Tamoxifen

Subjects: Oncology

Contributor: Günter Emons

Tamoxifen is a selective estrogen receptor modulator (SERM) originally developed as a contraceptive or morning-after pill [1].

Keywords: tamoxifen ; estrogen agonist ; estrogen antagonist, ; ,

1. Introduction

Tamoxifen failed in this indication before its antiestrogenic properties were discovered to be efficacious in the treatment of estrogen receptor (ER)—positive breast cancer [1][2]. In the last few decades, tamoxifen has become one of the most frequently prescribed anticancer drugs worldwide, also used for the chemoprevention of breast cancer for women at high risk [3].

In 1985, Killackey et al. suggested a possible link between tamoxifen use and the development of endometrial cancer (EC) [4], a claim substantiated by a series of later studies [3][5], with an increased risk of EC ranging from 1.5 to 6.9-fold in tamoxifen users [6]. In addition, the ECs in tamoxifen users often belong to less favorable subtypes and have relatively poor prognoses [6]. While tamoxifen has an antiestrogenic effect in the breast, it can act as a weak estrogen agonist on the endometrium. Tamoxifen-associated changes include endometrial hyperplasia, atypia, and malignancy [1][2][3][4][5].

On the other hand, tamoxifen has been successfully used as treatment in advanced or recurrent EC [7]. It is suggested to be the preferred second-line hormonal therapy after first-line progestin treatment, particularly in patients with endometrial tumors and a positive estrogen receptor status, achieving response rates of 10–53% [7]. Thus, tamoxifen is a Janus-headed drug regarding EC: on the one hand, it increases the risk for the development of this disease, and it represents a remedy for certain forms of this cancer on the other.

2. Application of Tamoxifen in Endometrial Cancer (EC)

2.1. Tamoxifen as Treatment for EC

Endogenous and exogenous estrogens are most important risk factors for type 1 ECs, as are estrogen medication, nulliparity, early menarche, late menopause, and obesity [7][8]. Tamoxifen has been used for the treatment of advanced or recurrent EC since the 1980s, at that time considered to act primarily as an antiestrogen by blocking the estrogen receptor α (ERα) [9]. In 2001, a phase II trial by the Gynecologic Oncology Group (GOG) involving 68 eligible patients with advanced or recurrent EC was performed with 40 mg of tamoxifen/day. Three complete (4%) and four (6%) partial responders were observed [9]. However, 50% of the patients had Grade 3 tumors and at least 20% had Type 2 tumors that were not candidates for endocrine therapy due to the lack of ER [10][11][12]. The authors concluded that tamoxifen demonstrated modest activity at best and did not warrant further investigation as a single agent in this population [9].

In a subsequent phase II trial, the GOG combined tamoxifen with intermittent medroxyprogesterone acetate (MPA) or megestrol acetate. The rationale was that tamoxifen induced the expression of progesterone receptors, downregulated by continuous progestin treatment, via its estrogen-agonistic activity. Overall response rates of 33% (tamoxifen plus MPA) [13] and 27% (tamoxifen plus megestrol acetate) [14] were observed. The median overall survival was 13.14 months [13][14]. Estrogen receptor α measured in metastatic EC tissue prior to hormonal therapy was statistically significantly related to clinical response to daily tamoxifen and intermittent MPA [10].

In 2010, a systematic Cochrane review did not find evidence that hormonal therapy improved survival in patients with recurrent or primarily advanced EC [15]. This entry, however, looked at randomized controlled trials focusing on overall survival or 5 years disease-free survival benefits and did not include phase II trials or observational studies. Furthermore, due to insufficient and heterogeneous data, the authors were not able to pool data and perform meta-analyses. In addition, the role of hormone receptor expression was not explored [15]. A later systematic review tried to overcome the

limitations of the Cochrane analysis and found an objective response rate for tamoxifen in first-line treatment of 21.4% ± 12.1% and clinical benefit rate of 57.1 ± 10.4%. In second-line treatment, an objective response rate of 20.6 ± 13% and a clinical benefit rate of 36.3 ± 16% were calculated [12].

For the combination of SERMs (mostly tamoxifen) plus progestins, an objective response rate of 24.2 ± 8.3% and clinical benefit rate of 32.3 ± 15.8% were observed [12].

