to promote antiestrogen resistance in breast cancer. *Cancer Res*. 2009;69:4192–4201.

[98] Fan P, Yue W, Wang JP, et al. Mechanisms of resistance to structurally diverse antiestrogens differ under premenopausal and postmenopausal conditions: evidence from in vitro breast cancer cell models. *Endocrinology*. 2009;150:2036–2045.

[99] Roberts KG, Smith AM, McDougall F, et al. Essential requirement for PP2A inhibition by the oncogenic receptor c-KIT suggests PP2A reactivation as a strategy to treat c-KIT + cancers. *Cancer Res*. 2010;70:5438–5447.