ASCO Expert Corner: Hormone Therapy Options for Early-Stage Breast Cancer

Hormone therapy is a treatment option for women with early-stage, hormone-sensitive breast cancer, which is identified by the presence of hormone receptors. When used after surgery for curable cancer, hormone therapy lowers the risk of recurrence (cancer that returns after the original treatment) by blocking tumor growth caused by hormones so that cancer cells either die or remain inactive.

The earliest hormone therapy involved removing the ovaries of young women, but now there are non-surgical options like drugs that directly block the estrogen receptor, including tamoxifen, and other drugs that block the production of estrogen, known as aromatase inhibitors (AIs). AIs inhibit the enzyme aromatase, which is necessary for estrogen production. In the United States, there are three AIs available, anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), and they are used individually in women who have gone through menopause, either in place of tamoxifen or following tamoxifen treatment. Currently there are clinical trials that are exploring optimal ways to use these drugs, as well as the potential benefits of combining them with newer therapies.

To learn more about women?s options for hormone therapy and what they should know, Cancer.Net talked with Clifford A. Hudis, MD in 2009. This article was updated in 2012.

Q: What are the primary differences between how tamoxifen and AIs work?
A: Tamoxifen is one of several drugs called SERMs. SERM stands for ?selective estrogen receptor modulator.? SERMs interact with the estrogen receptor on breast cancer cells and in other tissues of the body, and in each case can cause different kinds of effects. In the case of breast cancer, we somewhat simplify things by stating that the SERMs act like ?anti-estrogen?? blocking the naturally produced hormone from interacting with the receptor, and thereby depriving the cell of a needed signal for growth. The truth is far more complicated, but SERMs do lead to breast cancer cell death in many (but not all) cases. In other tissues like the uterus or bones, SERMs can closely mimic the effects of estrogen, and that is why they may cause an increased risk of uterine cancer and blood clots while helping to prevent osteoporosis (thinning of the bones).

AIs block the aromatase enzyme that exists in many tissues throughout the body. This enzyme is critical to the generation of estrogen, so by blocking it we lower the amount of available estrogen, thereby decreasing the ability of the estrogen receptor to drive growth in the breast cancer cells. Tamoxifen works directly within the cancer cell, while an AI can be thought of as working at a distance to deprive the cell of estrogen. A critical issue to remember is that the current AIs are not known to be effective when a woman?s ovaries are still functioning (meaning before menopause), whereas tamoxifen?s effects are established for both premenopausal and postmenopausal women.

Q: What side effects are associated with tamoxifen and AIs?
A: All drugs have side effects, and widely used drugs will have very long lists of potential risks. For tamoxifen, the serious side effects that are most well established are associated with its estrogen-like effects and include blood clots and uterine cancer. Less serious (but annoying) side effects include hot flashes, while less common side effects can include a small amount of fluid retention and a long list of other concerns.

For AIs, the side effects are more easily associated with the lower levels of estrogen and can include accelerated bone density loss and osteoporosis, hot flashes, and a poorly understood syndrome of joint aches and stiffness. Both drugs can cause vaginal dryness and may have an impact on sexual function. The good news is that there are highly effective remedies for most of these possible side effects, and most women do not experience any of these side effects to a significant extent.

Q: If my doctor recommends either tamoxifen or an AI, how I do choose between them?
A: The first question to ask is which one your doctor specifically recommends. While tamoxifen use has been standard and standardized for years, the AIs have been shown to be somewhat more active and (from a medical perspective) slightly safer because they do not cause blood clots or uterine cancer when used in very specific groups of patients. However, premenopausal women should not be offered aromatase inhibitors. Therefore, your choice should be based on data from one of the reported clinical trials.

Q: Women are often advised to stop taking AIs or tamoxifen after five years. Why is this?
A: For tamoxifen, longer durations of therapy (up to five years) were superior to shorter durations. In one study, 10 years of treatment produced no better results than five years, but this is being reconsidered based on some clinical trials that lasted for more than five years. For purposes of comparison, five years of tamoxifen was a benchmark against which the AIs could be compared. It is not clear whether there is a single ideal duration of therapy, but it is also not clear whether treatment with any of these drugs is effective beyond five years of continuous use. Clinical trials

are currently testing different durations of use beyond five years.

Q: Can a woman go on tamoxifen or an alternate AI after five years?
A: After five years of continuous treatment with tamoxifen, a woman can go onto an AI for five more years if she is postmenopausal. The reverse approach has not been tested, nor have we tested switching from one AI to another.

Q: What does the research show about taking one drug versus switching to a different drug?
A: Overall, the studies show that including an AI for at least a portion of the initial five-year treatment period improves outcomes for postmenopausal women. It does not clearly prove that switching drugs is superior to an uninterrupted course of AI treatment for five years, nor does it address switching from one AI to another.

Q: Is there an optimal sequence of these drugs?
A: It is not clear that there is an optimal sequence, although many more studies have tested tamoxifen first followed by an AI than the reverse. One study that examined the impact of taking an AI followed by tamoxifen did not find any advantage compared to taking an AI alone for five years.

Q: What questions should women ask their doctors about hormone therapy for breast cancer?
A: The first and most important question is how a woman?s menopausal status has been established. To be confident that a woman with ovaries is menopausal and a candidate for an AI, the doctor should document that menses (periods) stopped naturally at least one year before starting either chemotherapy or hormone therapy for breast cancer. If chemotherapy caused a woman?s menses to stop, then she should be considered pre- or perimenopausal (the time when menstrual periods become irregular as a woman approaches menopause), and initial hormone therapy should include tamoxifen and not an AI. If an AI is suggested as initial therapy, it may be helpful to ask what the plan will be if a woman has intolerable side effects. Finally, it?s fair to ask which clinical trial your doctor is using to inform your treatment plan.

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More Information

What to Know: ASCO's Guideline on Hormonal Therapy for Hormone Receptor-Positive Breast Cancer [1]

Guide to Breast Cancer [2]

Clinical Trials [3]

Understanding Cancer Research Studies [4]

Links:
[1] http://www.cancer.net/node/29866
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