For all hormonal treatments, the response rates were higher in ER+ (26.5%) and PGR+ (35.5%) disease and lower in ER- (9.2%) or PGR- (12.1%) tumors. The response rates in second-line treatment were significantly higher when a response had been achieved in first-line HT [12].

Another systematic review on antiestrogen treatment in endometrial cancer found response rates for tamoxifen monotherapy ranging from 10% to 53% and for combined tamoxifen/progestin treatment of 19–58% [7]. The authors concluded that tamoxifen alone or in combination with a progestogen should be the preferred second-line hormonal treatment. The response rates were comparable to those for first-line progestogen treatment, and toxicity was low. The efficacy of tamoxifen therapy could be further improved by selecting patients with endometrioid EC and positive ER and/or PR status, preferably based on an actual biopsy [7].

2.2. Molecular Mechanisms of Tamoxifen in EC

Tamoxifen was originally considered to be an antiestrogen before its estrogen-agonistic activities on various organs, including the uterus and the breast, became evident [1][2]. This led to the paradigm “tamoxifen is an estrogen antagonist in the breast and an agonist in the endometrium”[1][2]. This concept was elegantly supported by experiments from the group of Jordan. They examined the effects of tamoxifen on an estrogen-dependent human breast cancer cell line and an estrogen-dependent human EC cell line xenotransplanted into athymic mice. In the same animal, tamoxifen treatment stimulated the endometrial cancers while inhibiting the breast cancer transplant [16]. This suggested that not the host metabolism but rather tissue-specific actions of tamoxifen led to the contrasting effects of the drug [16]. It was later shown that the recruitment of co-activators and co-repressors of the ER might determine cell type-specific cellular responses to tamoxifen [6][17].

Tamoxifen is metabolized to a variety of molecules, including intermediates that could form protein or DNA adducts and cause DNA damage [6]. Tamoxifen is a strong liver carcinogen in rats. The analysis of tamoxifen-DNA adducts in endometrial tissues from women with breast cancer taking tamoxifen has not provided convincing results. The risk of women treated with tamoxifen developing hepatocellular cancer is minimal, and the formation of tamoxifen-DNA adducts in endometrial tissues occurred at extremely low levels and in only a few patients [6].

The Dutch TAMARISK group investigated whether ECs that developed after long-term (>2 years) tamoxifen treatment for breast cancer was genetically different from ECs occurring without exposure to tamoxifen. An analysis of endometrioid ECs, serous ECs, and carcinosarcomas found neither more nor different genomic aberrations between tumors that developed after prolonged tamoxifen use and those that developed in the absence of tamoxifen [18].

Genes typically mutated in EC include p53 (type 2 EC), PTEN (phosphatase and tensin homology), and the DNA mismatch repair family genes. In the majority of cases, patients exposed to tamoxifen had similar mutation rates as non-exposed females with EC [6].

The long-term treatment of estrogen-dependent breast cancer eventually results in tamoxifen resistance, even after an initial remission of the tumors [1][2]. It could be shown that tamoxifen not only lost its estrogen-antagonistic activity but could even stimulate the growth of some of these tumors [1][2]. Apart from the well-characterized ERα and ERβ, a third estrogen receptor has been identified in a variety of tissues, which is located in the plasma membrane and mediates certain rapid actions of estrogens. [6][19]. This seven-transmembrane receptor (GPR-30) is coupled to G-protein and activates the epidermal growth factor/MAPK pathway [6][19]. As it is potently activated by estrogens, it has been renamed to G-protein coupled estrogen receptor 1 (GPER1) [19].

Apart from estrogens, tamoxifen and fulvestrant—considered to be a pure antiestrogen—and a number of phytoestrogens and endocrine disruptors act as agonists [19]. The expression of GPER1 is increased in breast cancers with acquired tamoxifen resistance [19].

Vivacqua et al. showed that tamoxifen antagonized the activation of ERα by estradiol in Ishikawa EC cells and, at the same time, stimulated the mitogenic signaling pathways through GPER1, leading to cell proliferation [20]. When the expression of GPER1 was suppressed, tamoxifen inhibited estrogen-induced proliferation by blocking ERα [20]. GPER1

was found to be overexpressed in endometrial cancers where ER and PR were downregulated, and in high-risk endometrial cancers with lower survival rates [21].

