AU InforMed

Volume 14 Number 7 (Issue 286) *Monday, October 3, 2016*

Guest Editors: Alexandria Flowers, Gaige Gay, Lauren Johnson, Pharm.D. Candidates
Bernie Olin, Pharm.D.

Key Inforbits

- What is breast cancer?
- Early Diagnosis
- Recently FDA Approved Drugs

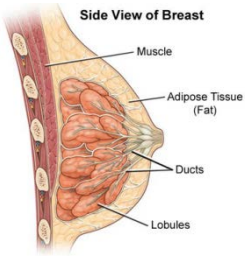
What is Breast Cancer?

Overview

Breast cancer is the leading cause of death for women between the ages of 20 and 59. Many believe that breast cancer only affects the female population, but just under 2,300 cases were male in 2013. Men also experience higher mortality rates after diagnosis. Breast cancer is defined as tumor cells that originate in the breast and more specifically in the ductal and lobular tissues. These can be further categorized into invasive (cancer invading through the basement membrane of the duct) and in situ (not invading the basement membrane) carcinomas.[1]

Presentation

Typically, a localized mass will be hard, solid irregular, solitary, unilateral, and immobile. Some atypical signs and symptoms can be skin edema, redness/warmth, and nipple discharge, retraction or dimpling. Signs of further metastasizing include: bone pain, difficulty breathing, abdominal enlargement, jaundice, and mental status change.[1-2]



John Hopkins Medicine[3]

Risk Factors

Breast cancer is associated with increasing age. Risk factors can be endocrine associated (early menarche before 12 years; late menopause after 55 years; nulliparity or late childbirth after 30 years; post-menopausal HRT), genetically associated (intraductal papillomatosis; ductal or lobular hyperplasia; dense breast tissue; history of ovarian or uterine cancer; personal or family history of breast cancer), or environmentally associated (women of Asian heritage; high dietary fat intake; intake of red meat or processed meat; phytoestrogens including soy, seeds, berries, nuts; increased post-menopausal body weight; alcohol consumption; and radiation to breast tissue before 20 years).[1-2]

Statistics

An estimated 246,660 women in the US will be newly diagnosed with invasive breast cancer in 2016, and close to 40,450 deaths will occur from the disease. For men there will be about 2,600 new cases of breast cancer and 440 deaths this year. Early detection is important because the sooner breast cancer is diagnosed the higher the chance of survival. Stage 0 breast cancer has a five-year survival rate of 93%, whereas stage IV breast cancer has only a 15% survival rate. Getting regular screenings is the best way to detect breast cancer early, and to decrease the risk of dying from breast cancer.[4]

Early Diagnosis

Mammography Screening Recommendations	
American Cancer Society[5]	**US Preventative Service Task Force[6]**
• Women 40-44 years of age have the option to begin annual screening • Women 45-54 years of age should be screened annually • Women 55 years and older should be screened every two years • Screenings should continue as long as the woman is in good health and has a life expectancy of ≥10 years	• Women 40-49 years of age have the option to begin screening every two years • Women 50-74 years of age should be screened every two years

Staging[3]

Stage 0	• Carcinoma in situ • Non-Invasive
Stage 1A	• Invasive tumor ≤20 mm AND • No lymph node involvement
Stage 1B	• No tumor to tumor ≤20 mm AND • Axillary lymph node involvement >0.2 mm to ≤2 mm
Stage IIA	• No tumor to tumor size of ≤50 mm AND • No lymph node involvement to 1-3 axillary node involvement
Stage IIB	• Tumor size >20 mm to >50 mm AND • No lymph node involvement to 1-3 axillary node involvement
Stage IIIA	• No tumor and 4-9 axillary lymph nodes involved OR • Invasive tumor is ≤20mm and cancer is in 4-9 lymph nodes OR • Invasive tumor is >20 to ≤50mm and cancer is in 4-9 lymph nodes OR • Cancer in internal mammary lymph nodes (no axillary node involvement) o Without axillary lymph node involvement
Stage IIIB	• Tumor of any size has invaded chest wall or skin and either: o No lymph node involvement OR o Cancer in 1-9 axillary lymph nodes OR o Cancer in internal mammary lymph nodes (no axillary involvement)
Stage IIIC	• Invasive tumor of any size AND • Involves 10 or more axillary nodes
Stage IV	• Invasive tumor of any size AND • Metastasized throughout the body

