ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Development of Endoxifen for Breast Cancer

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H&O Could you please describe how tamoxifen works, and its history as a treatment for breast cancer?

MG Tamoxifen is a selective estrogen receptor modulator (SERM). This means that it exhibits estrogen-blocking capabilities in some tissues, whereas in others, it acts more like an estrogen. In the breast, tamoxifen mainly exhibits antiestrogenic effects.

Tamoxifen was originally developed as an oral contraceptive, but it was unsuccessful in this capacity. In the 1960s and 1970s, tamoxifen was shown to have anticancer effects. It was developed as a treatment for women with estrogen receptor–positive breast cancer, with the idea that blocking this receptor could promote anticancer effects. The US Food and Drug Administration (FDA) first approved tamoxifen in 1977 for metastatic breast cancer. However, it was the subsequent 3 decades of clinical trial research that led to the critical observations that the administration of tamoxifen after surgery reduced breast cancer recurrence and mortality and, most importantly, prolonged survival. During that time, studies identified the estrogen receptor as the critical predictive biomarker and defined the importance of duration (first 5 years, and then 10 years). Later, studies demonstrated the benefit of tamoxifen for the adjuvant treatment of ductal carcinoma in situ, as well as in the prevention setting for women at increased risk of developing breast cancer. Tamoxifen is also approved for the treatment of male breast cancer.

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H&O How many women with breast cancer develop relapsed or refractory disease after treatment with tamoxifen?

MG Women who have early-stage, estrogen receptor–positive breast cancer most commonly receive 5 years of tamoxifen as adjuvant treatment—that is, after the tumor has been surgically removed—to prevent recurrence. In this setting, the Oxford Overview demonstrated that for a strongly estrogen receptor–positive breast cancer, tamoxifen reduces the risk of recurrence by nearly 50%. However, after 10 years of follow-up, approximately 22% of patients will have experienced a breast cancer recurrence. In the metastatic setting, tamoxifen is effective for approximately a year, on average.

Resistance is commonly classified into 2 types: primary and secondary. In patients with primary resistance, progression occurs early (eg, within the first 2 years of adjuvant tamoxifen therapy), and subsequent lines of endocrine therapy tend to be less effective. There are many diverse reasons for primary tamoxifen

resistance, but one of the most important occurs when the estrogen receptor is either not expressed or expressed at very low levels in the breast cancer. Needless to say, if the estrogen receptor is not expressed, then tamoxifen will be ineffective. Throughout the past 30 years, there has been a great effort to standardize measurement of the estrogen receptor because it is the most critical aspect in determining whether tamoxifen or any endocrine therapy will be effective.

Other factors beyond the estrogen receptor can contribute to resistance. Growth factor receptors, such as the human epidermal growth factor receptor 2 (HER2), the epidermal growth factor receptor, and the fibroblast growth factor receptor, can cause resistance when they are coexpressed with the estrogen receptor. This resistance may be related to crosstalk between the estrogen receptor and these growth factor receptors and their downstream effectors. One of the most important drugs to address this type of resistance is trastuzumab, a monoclonal antibody that targets HER2. Although trastuzumab is effective for preventing recurrence of HER2-expressing breast cancer regardless of estrogen receptor expression, it is important to note that many of the early "primary" recurrences that previously occurred in estrogen receptor–positive/HER2-positive settings are now effectively prevented with trastuzumab-based adjuvant therapy.

Binding of tamoxifen to the estrogen receptor results in recruitment of proteins that act as either coactivators or corepressors that impact drug response phenotypes. In general, the binding of tamoxifen to estrogen receptor–expressing breast cancer tissue results in recruitment of corepressors, leading to an overall antiestrogenic effect. However, with certain aggressive breast cancers, or in the uterus, tamoxifen binding recruits coactivators, such as SRC1 and SRC3. These coactivators, when present, can lead to agonistic effects. This is one of the purported mechanisms by which tamoxifen elicits estrogenic effects in the uterus and is believed to be an important mechanism for the development of resistance to endocrine therapy in general.