Ignatov et al. [22] demonstrated a significant stimulation of endometrial cancer cell lines by tamoxifen in vitro through GPER1. In vivo, they found a significant correlation between GPER1 expression and tamoxifen-induced endometrial pathology. Tsai et al. [23] showed that both estradiol and tamoxifen induce the cell migration of endometrial cancers with low or no nuclear ERα, through GPER1 activation.

Other mechanisms possibly involved in tamoxifen's action include the unfolded protein response (UPR) pathway, mTOR signaling, calcyphosin, and stathmin [6][24].

3. Conclusions

Tamoxifen can induce EC during chronic exposure (adjuvant or preventive therapy) at a low frequency, preferably in postmenopausal women and those with typical risk factors for EC. This risk can be minimized by detecting and treating endometrial pathologies before the initiation of tamoxifen treatment [25]. The reduction of breast cancer mortality by adjuvant tamoxifen therapy far outweighs the slightly increased risks of EC.

For patients with advanced or recurrent EC, tamoxifen alone or in combination with a progestogen is an efficacious treatment option with low toxicity [7][8][12].

The molecular mechanisms for the Janus-headed activity of tamoxifen (estrogen-antagonist/estrogen-agonist) are still elusive. Tamoxifen can act as an agonist or antagonist through ERα depending on cellular differences in co-activators or co-repressors. Tamoxifen acts as an estrogen agonist through GPER-1, which is more highly expressed in breast and endometrial cancer cells that show primary or secondary resistance to tamoxifen. As tamoxifen is and will be one of the most valuable anticancer drugs due to its high efficacy, low toxicity, and availability, further research to elucidate its mode of action should be encouraged.

References

1. Jordan, V.C. The 38th David A. Karnofsky lecture: The paradoxical actions of estrogen in breast cancer—Survival or death? J. Clin. Oncol. 2008, 26, 3073–3082.
2. Jordan, V.C. The SERM Saga, Something from Nothing: American Cancer Society/SSO Basic Science Lecture. Ann. Surg. Oncol. 2019, 26, 1981–1990.
3. Potkul, R.K.; Unger, J.M.; Livingston, R.B.; Crew, K.D.; Wilczynski, S.P.; Salomon, C.G.; Smith, B.L.; Wong, L.; Campbell, D.L.; Einspahr, D.E.; et al. Randomized trial of medroxyprogesterone acetate for the prevention of endometrial pathology from adjuvant tamoxifen for breast cancer: SWOG S9630. NPJ Breast Cancer 2016, 2, 16024.
4. Killackey, M.A.; Hakes, T.B.; Pierce, V.K. Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. Cancer Treat. Rep. 1985, 69, 237–238.
5. Fleming, C.A.; Heneghan, H.M.; O'Brien, D.; McCartan, D.P.; McDermott, E.W.; Prichard, R.S. Meta-analysis of the cumulative risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy. Br. J. Surg. 2018, 105, 1098–1106.
6. Hu, R.; Hilakivi-Clarke, L.; Clarke, R. Molecular mechanisms of tamoxifen-associated endometrial cancer. Oncol. Lett. 2015, 9, 1495–1501.
7. van Weelden, W.J.; Massuger, L.F.; Pijnenborg, J.M.A.; Romano, A. Anti-estrogen Treatment in Endometrial Cancer: A Systematic Review. Front. Oncol. 2019, 9, 359.
8. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom, Langversion 1.0, 2018, AWMF Registernummer: 032/034-OL. Available online: http://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/ (accessed on 3 July 2020). (In German).
9. Thigpen, T.; Brady, M.F.; Homesley, H.D.; Soper, J.T.; Bell, J. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. J. Clin. Oncol. 2001, 19, 364–367.
10. Singh, M.; Zaino, R.J.; Filiaci, V.J.; Leslie, K.K. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: A Gynecologic Oncology Group Study. Gynecol. Oncol. 2007, 106, 325–333.