Recently FDA Approved Drugs

In general, treatment after diagnosis depends on the stage and whether the cancer is Hormone Receptor positive or negative, Human Epidermal growth factor Receptor 2 protein (HER2) - positive or –negative, or premenopausal or post-menopausal. Past landmark treatment has included drugs such as tamoxifen, aromatase inhibitors, anthracycline-based chemotherapy, and adjuvant taxane chemotherapy. Most of these medications are often first-line therapy, and their success has allowed for research that focuses in on specific patient populations. Two of the newest therapies are Kadcyla® (ado-trastuzumab emtansine) and Ibrance® (palbociclib).[7]

Kadcyla® (ado-trastuzumab emtansine): On February 22, 1013, the FDA approved Kadcyla® for use as a single agent to treat HER2-positive, metastatic breast cancer in patients who were previously treated with trastuzumab and a taxane. Kadcyla® is a Human Epidermal growth factor Receptor 2 protein (HER2) antibody drug conjugate that incorporates the HER2 targeted actions of trastuzumab with the microtubule inhibitor DM1, a maytansine derivative. Trastuzumab is a monoclonal antibody that binds to the extracellular domain of the HER2 protein and mediates antibody-dependent cellular cytotoxicity by inhibiting the proliferation of cells that overexpress the HER2 protein. Kadcyla® is available in 100mg and 160mg vials for IV administration and is dosed at 3.6 mg/kg every three weeks. Each 100 mg vial cost about $3,380, and each 160mg vial cost about $5,400. Because most patients will use about 2 vials, cost usually ranges from $6,700-10,800 every three weeks.[8-11]

Kadcyla® has four black box warnings, including hepatotoxicity risk, cardiotoxicity risk, pregnancy risk (embryo-fetal harm), and a "Do not interchange" warning that explains not to substitute this medication for trastuzumab alone. Concurrent use of a contraceptive is recommended in women of a childbearing age. Use is not recommended in patients with a cardiac disease, especially those with a left ventricular ejection fraction <50%. Additionally, left ventricular function must be evaluated prior to treatment. Hepatotoxicity usually manifests as asymptomatic increases in transaminases, and caution is advised in patients with increased transaminases or bilirubin.[9,10]

The most common (≥25%) adverse events observed in patients include fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, elevated transaminases, and constipation. Serious hepatobiliary disorders, including two fatal cases of severe drug-induced liver injury, have been reported in trials. Some other significant reactions include left ventricular dysfunction, interstitial lung disease, infusion site reactions, hypokalemia, and fever. A portion of Kadcyla® (DM1) is metabolized via CYP3A4 and CYP3A5 isozymes, and it should therefore not be taken with strong CYP3A4 inhibitors due to increased cytotoxicity. Additionally, it should not be taken with additional monoclonal antibodies in general, as this can increase the risk of toxicity and immunosuppression.[9-10, 12]

Ibrance® (palbociclib): On February 3, 2015, the FDA approved Ibrance® capsules to treat advanced (metastatic) breast cancer. Ibrance® works to inhibit cyclin-dependent kinases (CDKs) 4 and 6, which are responsible for promoting the growth of cancer cells. Ibrance® is approved for use in postmenopausal women with estrogen receptor (ER)-positive, HER2-negative advanced breast cancer. It is used with letrozole as initial (first-line) endocrine-based therapy, or it can be used in combination with fulvestrant for women with disease progression following endocrine therapy (second-line). Ibrance® is available in 75, 100, and 125mg capsules with a cost of $12,411 for a 28-day supply. Ibrance® is taken by mouth once daily for 21 days, followed by no medication for 7 days to complete one dose cycle.[13-16]

Warnings and precautions associated with Ibrance® use include bone marrow suppression, infection, thromboembolic events, and GI toxicity. Neutropenia, which can cause bone marrow suppression, was a common occurrence in clinical studies, and it is recommended that blood cell counts be monitored prior to initial therapy, at the beginning of each dosing cycle, and on day 14 of the first two dose cycles. Infection and thromboembolic risks are recommended to be monitored on a regular basis.[13,14]

Ibrance® is also extensively metabolized by CYP3A4, and this leads to significant drug interactions with CYP3A4 inhibitors/inducers. Additionally, avoid use with other agents that cause immunosuppression or myelosuppression. The long list of side effects with Ibrance® use include neutropenia, leukopenia, anemia, thrombocytopenia, upper respiratory infection, nausea, stomatitis, alopecia, asthenia, peripheral neuropathy, and epistaxis.[13-15]

References:

1. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, et al. NCCN Clinical Practice Guidelines in Oncology Version 1.2016. Breast Cancer. 2016 Jan, 22. Available from: www.nccn.org/patients
2. Barnett CM, Michaud LB, Esteva FJ. Breast Cancer. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiological approach. 9th ed. New York: McGraw – Hill Medical; c. 2014. Chapter 105.
3. John Hopkins Medicine [internet]. Maryland: John Hopkins Medicine. Mammography [cited 14 September 2016]; [about 4 screens]. Available from: http://www.hopkinsmedicine.org/healthlibrary/conditions/radiology/mammography_85,P01288/
4. Breast Cancer Facts and Statistics. Susan G. Komen For the Cure. Dallas, TX: Susan G. Komen for the Cure; 2016. [cited 2016 Sep 19]. Available from: http://ww5.komen.org/BreastCancer/AboutBreastCancer.html
5. Oeffinger KC, Fontham EH, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. JAMA [Internet]. 2015 Oct 20 [cited 2016 Sept 18];314(15):1599-1614. Available from: http://jama.jamanetwork.com/article.aspx?articleid=2463262
6. Final Recommendation Statement: Breast Cancer: Screening. U.S. Preventive Services Task Force [Internet]. February 2016 [cited 2016 Sept 18]. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-screening1
7. NIH: turning discovery into health [Internet]. Bethesda, MD: National Cancer Institute; c2016. Breast cancer treatment (PDQ®) – Health professional version; 2016 Aug 11 [cited 2016 Sep 25]; [about 100 screens]. Available from: https://www.cancer.gov/types/breast/hp/breast-treatment-pdq
8. NIH: turning discovery into health [Internet]. Bethesda, MD: National Cancer Institute; c2016. FDA approval for ado-trastuzumab emtansine; 2013 Feb 22 [cited 2016 Sep 18]; [about 4 screens]. Available from: https://www.cancer.gov/about-cancer/treatment/drugs/fda-ado-trastuzumab-emtansine
9. Ado-trastuzumab emtansine (Lexi-Drugs). In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Wolters Kluwer Health/Lexi-Comp, Inc. [updated 2016 Sep 1, cited 2016 Sep 18]. [about 10 p.]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4177902
10. Ado-trastuzumab emtansine. In: Drug Facts and Comparisons (Facts and Comparisons eAnswers) [AUHSOP Intranet]. St. Louis: Wolters Kluwer Health/Facts and Comparisons [updated 2016 May, cited 2016 Sep 18]. [2 p.]. Available from: http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp19032&quick=904454%7c5&search=904454%7c5&isstemmed=True&NDCmapping=-1&fromTop=true#firstMatch
11. Trastuzumab (Lexi-Drugs). In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Wolters Kluwer Health/Lexi-Comp, Inc. [updated 2016 Aug 19, cited 2016 Sep 18]. [about 10 p.]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7802
12. Kadcyla (ado-trastuzumab emtansine) for injection, for intravenous infusion [package insert]. South San Francisco, CA: Genentech, Inc. July 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf
13. NIH: turning discovery into health [Internet]. Bethesda, MD: National Cancer Institute; c2016. Palbociclib (Ibrance Capsules); 2015 Feb 5 [cited 2016 Sep 18]; [about 3 screens]. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm432871.htm
14. Palbociclib. In: Drug Facts and Comparisons (Facts and Comparisons eAnswers) [AUHSOP Intranet]. St. Louis: Wolters Kluwer Health/Facts and Comparisons [updated 2016 April, cited 2016 Sep 18]. [2 p.]. Available from: http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp19837&quick=909499%7c5&search=909499%7c5&isstemmed=True&NDCmapping=-1&fromTop=true#firstMatch
15. Palbociclib (Lexi-Drugs). In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Wolters Kluwer Health/Lexi-Comp, Inc. [updated 2016 Sep 1, cited 2016 Sep 18]. [about 8 p.]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/5526665
16. Ibrance® (palbociclib) capsules, for oral use [package insert]. New York, NY: Pfizer Labs, Inc. Feb 2016. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=2191

The last "dose" …

"If you quit, you lose. If you fight, you survive. Be a fighter, not a quitter."

– anonymous

An electronic bulletin of drug and health-related news highlights, a service of …
Auburn University, Harrison School of Pharmacy, Drug Information Center
• Phone 334-844-4400 • Fax 334-844-8366 • http://www.pharmacy.auburn.edu/dilrc/dilrc.htm
Bernie R. Olin, Pharm.D., Director
Archived issues are available at: http://pharmacy.auburn.edu/dilrc/au_informed.htm