Tamoxifen

Tamoxifen (**TMX**), sold under the brand name **Nolvadex** among others, is a medication that is used to prevent breast cancer in women and treat breast cancer in women and men.[3] It is also being studied for other types of cancer.[3] It has been used for Albright syndrome. Tamoxifen is typically taken daily by mouth for five years for breast cancer.[4]

Serious side effects include a small increased risk of uterine cancer, stroke, vision problems, and pulmonary embolism. Common side effects include irregular periods, weight loss, and hot flashes. It may cause harm to the baby if taken during pregnancy or breastfeeding.[4] It is a selective estrogen-receptor modulator (SERM) that works both by decreasing factors that increase the growth of breast cells and increasing factors that decrease the growth of breast cells.[4][5] It is of the triphenylethylene group.[6]

Tamoxifen was discovered in 1967.[7] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[8] Tamoxifen is available as a generic medication.[4] The wholesale price in the developing world is about 0.07 to 0.23 USD per day.[9] In the United States it costs about 2 USD a day.[4]

1 Medical uses

1.1 Breast cancer

Tamoxifen is currently used for the treatment of both early and advanced estrogen receptor (ER)-positive (ER+) breast cancer in pre- and post-menopausal women.[10] Additionally, it is the most common hormone treatment for male breast cancer.[11] It is also approved by the FDA for the prevention of breast cancer in women at high risk of developing the disease.[12] It has been further approved for the reduction of contralateral (in the opposite breast) cancer. The use of tamoxifen is recommended for 10 years.[13]

In 2006, the large STAR clinical study concluded that raloxifene is equally effective in reducing the incidence of breast cancer, but after an average 4-year follow-up there were 36% fewer uterine cancers and 29% fewer blood clots in women taking raloxifene than in women taking tamoxifen, although the difference was not statistically significant.[14][15][16]

1.2 Infertility

Tamoxifen is used to treat infertility in women with anovulatory disorders. It is given at days 3–7 of a woman's cycle.[17]

Tamoxifen improves fertility in males with infertility by disinhibiting the hypothalamic-pituitary-adrenal axis (via ER antagonism) and thereby increasing the secretion of luteinizing hormone and follicle-stimulating hormone and increasing testicular testosterone production.[18]

1.3 Gynecomastia

Tamoxifen is used to prevent estrogen-related gynecomastia, resulting from elevated estrogenic levels. It is taken as a preventative measure in small doses, or used at the onset of any symptoms such as nipple soreness or sensitivity. Other drugs are taken for similar purposes such as clomiphene citrate and the anti-aromatase drugs which are used in order to try to avoid the hormone-related adverse effects. Tamoxifen is also sometimes used to treat or prevent gynecomastia in sex offenders undergoing temporary chemical castration.[19]

1.4 Others

Occasionally tamoxifen is used in treatment of the rare conditions of retroperitoneal fibrosis[20] and idiopathic sclerosing mesenteritis.[21]

2 Side effects

A report in September 2009 from Health and Human Services' Agency for Healthcare Research and Quality suggests that tamoxifen, raloxifene, and tibolone used to treat breast cancer significantly reduce invasive breast cancer in midlife and older women, but also increase the risk of adverse side effects.[22]

Some cases of lower-limb lymphedema have been associated with the use of tamoxifen, due to the blood clots and deep vein thrombosis (DVT) that can be caused by this medication. Resolution of the blood clots or DVT is needed before lymphedema treatment can be initiated.

2.1 Bone

A beneficial side effect of tamoxifen is that it prevents bone loss by acting as an ER agonist (i.e., mimicking the effects of estrogen) in this cell type. Therefore, by inhibiting osteoclasts, it prevents osteoporosis.[23][24] When tamoxifen was launched as a drug, it was thought that tamoxifen would act as an ER antagonist in all tissue, including bone, and therefore it was feared that it would contribute to osteoporosis. It was therefore very surprising that the opposite effect was observed clinically. Hence tamoxifen's tissue selective action directly led to the formulation of the concept of SERMs.[25] In contrast tamoxifen appears to be associated with bone loss in premenopausal women who continue to menstruate after adjuvant chemotherapy.[26]

2.2 Endometrial cancer

Tamoxifen is a SERM.[27] Even though it is an antagonist in breast tissue it acts as partial agonist on the endometrium and has been linked to endometrial cancer in some women. Therefore, endometrial changes, including cancer, are among tamoxifen's side effects.[28] With time, risk of endometrial cancer may be doubled to quadrupled, which is a reason tamoxifen is typically only used for 5 years.[29]

The American Cancer Society lists tamoxifen as a known carcinogen, stating that it increases the risk of some types of uterine cancer while lowering the risk of breast cancer recurrence.[30] The ACS states that its use should not be avoided in cases where the risk of breast cancer recurrence without the drug is higher than the risk of developing uterine cancer with the drug.

