Journal of Cancer Research and Treatment, 2016, Vol. 4, No. 3, 37-40
Available online at http://pubs.sciepub.com/jcrt/4/3/1

DOI:10.12691/jcrt-4-3-1

Tamoxifen-resistant Breast Cancer: Causes of resistance and Possible Management

Ahmed M. Kabel[1,2,*], Dania Altalhi[3], Hanan Alsharabi[3], Ola Qadi[3], Maram Ad khan[3]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, KSA
[2]Department of Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt
[3]Fifth year student, College of Pharmacy, Taif University, Taif, KSA
*Corresponding author: drakabel@gmail.com

Abstract Tamoxifen has been used for the systemic treatment of patients with breast cancer by block the action of estrogen is also used to lower a woman's chance of developing breast cancer if she has a high risk . Treatment success is primarily dependent on the presence of the estrogen receptor (ER) in the breast carcinoma. While about half of patients with advanced ER-positive disease immediately fail to respond to tamoxifen, in the responding patients the disease ultimately progresses to a resistant phenotype. The possible causes for intrinsic and acquired resistance have been attributed to the pharmacology of tamoxifen, alterations in the structure and function of the ER and the interactions with the tumor environment and genetic alterations in the tumor cells.

Keywords: *tamoxifen; resistance; breast; cancer*

Cite This Article: Ahmed M. Kabel, Dania Altalhi, Hanan Alsharabi, Ola Qadi, and Maram Ad khan, "Tamoxifen-resistant Breast Cancer: Causes of resistance and Possible Management." *Journal of Cancer Research and Treatment*, vol. 4, no. 3 (2016): 37-40. doi: 10.12691/jcrt-4-3-1.

1. Introduction

Estrogen receptor (ER) is expressed in about 75% of human breast cancers which is the one of the leading cause of death for women globally. The estrogen-bound ER functions through ligand-activated transcriptional regulation (genomic actions) and by acting as a component of signaling cascades outside of the nucleus (non-genomic actions) [1,2,3,4]. Clinical observations and laboratory studies suggest ER signaling pathway is the major driver in promoting proliferation, survival and invasion of ER-positive breast cancer cells . Endocrine therapy is the mainstay of treatment for patients with ER-positive breast cancer, especially those with metastatic disease There is evidence that some breast tumors are more resistant to endocrine therapy than others, despite expressing ER. This is supported by stratification of ER positive tumors into luminal A and luminal B subtypes based on molecular profiling studies over the last decade. The luminal B subtype is more aggressive and less endocrine sensitive, while the luminal A subtype is more indolent and endocrine responsive [5,6,7].

Tamoxifen, a nonsteroidal SERM, is the standard endocrine treatment for hormone receptor-positive breast cancer [8]. The widespread use of tamoxifen over the last 20 years is probably one of the major reasons for the observed decrease in breast cancer mortality in the past decade. AI (estrogen depletion) have recently been proven superior to tamoxifen [9]. If so, tamoxifen will remain a useful therapeutic option in advanced disease.

However, although tamoxifen is initially effective in many patients, and in general is very well tolerated, a major obstacle to its use is tumor resistance. Almost 50% of breast cancers, despite the presence of ER, fail to respond to tamoxifen; furthermore, even patients who initially respond eventually acquire tamoxifen resistance, leading to tumor progression and death. In general, acquired resistance to tamoxifen is not attributable to loss of or alteration in the ER, and resistant tumors often respond to second-line endocrine therapy [10,11] .

2. Types of Tamoxifen Resistant Breast Cancers

A) De novo (At the beginning of treatment), is characterized by loss of ER (the ERα isoform) expression and ER gene mutations such as deletion and point mutation. Patients carrying inactive alleles of cytochrome P4502D6 (CYP2D6) deficiency cannot convert tamoxifen to its active metabolite, endoxifen, therefore are resistant to tamoxifen [12].

B) Acquired during treatment, Almost all the metastatic cases developed resistance to endocrine therapy.

3. Causes of Resistance of Breast Cancers to Tamoxifen

Several mechanisms of resistance of breast cancer to endocrine therapy have been hypothesized and a include loss of ERs, alterations in cell cycle and cell survival signaling molecules, activation of escape pathways, altered expression of microRNAs, tamoxifen metabolism, and epigenetic mechanism regulation ER expression [7].