11. Emons, G.; Gunthert, A.; Thiel, F.C.; Camara, O.; Strauss, H.G.; Breitbach, G.P.; Kolbl, H.; Reimer, T.; Finas, D.; Rensing, K.; et al. Phase II study of fulvestrant 250 mg/month in patients with recurrent or metastatic endometrial cancer: A study of the Arbeitsgemeinschaft Gynakologische Onkologie. Gynecol. Oncol. 2013, 129, 495–499.
12. Ethier, J.L.; Desautels, D.N.; Amir, E.; MacKay, H. Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis. Gynecol. Oncol. 2017, 147, 158–166.
13. Whitney, C.W.; Brunetto, V.L.; Zaino, R.J.; Lentz, S.S.; Sorosky, J.; Armstrong, D.K.; Lee, R.B. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol. Oncol. 2004, 92, 4–9.
14. Fiorica, J.V.; Brunetto, V.L.; Hanjani, P.; Lentz, S.S.; Mannel, R.; Andersen, W. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol. Oncol. 2004, 92, 10–14.
15. Kokka, F.; Brockbank, E.; Oram, D.; Gallagher, C.; Bryant, A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst. Rev. 2010, 12, CD007926.
16. Gottardis, M.M.; Robinson, S.P.; Satyaswaroop, P.G.; Jordan, V.C. Contrasting actions of tamoxifen on endometrial and breast tumor growth in the athymic mouse. Cancer Res. 1988, 48, 812–815.
17. Shang, Y.; Brown, M. Molecular determinants for the tissue specificity of SERMs. Science 2002, 295, 2465–2468.
18. Fles, R.; Hoogendoorn, W.E.; Platteel, I.; Scheerman, C.E.; de Leeuw-Mantel, G.; Mourits, M.J.; Hollema, H.; van Leeuwen, F.E.; van Boven, H.H.; Nederlof, P.M. Genomic profile of endometrial tumors depends on morphological subtype, not on tamoxifen exposure. Genes Chromosomes Cancer 2010, 49, 699–710.
19. Girgert, R.; Emons, G.; Grundker, C. Estrogen Signaling in ERalpha-Negative Breast Cancer: ERbeta and GPER. Front. Endocrinol. 2018, 9, 781.
20. Vivacqua, A.; Bonofiglio, D.; Recchia, A.G.; Musti, A.M.; Picard, D.; Ando, S.; Maggiolini, M. The G protein-coupled receptor GPR30 mediates the proliferative effects induced by 17beta-estradiol and hydroxytamoxifen in endometrial cancer cells. Mol. Endocrinol. 2006, 20, 631–646.
21. Smith, H.O.; Leslie, K.K.; Singh, M.; Qualls, C.R.; Revankar, C.M.; Joste, N.E.; Prossnitz, E.R. GPR30: A novel indicator of poor survival for endometrial carcinoma. Am. J. Obstet. Gynecol. 2007, 196, 386.e1–386.e9, discussion 386.e9–e11.
22. Ignatov, T.; Eggemann, H.; Semczuk, A.; Smith, B.; Bischoff, J.; Roessner, A.; Costa, S.D.; Kalinski, T.; Ignatov, A. Role of GPR30 in endometrial pathology after tamoxifen for breast cancer. Am. J. Obstet. Gynecol. 2010, 203, 595.e9–595.e16.
23. Tsai, C.L.; Wu, H.M.; Lin, C.Y.; Lin, Y.J.; Chao, A.; Wang, T.H.; Hsueh, S.; Lai, C.H.; Wang, H.S. Estradiol and tamoxifen induce cell migration through GPR30 and activation of focal adhesion kinase (FAK) in endometrial cancers with low or without nuclear estrogen receptor alpha (ERalpha). PLoS ONE 2013, 8, e72999.
24. Janacova, L.; Faktor, J.; Capkova, L.; Paralova, V.; Pospisilova, A.; Podhorec, J.; Ebhardt, H.A.; Hrstka, R.; Nenutil, R.; Aebersold, R.; et al. SWATH-MS Analysis of FFPE Tissues Identifies Stathmin as a Potential Marker of Endometrial Cancer in Patients Exposed to Tamoxifen. J. Proteome Res. 2020, 19, 2617–2630.
25. Garuti, G.; Grossi, F.; Centinaio, G.; Sita, G.; Nalli, G.; Luerti, M. Pretreatment and prospective assessment of endometrium in menopausal women taking tamoxifen for breast cancer. Eur. J. Obstet. Gynecol. Reprod. Biol. 2007, 132, 101–106.