2.3 Cardiovascular and metabolic

Tamoxifen treatment of postmenopausal women is associated with beneficial effects on serum lipid profiles. However, long-term data from clinical trials have failed to demonstrate a cardioprotective effect.[31] For some women, tamoxifen can cause a rapid increase in triglyceride concentration in the blood. In addition there is an increased risk of thromboembolism especially during and immediately after major surgery or periods of immobility.[32] Tamoxifen is also a cause of fatty liver, otherwise known as steatorrhoeic hepatosis or steatosis hepatis.[33]

2.4 Central nervous system

Tamoxifen-treated breast cancer patients show evidence of reduced cognition,[34] a major side effect of tamoxifen, and semantic memory scores.[35] However memory impairment in patients treated with tamoxifen was less severe compared with those treated with anastrozole (an aromatase inhibitor).[36]

A significant number of tamoxifen-treated breast cancer patients experience a reduction of libido.[37][38]

2.5 Premature growth plate fusion

While tamoxifen has been shown to antagonize the actions of estrogen in tissues such as the breast, its effects in other tissues such as bones has not been documented fully. There have been studies done in mice showing tamoxifen mimic the effects of estrogen on bone metabolism and skeletal growth. Thus increasing the possibility of pre-mature bone fusion. This effect would be less of a concern in adults who have stopped growing.[39]

3 Pharmacogenetics and drug interactions

Nolvadex (tamoxifen) 20 mg tablets

Patients with variant forms of the gene CYP2D6 (also called simply 2D6) may not receive full benefit from tamoxifen because of too slow metabolism of the tamoxifen prodrug into its active metabolites.[40][41] On 18 October 2006, the Subcommittee for Clinical Pharmacology recommended relabeling tamoxifen to include information about this gene in the package insert.[42]

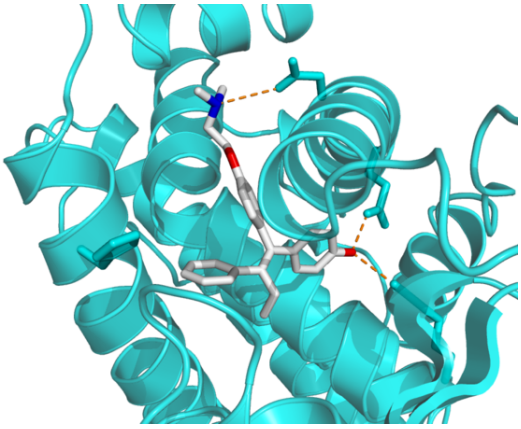
Certain CYP2D6 variations in breast cancer patients leads to a worse clinical outcome for tamoxifen treatment.[43] Genotyping therefore has the potential for identification of women who have these CYP2D6 phenotypes and for whom the use of tamoxifen is associated with poor outcomes.

Recent studies suggest that taking the selective serotonin reuptake inhibitors (SSRIs) antidepressants paroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft) can decrease the effectiveness of tamoxifen, as these drugs compete for the CYP2D6 enzyme which is needed to metabolize tamoxifen into its active forms.[44] A U.S. study

presented at the American Society of Clinical Oncology's annual meeting in 2009 found that after two years, 7.5% of women who took only tamoxifen had a recurrence, compared with 16% who took either paroxetine, fluoxetine or sertraline, drugs considered to be the most potent CYP2D6 inhibitors. That difference translates to a 120% increase in the risk of breast cancer recurrence. Patients taking the SSRIs; Celexa (citalopram), Lexapro (escitalopram), and Luvox (fluvoxamine), did not have an increased risk of recurrence, due to their lack of competitive metabolism for the CYP2D6 enzyme.[45] A newer study demonstrated a clearer and stronger effect from paroxetine in causing the worst outcomes. Patients treated with both paroxetine and tamoxifen have a 67% increased risk of death from breast cancer, from 24% to 91%, depending on the duration of coadministration.[46]