3.1. Loss or Modification in the ER Expression

ER expression is the main predictor of response to endocrine therapy, and lack of expression of ER is the principal mechanism of de novo resistance to hormonal therapy. Several mechanisms have been proposed to explain the absence of ER expression. These mechanisms involve epigenetic changes such as aberrant methylation CpG islands of the ER promoter and histone deacetylation, resulting in a compact nucleosome structure that limits transcription [13,14,15,16]. Other mechanisms proposed in the loss of ER expression are hypoxia, overexpression of EGFR (epidermal growth factor receptor) or HER2 (Human epidermal growth factor receptor, MAPKs (mitogen activated kinase pathway) hyperactivation [17]. Moreover, ER can also be present outside the nucleus, engaging with cytoplasmic and membrane signaling complexes, activate and regulate various growth factor receptors and other cellular signaling pathways. Hyperactivation of these signaling pathways increases the non-nuclear ER localization and its nongenomic activity, thus creating a positive feedback of cross-activation between the ER and growth factor receptor pathways. This non-nuclear ER activity can be activated by both estrogen and tamoxifen leading to resistance [18].

3.2. Regulation of Signal Transduction Pathway

Crosstalk between ER and different signaling pathways, such as growth factor receptor, cell survival (PI3K/AKT), stress and/or cytokine signaling pathway, have been implicated in acquired and intrinsic resistance to endocrine agents (Figure 1).

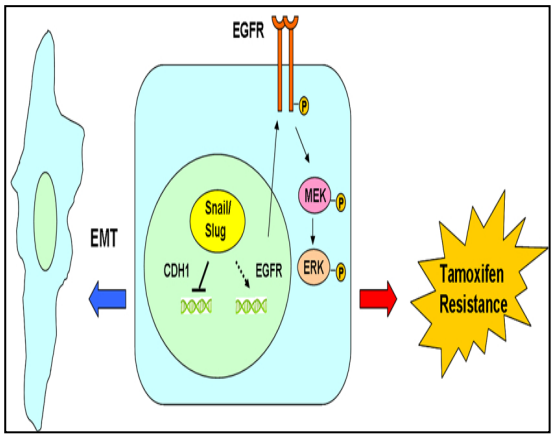

Figure 1. Signaling pathways and tamoxifen resistance

3.2.1. Growth Factor Receptor Signaling Pathways

The growth factor receptor signaling pathways can stimulate cancer growth either in concert with ER signaling or bypassing it. Preclinical and clinical evidence suggests that growth factor receptor signaling contributes to endocrine resistance. Reporter gene construct studies in tamoxifen resistant cells indicate that the EGFR/MAPK-promoted ER AF-1 phosphorylation enhances the agonistic behavior of tamoxifen, resulting in the expression of estrogen regulated genes. Indeed, overexpression of the co-activator AIB1 correlates with resistance to tamoxifen in breast cancer patients and in the EGFR/HER2/MAPK-dependent phosphorylation, and it has been proposed to mediate tamoxifen resistance in HER2 overexpressing MCF-7 cells [18].

3.2.2. PI3K Cell Survival Pathways

ER activity is also associated to the PI3K pathway, which is activated by tyrosine kinase receptors in response to growth factors. The PI3K/AKT signaling pathway has been extensively investigated for its role in oncogenic transformation. AKT is one of the downstream targets of PI3K, promotes cellular proliferation and anti-apoptotic responses [19,20].

3.2.3. Stress-Activated Protein Kinase/c-junNH2 Terminal Kinase Pathway

Stress-activated protein kinase/c-junNH2 terminal kinase pathway may interact with ER either by binding with the AP-1 transcription complex or by direct p38 MAPK activation. AP-1 is a complex of proteins composed of Jun and Fos family members of nuclear phosphoproteins, which dimerize and bind to DNA consensus sequences TGAC/GTCA (AP-1 sites) and modulates expression of the target genes [21].

3.3. Co-regulatory Proteins

Tamoxifen acts as an ER antagonist in breast cancer but as an agonist in other tissues such as uterus, cardiovascular system, and bone. These differences in tamoxifen activity could be explained by several mechanisms [22]. One of these mechanisms involves changes in the level of expression of coregulatory proteins (coactivators and corepressors) that can influence regulation of ER transcriptional activity [23,24].