With regard to the development of secondary resistance, a recent factor identified to drive secondary resistance is estrogen receptor gene (*ESR1*) mutations. These mutations typically become clinically apparent when tumors have been exposed to tamoxifen or aromatase inhibitors for a prolonged period and are considered "activating," given that they result in estrogen receptor signaling independent of estrogen binding to the estrogen receptor, thus conferring resistance to endocrine therapy.

Finally, much research in the past decade has focused on the pharmacology of tamoxifen, and the knowledge that liver metabolism results in the formation of the metabolites 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen), both of which exhibit substantially greater antiestrogenic effects than tamoxifen or its primary metabolite, N-desmethyltamoxifen. More than a decade ago, Dr David Flockhart discovered that endoxifen was formed by the CYP2D6-mediated hydroxylation of the most abundant tamoxifen metabolite, N-desmethyltamoxifen, and that genetic variation in *CYP2D6* drives much of the variability in endoxifen concentrations. These findings led to the hypothesis that *CYP2D6* could be a biomarker for tamoxifen effectiveness. Preclinical studies repeatedly confirmed this hypothesis, in that low concentrations of endoxifen (similar to those observed in women treated with tamoxifen who are poor metabolizers of CYP2D6) were insufficient to fully inhibit estrogen-induced proliferation and gene expression of estrogen receptor–positive breast cancer cells. In addition, the dose response curve for endoxifen closely mirrored the range of endoxifen concentrations observed in women taking tamoxifen.

H&O Are there any biomarkers to guide the use of tamoxifen?

MG Apart from the estrogen receptor, which is the most critical and important biomarker for selecting endocrine therapy, *CYP2D6* has been studied as a potential predictive biomarker that may identify patients who should be preferentially treated with alternative hormonal therapy. Pharmacogenetic variation in *CYP2D6* accounts for approximately 30% to 50% of the variation in endoxifen concentrations. Patients who poorly metabolize tamoxifen owing to low CYP2D6 enzyme activity have very low concentrations of endoxifen and a higher risk of breast cancer recurrence, as shown in multiple studies. In a secondary analysis of the ABCSG 8 clinical trial (Austrian Breast and Colorectal Cancer Study Group 8), women who were poor metabolizers of CYP2D6 had a higher risk of breast cancer recurrence if they were treated with tamoxifen, but not if they were switched from tamoxifen to anastrozole.

H&O What observations suggested that endoxifen might be an effective treatment?

MG From a laboratory standpoint, endoxifen is a superior drug compared with tamoxifen. Furthermore, clinical studies demonstrated that tamoxifen treatment may be less effective for some women with low CYP2D6 enzyme activity simply because they produce less endoxifen. So, we thought, what if we could bypass CYP2D6 altogether by treating patients with endoxifen instead of tamoxifen?

H&O How were you able to bring endoxifen into testing as a drug for women with breast cancer?

MG Because the chemical structure of endoxifen has been known for many years, pharmaceutical companies expressed concern that there was inadequate protection for intellectual property. I was part of a team of investigators at the Mayo Clinic who entered into discussions with the National Cancer Institute (NCI) that aimed to develop a public-private partnership to investigate if endoxifen had antitumor activity and could be used as a drug. To explore this idea, we first performed experiments in laboratory animals to determine the pharmacokinetics of endoxifen, and we determined that endoxifen exhibited excellent bioavailability when administered orally to rats and dogs. This led the NCI to develop a formulation called Z-endoxifen, which was tested in preclinical toxicology studies and eventually in patients.

H&O What is known about the pharmacokinetics of endoxifen?