Recent research has shown that 7–10% of women with breast cancer may not receive the full medical benefit from taking tamoxifen due to their unique genetic make-up. DNA Drug Safety Testing can examine DNA variations in the CYP2D6 and other important drug processing pathways. More than 20% of all clinically used medications are metabolized by CYP2D6 and knowing the CYP2D6 status of a person can help the doctor with the future selection of medications.[47] Other molecular biomarkers may also be used to select appropriate patients likely to benefit from tamoxifen.[48]

4 Mechanism of action



Crystallographic structure of 4-hydroxy-tamoxifen (carbon = white, oxygen = red, nitrogen = blue) complexed with ligand binding domain of estrogen receptor alpha (ERα) (cyan ribbon).[49]

Tamoxifen itself is a prodrug, having relatively little affinity for its target protein, the ER. It is metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 into active metabolites such as 4-hydroxytamoxifen (4-OHT) (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifen)[50] which have 30–100 times more affinity with the ER than tamoxifen itself.[51] These active metabolites compete with estrogen in the body for binding to the ER. In breast tissue, 4-OHT acts as an ER antagonist so that transcription of estrogen-responsive genes is inhibited.[52] Tamoxifen has 7% and 6% of the affinity of estradiol for the ERα and ERβ, respectively, whereas 4-OHT has 178% and 338% of the affinity of estradiol for the ERα and ERβ.[53]

4-OHT binds to ER, the ER/tamoxifen complex recruits other proteins known as co-repressors and then binds to DNA to modulate gene expression. Some of these proteins include NCoR and SMRT.[54] Tamoxifen function can be regulated by a number of different variables including growth factors.[55] Tamoxifen needs to block growth factor proteins such as ErbB2/HER2[56] because high levels of ErbB2 have been shown to occur in tamoxifen resistant cancers.[57] Tamoxifen seems to require a protein PAX2 for its full anticancer effect.[56][58] In the presence of high PAX2 expression, the tamoxifen/ER complex is able to suppress the expression of the pro-proliferative ERBB2 protein. In contrast, when AIB-1 expression is higher than PAX2, tamoxifen/ER complex upregulates the expression of ERBB2 resulting in stimulation of breast cancer growth.[56][59]

4-OHT binds to ER competitively (with respect to the endogenous agonist estrogen) in tumor cells and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects. It is a nonsteroidal agent with potent antiestrogenic properties which compete with estrogen for binding sites in breast and other tissues. Tamoxifen causes cells to remain in the G_0 and G_1 phases of the cell cycle. Because it prevents (pre)cancerous cells from dividing but does not cause cell death, tamoxifen is cytostatic rather than cytocidal.

The scientific literature is complex with respect to the activity of tamoxifen, and care should be taken to establish whether tamoxifen, or the 4-hydroxy metabolite was used, especially in in vitro assays.

N,N-Didesmethyl-4-hydroxytamoxifen (norendoxifen), another active metabolite of tamoxifen, has been found to act as a potent competitive aromatase inhibitor (IC_{50} = 90 nM), and may also be involved in its antiestrogenic activity.[60]

5 History

In the late 1950s, pharmaceutical companies were actively researching a newly discovered class of anti-estrogen compounds in the hope of developing a morning-after contraceptive pill. Arthur L Walpole was a reproductive endocrinologist who led such a team at the Alderley Park research laboratories of ICI Pharmaceuticals. It was there in 1966 that Dora Richardson first synthesised tamoxifen, known then as ICI-46,474.[61] Walpole and his colleagues filed a UK patent covering this compound in 1962, but patent protection on this com-

pound was repeatedly denied in the US until the 1980s.[62] Tamoxifen did eventually receive marketing approval as a fertility treatment, but the class of compounds never proved useful in human contraception. A link between estrogen and breast cancer had been known for many years, but cancer treatments were not a corporate priority at the time, and Walpole's personal interests were important in keeping support for the compound alive in the face of this and the lack of patent protection.[7]