The ER coactivator AIB1 (also known as SRC-3) is considered to be a proto-oncogene, which is overexpressed in more than 30%, and genetically amplified in 5%–10%, of breast tumors [25,26,27,28]. High levels of ER coactivators may enhance the estrogen-agonist activity of tamoxifen and contribute to tamoxifen resistance [23,29,30], Both preclinical and clinical evidence suggested that HER2 over-expression confers resistance to anti-estrogen agents in ER positive tumors [31]. Activation of the Her2 pathway, even without HER overexpression, confers tamoxifen resistance in ER positive cancer cells [32].

3.4. Altered Expression of microRNAs

MicroRNAs (miRNAs) are a class of small non-coding RNAs which have the ability to post-transcriptionally regulate gene expression. Although the role of a few miRNAs has been described in tamoxifen resistance, little is known about how concerted actions of miRNAs targeting biological networks contribute to its resistance. Researchers identified that miR-155 is frequently up-regulated in breast cancer with tamoxifen resistance , whereas inhibition of miR-155 causes cells to apoptosis and enhances TAM sensitivity [33].

3.5. Tamoxifen Metabolism and Genetically Based Resistance

Tamoxifen is metabolized in the liver mainly by two P450 cytochromes: CYP3A4 and CYP2D6, which produce N-desmethyltamoxifen and 4-hydroxytamoxifen, respectively.

Afterwards, further oxidation of these metabolites results in the formation of a very active metabolite: 4-hydroxy-N-desmethyltamoxifen, also known as endoxifen, which production is mostly catalyzed by CYP2D6 [34,35]. Endoxifen and 4-hydroxytamoxifen have greater binding affinities for ERs and suppress cell proliferation more effectively than tamoxifen itself. Indeed, polymorphism in the gene coding for CYP2D6 significantly affects enzymatic activity, providing a potential mechanism for drug resistance. More than 75 CYP2D6 alleles have now been described and classified depending on their effects on CYP2D6 enzyme activity [36]. In this manner, extensive, intermediate or poor metabolizer alleles have been defined depending on how effectively tamoxifen is metabolized, which finally results in differential therapeutic responses to standard doses of the drug [36,37]. Therefore, CYP2D6 genotyping is advised in order to guide the correct selection and dosing of tamoxifen in a tailored manner. While tamoxifen is mainly metabolized in the liver, tumor cells may also contribute to this process by expressing functional P450 species. Indeed, the impaired ability of a tumor to efficiently bioactivate tamoxifen is another mechanism to explain resistance to therapy.

3.6. Epigenetics Mechanisms Regulating ER Expression

Several epigenetic mechanisms that regulate the expression of many genes also regulate ER expression. Nowadays, epigenetic studies could provide new biomarkers to predict and diagnose acquired resistance in response to treatment [38].

4. Mangement of Tamoxifen-resistant Breast Cancer

The resistance can be reversed by mTOR inhibitors, HER 2 blockade, EGFR inhibitors, PI3K inhibitors, Hystone or deactylase inhibitors, Src inhibitors and IGF-1R inhibitors and genetic map to know if the patient will be resistant or not [18].

4.1. mTOR Inhibitors

Mammalian target of repamycin (mTOR) is signal transduction Kinase in the PI3K pathway that exist in tow multiprotien complex , (mTOR 1 and 2), mTOR 1 consist of MTOR that is association with raptor (regulatory protein of mTOR) and is downstream of AKT , while mTOR 2 is associated with rictor (repamycin –insensitive companion pf mTOR) and phosphorylate AKT . Everolimus is repamycin analogue that inhibit mTORC1 Kinase [18].

4.2. HER-2 Antagonists

9% of patient express both HER2 and ER positively. Trustuzumab, the monoclonal antibody against HER2 , reduce downstream MAPK/ERK signaling and at least partially reverse tamoxifen resistance [39].

4.3. EGFR Inhibitors

It is transmembrane growth factor receptor tyrosine kinase (TK) commonly expressed in epithelial tumors, the binding of which will activate the MAP and PI3K pathway. Gefitinib is small molecule that reversibly inhibit EGER and inhibit the pathway signaling. Lapatinip is an oral tyrosine kinase inhibitors for both HER2 and EGFR [38].

5. Conclusion

The resistance to tamoxifen involves multiple mechanisms and so, the molecular signature of each tumor should be determined in order to accurately select the therapeutic approach, predict prognosis and response to therapies. The combination of endocrine therapy with other drugs targeting key molecules involved in hormone resistance is the most promising approach to prevent and/or overcome endocrine resistance and benefit these breast cancer patients.