MG In the phase 1 clinical trial, Z-endoxifen was administered orally once daily starting at a dose level of 20 mg/day. Dose escalation ceased after reaching 160 mg/day. Peak concentrations of endoxifen were achieved within 2 to 4 hours after the first dose. The concentrations increased in proportion to the dose. Importantly, the steady-state endoxifen concentrations achieved in the phase 1 study were substantial (from 1-5 μM), and they meet or exceed the concentrations needed to inhibit the growth of multiple different estrogen receptor–positive breast cancer cell lines that are either sensitive or resistant to tamoxifen. Perhaps as importantly, we demonstrated that clearance of endoxifen was unaffected by the *CYP2D6* genotype.

H&O Could you please describe the data from trials of endoxifen in women with breast cancer?

MG The phase 1 study mentioned previously enrolled women with estrogen receptor–positive, metastatic breast cancer who had developed progressive disease during treatment with aromatase inhibitors. Many of the patients had also been treated with fulvestrant (Faslodex, AstraZeneca), and others had received prior tamoxifen (nearly half of whom had developed progressive disease). There was little, if any, toxicity observed with endoxifen, and dose escalation was halted at 160 mg daily, without observation of a maximum tolerated dose. The overall clinical benefit rate was approximately 26% and included 3 partial responses. (The clinical benefit rate was defined as patients who were enrolled in the trial for at least 6 months.) Several patients remained on study for longer than 2 years, and 1 patient continues on treatment now more than 3 years after registration.

Some interesting observations were made, including that Z-endoxifen exhibited antitumor activity in patients who had previously developed progressive disease during treatment with fulvestrant or everolimus (Afinitor, Novartis), an inhibitor of the mammalian target of rapamycin that is given in combination with aromatase inhibitors. The promising antitumor activity prompted a larger, randomized phase 2 clinical trial. This trial, from the Alliance Cooperative Group, compared tamoxifen and Z-endoxifen hydrochloride among women with metastatic breast cancer that had progressed during endocrine therapy. The trial recently closed, and results are expected in 2018.

H&O What is next for endoxifen?

MG There are several potential paths forward. Ongoing studies are aiming to determine whether endoxifen has activity in patients who cannot tolerate treatment with tamoxifen or who have predicted or confirmed low concentrations of endoxifen (eg, those who are poor metabolizers of CYP2D6). One regulatory path forward is for Z-endoxifen to be studied and eventually approved for this specific group of patients (ie, those with low concentrations of endoxifen). This group will include women who poorly metabolize CYP2D6, but there are other reasons that concentrations of endoxifen might be low. For example, some drugs, including several antidepressants, inhibit CYP2D6 enzyme activity. In that situation, patients who would have previously been advised to discontinue drugs that inhibit CYP2D6 enzyme activity could remain on them while being treated with endoxifen instead of tamoxifen

Endoxifen may hold the greatest promise, however, in premenopausal women. In premenopausal women with early-stage, estrogen receptor–positive breast cancer, an updated analysis of the International Breast Cancer Study Group 24-02 study demonstrated that strategies that more deeply suppress estrogen (eg, ovarian function suppression in addition to tamoxifen or an aromatase inhibitor) are superior to tamoxifen monotherapy. Although this latter approach is likely the most effective, it is associated with substantial short-term and potential long-term side effects. Therefore, endoxifen may be an effective but more tolerable approach to targeting the estrogen receptor in premenopausal women with early-stage breast cancer.

H&O Does the development of endoxifen have implications for the development of other types of therapies?

MG It does. Tamoxifen has saved thousands of lives over the past 30 years. It was not until 30 years after tamoxifen was first approved that a new understanding of the pharmacology of this agent became known. It was this new understanding that led to the development of endoxifen. Similarly, there are likely many other drugs for which a better understanding of pharmacology and pharmacodynamics could result in better tailoring of treatment or even "repurposing" for other indications.

Disclosure

Dr Goetz has a consulting or advisory role for Eli Lilly, Biotheranostics, Biovica, Myriad, and Genomic Health. He has received research funding from Eli Lilly and Pfizer.

Suggested Readings

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