Tamoxifen is one of three drugs in an anti-angiogenetic protocol developed by Dr. Judah Folkman, a researcher at Children's Hospital at Harvard Medical School in Boston. Folkman discovered in the 1970s that angiogenesis – the growth of new blood vessels – plays a significant role in the development of cancer. Since his discovery, an entirely new field of cancer research has developed. Clinical trials on angiogenesis inhibitors have been underway since 1992 using myriad different drugs. The Harvard researchers developed a specific protocol for a golden retriever named Navy who was cancer-free after receiving the prescribed cocktail of celecoxib, doxycycline, and tamoxifen – the treatment subsequently became known as the Navy Protocol.[63] Furthermore, tamoxifen treatment alone has been shown to have anti-angiogenetic effects in animal models of cancer which appear to be, at least in part, independent of tamoxifen's ER antagonist properties.[64]

The first clinical study took place at the Christie Hospital in 1971, and showed a convincing effect in advanced breast cancer,[65] but nevertheless ICI's development programme came close to termination when it was reviewed in 1972. Tamoxifen's further development may have been bolstered by a second clinical study by Harold W.C. Ward [66] at the Queen Elizabeth Hospital, Birmingham. Ward's study showed a more definitive response to the drug at a higher dosage. Walpole also may have helped to convince the company to market tamoxifen for late stage breast cancer in 1973.[62] He was also instrumental in funding V. Craig Jordan to work on tamoxifen. In 1972, ICI Pharmaceuticals Division abandoned development of tamoxifen for financial reasons. The drug was subsequently reinvented from a failed contraceptive, to become tamoxifen, the gold standard for the adjuvant treatment of breast cancer and the pioneering medicine for chemprevention for high risk women.[67] Two books, *Estrogen Action, Selective Estrogen Receptor Modulators and Women's Health* (Imperial College Press 2013) and *Tamoxifen Pioneering Medicine in Breast Cancer* (Springer 2013) tell this story.

1980 saw the publication of the first trial to show that tamoxifen given in addition to chemotherapy improved survival for patients with early breast cancer.[68] In advanced disease, tamoxifen is now only recognized as effective in ER+ patients, but the early trials did not select ER+ patients, and by the mid 1980s the clinical trial picture was not showing a major advantage for tamoxifen.[69] Nevertheless, tamoxifen had a relatively mild side-effect profile, and a number of large trials continued.

The pharmacology of SERMs was discovered, defined, and deciphered during the 1980s [70] A clinical strategy was described [71] that led to the creation of SERMs as a group of multifunctional medicines aimed at the treatment or prevention of many conditions in postmenopausal women, e.g.: osteoporosis and breast cancer. This story is told in: V. Craig Jordan, ed. 2013. "Estrogen Action, Selective Estrogen Receptor Modulators and Women's Health" Imperial College Press, Singapore.

It was not until 1998 that the meta-analysis of the Oxford-based Early Breast Cancer Trialists' Collaborative Group showed definitively that tamoxifen saved lives in early breast cancer.[72]

6 Society and culture

6.1 Economics

Global sales of tamoxifen in 2001 were $1,024 million.[73] Since the expiration of the patent in 2002, it is now widely available as a generic drug around the world. As of 2004, tamoxifen was the world's largest selling hormonal drug for the treatment of breast cancer.[74]

7 Research

Tamoxifen is used as a research tool to trigger tissue-specific gene expression in many conditional expression constructs in genetically modified animals including a version of the Cre-Lox recombination technique.[75]

The drug has also been studied in several additional indications.

7.1 Riedel's thyroiditis

Tamoxifen has been proposed as part of a treatment plan for Riedel's thyroiditis.[76]

7.2 Bipolar disorder

Tamoxifen has been shown to be effective in the treatment of mania in patients with bipolar disorder by blocking protein kinase C (PKC), an enzyme that regulates neuron activity in the brain. Researchers believe PKC is over-active during the mania in bipolar patients.[77][78]

7.3 McCune-Albright syndrome

In McCune-Albright syndrome (MAS) tamoxifen has been used to treat premature puberty and the consequences of premature puberty. Tamoxifen has been seen

to decrease rapid bone maturation which is the result of excessive estrogen and alter predicted adult height (PAH).[79][80] The same effects have also been seen in short pubertal boys.[81]

However, one *in vitro* study in 2007 and later an *in vivo* study in 2008 have shown that tamoxifen induces apoptosis in growth plate chondrocytes, reduces serum IGF-I levels and causes persistent retardation of longitudinal and cortical radial bone growth in young male rats, leading the researches to express concern giving tamoxifen to growing individuals.[39][82]

8 See also

- Ethamoxytriphetol
- Trioxifene
- Clomifene citrate
- Fulvestrant

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- Tamoxifen at DMOZ

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