References

[1] Kabel A.M., Elkhoely A.A. Ameliorative potential of fluoxetine/raloxifene combination on experimentally-induced breast cancer. Tissue and Cell 2016; 48(2):89-95.

[2] McDonnell D.P., Norris J.D. Connections and regulation of the human estrogen receptor. Science 2002; 296:1642-1644.

[3] Musgrove E.A., Sutherland R.L. Biological determinants of endocrine resistance in breast cancer. Nat. Rev. Cancer 2009;9:631-643.

[4] Kabel A.M., El Rashidy M.A., Omar M.S. Ameliorative Potential of Tamoxifen/Thymoquinone Combination in Patients with Breast Cancer: A Biochemical and Immunohistochemical Study. Cancer Med. Anticancer Drug. 2016; 1:102.

[5] Perou C.M., Sørlie T., Eisen M.B., van de Rijn M., Jeffrey S.S., Rees C.A., et al. Molecular portraits of human breast tumours. Nature. 2000; 406:747–752.

[6] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012; 490:61-70.

[7] Britton D.J., Hutcheson I.R., Knowlden J.M., Barrow D., Giles M., McClelland R.A., Gee J.M., Nicholson R.I. Bidirectional cross talk between ERalpha and EGFR signalling pathways regulates tamoxifen-resistant growth. Breast Cancer Res Treat. 2006;96:131-146.

[8] Osborne C.K., Fuqua S.A. Mechanisms of tamoxifen resistance. Breast Cancer Res. Treat., 32: 49-55, 1994.

[9] Osborne C.K., Jarman M., McCague R., Coronado E. B., Hilsenbeck S.G., Wakeling A. E. The importance of tamoxifen metabolism in tamoxifen-stimulated breast tumor growth. Cancer Chemother. Pharmacol., 34: 89-95, 1994.

[10] Gottardis M. M., Jordan V. C. Development of tamoxifen-stimulated growth of MCF-7 tumors in athymic mice after long-term antiestrogen administration. Cancer Res. 1988; 48: 5183-5187.

[11] Legault-Poisson S., Jolivet J., Poisson R., Beretta-Piccoli M., Band P. R. Tamoxifen-induced tumor stimulation and withdrawal response. Cancer Treat. Rep. 1979; 63: 1839-1841.

[12] Hoskins J.M., Carey L.A., McLeod H.L. CYP2D6 and tamoxifen: DNA matters in breast cancer. Nat. Rev. Cancer 2009;9:576-586.

[13] Yang X., Phillips D.L., Ferguson A.T., Nelson W.G., Herman J.G., Davidson N.E. Synergistic activation of functional estrogen receptor (ER)-α by DNA methyltransferase and histone deacetylase inhibition in human ER-α-negative breast cancer cells. Cancer Res. 2001;61:7025-7029.

[14] Parl F.F. Multiple mechanisms of estrogen receptor gene repression contribute to ER-negative breast cancer. Pharmacogenomics J. 2003;3:251-253.

[15] Weigel R.J., deConinck E.C. Transcriptional control of estrogen receptor in estrogen receptor-negative breast carcinoma. Cancer Res. 1993;53:3472-3474.

[16] Ottaviano Y.L., Issa J.P., Parl F.F., Smith H.S., Baylin S.B., Davidson N.E. Methylation of the estrogen receptor gene CpG

island marks loss of estrogen receptor expression in human breast cancer cells. Cancer Res. 1994;54:2552-2555.

[17] Creighton C.J., Hilger A.M., Murthy S., Rae J.M., Chinnaiyan A.M., El-Ashry D. Activation of mitogen-activated protein kinase in estrogen receptor α-positive breast cancer cells in vitro induces an in vivo molecular phenotype of estrogen receptor α-negative human breast tumors. Cancer Res. 2006;66:3903-3911.

[18] Osborne C.K., Bardou V., Hopp T.A., Chamness G.C., Hilsenbeck S.G., Fuqua S.A., Wong J., Allred D.C., Clark G.M., Schiff R. Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J. Natl. Cancer Inst. 2003; 95:353-361.

[19] Chang F., Lee J.T., Navolanic P.M., Steelman L.S., Shelton J.G., Blalock W.L., Franklin R.A., McCubrey J.A. Involvement of PI3K/Akt pathway in cell cycle progression, apoptosis, and neoplastic transformation: A target for cancer chemotherapy. Leukemia. 2003;17:590-603.

[20] Datta S.R., Brunet A., Greenberg M.E. Cellular survival: A play in three Akts. Genes Dev. 1999;13:2905-2927.

[21] Angel P., Karin M. The role of Jun, Fos and the AP-1 complex in cell-proliferation and transformation. Biochim. Biophys. Acta. 1991;1072:129-157.

[22] Sommer S., Fuqua S.A. Estrogen receptor and breast cancer. Semin. Cancer Biol. 2001;11:339-352.

[23] Smith C.L., Nawaz Z., O'Malley B.W. Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. Mol. Endocrinol. 1997;11:657-666.

[24] Jordan V.C., O'Malley B.W. Selective estrogen-receptor modulators and antihormonal resistance in breast cancer. J. Clin. Oncol. 2007;25:5815-5824.

[25] Lydon J.P., O'Malley B.W. Minireview: Steroid receptor coactivator-3: A multifarious coregulator in mammary gland metastasis. Endocrinology. 2011;152:19-25.

[26] Azorsa D.O., Tanner M.M., Guan X.Y., Sauter G., Kallioniemi O.P., Trent J.M., Meltzer P.S. AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. Science. 1997;277:965-968.

[27] Murphy L.C., Simon S.L., Parkes A., Leygue E., Dotzlaw H., Snell L., Troup S., Adeyinka A., Watson P.H. Altered expression of estrogen receptor coregulators during human breast tumorigenesis. Cancer Res. 2000;60:6266-6271.

[28] List H.J., Reiter R., Singh B., Wellstein A., Riegel A.T. Expression of the nuclear coactivator AIB1 in normal and malignant breast tissue. Breast Cancer Res. Treat. 2001;68:21-28.

[29] Tzukerman M.T., Esty A., Santiso-Mere D., Danielian P., Parker M.G., Stein R.B., Pike J.W., McDonnell D.P. Human estrogen receptor transactivational capacity is determined by both cellular and promoter context and mediated by two functionally distinct intramolecular regions. Mol. Endocrinol. 1994;8:21-30.

[30] Knowlden J.M., Hutcheson I.R., Barrow D., Gee J.M., Nicholson R.I. Insulin-like growth factor-I receptor signaling in tamoxifen-resistant breast cancer: A supporting role to the epidermal growth factor receptor. Endocrinology. 2005;146:4609-4618.

[31] Arpino G., Wiechmann L., Osborne C.K., Schiff R. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. Endocr Rev. 2008;29:217-233.

[32] Loi S., Sotiriou C., Haibe-Kains B., Lallemand F., Conus N.M., Piccart M.J., Speed T.P., McArthur G.A. Gene expression profiling identifies activated growth factor signaling in poor prognosis (Luminal-B) estrogen receptor positive breast cancer. BMC Med Genomics 2009;2:37.

[33] Iorio M.V., Casalini P., Piovan C., Braccioli L., Tagliabue E. Breast cancer and microRNAs: Therapeutic impact. Breast 2011;20:S63-S70.

[34] Desta Z., Ward B.A., Soukhova N.V., Flockhart D.A. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: Prominent roles for CYP3A and CYP2D6. J. Pharmacol. Exp. Ther. 2004;310:1062-1075.

[35] Kiyotani K., Mushiroda T., Nakamura Y., Zembutsu H. Pharmacogenomics of tamoxifen: roles of drug metabolizing enzymes and transporters. Drug Metab. Pharmacokinet. 2012;27:122-131.

[36] Hoskins J.M., Carey L.A., McLeod H.L. CYP2D6 and tamoxifen: DNA matters in breast cancer. Nat. Rev. Cancer. 2009;9:576-586.

[37] Weinshilboum R. Inheritance and drug response. N. Engl. J. Med. 2003;348:529-537.

[38] Trimarchi M.P., Mouangsavanh M.,HuangT.H. Cancer epigenetics: A perspective on the role of DNA methylation in acquired endocrine resistance. Chin. J. Cancer. 2011;30:749-756.

[39] Raina D., Uchida Y., Kharbanda A., Rajabi H., Panchamoorthy G., Jin C., Kharbanda S., Scaltriti M., Baselga J., Kufe D. Targeting the MUC1-C oncoprotein downregulates HER2 activation and abrogates trastuzumab resistance in breast cancer cells. Oncogene 2014; 33(26): 3422-3431.