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Case Review

Breast Cancer Awareness

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October is observed as the Breast Cancer Awareness Month all around the world. The National Breast Cancer Awareness Month (NBACM) was initiated in October 1985 by the American Cancer Society (ACS) and the anti-breast cancer drug generating pharmaceutic division of Imperial Chemical Industries (presently a part of Astra Zeneca). The main aim of this initiative was to campaign for mammography mediated detection of breast cancer. Today the program stands as an annual international campaign aiming to increase awareness and provide support. It is also instrumental in raising funds for research in the field of causes, prevention, early diagnosis, treatment, and cure of breast cancer. The major goal is increasing awareness among people, emphasizing on the importance of screening for early detection. This issue of Acta Scientific Cancer Biology includes special articles on the theme of "Awareness on Breast Cancer" along with other regular articles, to honor and reflect the specialty of this month.

Breast cancer stages and types

Breast cancer stages are determined by the TMN system overseen by the American Joint Committee on Cancer (AJCC), where 'T' denotes size of the tumor, 'N' denotes presence in the lymph nodes, and 'M' denotes the status of metastasis. In addition to these measures, AJCC has updated additional features including the tumor grade, estrogen receptor (ER), progesterone receptor (PR), HER2/neu status, oncotype DX scoring, menopausal status, general health of the patient, etc. This has led to assigning 5 stages: 0 to IV, for grading breast cancers. Stage 0 is the only non-invasive stage, while stages I to IV are invasive, showing presence of masses in adjacent tissues, and in distant metastatic locations. Stage I invades adjacent normal tissues. It can be subdivided into 2 categories: IA and IB. Stage II is categorized into IIA and IIB. Stage III is categorized into IIIA, IIIB and IIIC. Stage IV is the most advanced stage with metastatic features (Table 1).

Stage		Invasive property	Characteristic features
0		Non-invasive	Cancerous or non-cancerous abnormal cells are confined to the site of initiation without invading adjacent normal tissues.
I	IA	Invasive	Tumor is up to 2 cm but there is no lymph node involvement. Tumors are likely to be ER or PR positive, and microscopic evaluation may show minor invasion of adjacent tissues with about 1 mm sized masses.
	IB	Invasive	There are small groups of cancer cells measuring 0.2 – 2 mm in the lymph nodes with or without the presence of up to 2 cm tumor mass in the breast.
II	IIA	Invasive	Tumors measuring 2 – 5 cm, and/or >2 mm cancerous masses in 1 – 3 axillary lymph nodes or sentinel lymph nodes, and may be HER2 or PR positive.
	IIB	Invasive	Tumors measuring 2 – 5 cm, always associated with cancerous masses in the axillary or sentinel lymph nodes, or even tumors as large as 5 cm without lymph node presence.
III	IIIA	Invasive	May exhibit no breast tumors or tumors of any size (even >5 cm) with invasion to 4 – 9 axillary lymph nodes and/or sentinel lymph nodes (or 1 – 3 when tumor is >5 cm).
	IIIB	Invasive	Typically has the features of inflammatory breast cancer (IBC), where the breast tumor may be of any size, and may have spread to up to 9 axillary lymph nodes, or the sentinel lymph nodes, or the chest wall and/or skin of the breast, causing reddening or warmness of skin, inflammation, and/or ulceration.
	IIIC	Invasive	Tumor may be absent or of any size, and may have spread to 10 or more axillary lymph nodes, or the sentinel lymph nodes, or supraclavicular lymph nodes, or the chest wall and/or skin of the breast.
IV		Invasive	The cancer has spread beyond the breast tissue and nearby lymph nodes to distant lymph nodes and other organs like skin, bones, liver, lungs, brain, etc. (MBC).

Table 1: Classification of breast cancer stages with characteristic features.

When considering the types of breast cancer, they can be broadly categorized into 5 types: Ductal carcinoma in situ (DCIS), a non-invasive early stage with abnormal cells found in the lining of the milk ducts and can be designated as stage 0 breast cancer. Invasive or infiltrative ductal carcinoma (IDC), an invasive form where the abnormal cells spread from the milk ducts to other parts of the breast tissue or body. IDC accounts for about 70–80% of cases diagnosed. Triple negative breast cancer (TNBC) is negative for all 3 hormone receptors – ER, PR and HER2/neu and therefore is unresponsive to hormone therapy. Inflammatory breast cancer (IBC) is very aggressive exhibiting infiltration into skin and lymph nodes and is designated as stage III breast cancer. Metastatic breast cancer (MBC) is designated as stage IV with metastasis to other organs including lungs, liver, bones and brain. Some other rarer cases can be considered as other types including medullary breast carcinoma, a subtype of IDC which accounts for about 3–5% cases; tubular breast carcinoma, also a subtype of IDC which exhibits tubular structures microscopically, and accounts for about 2% cases; and mucinous or colloid breast carcinoma, also a subtype of IDC, accounting for about 1-2% cases with poorly defined cell structures and presence of mucin (a mucus product). Paget disease of the breast is very rare and in 97% cases is associated with DCIS or IBC.

Awareness and diagnosis

Creating awareness in masses is crucial in early detection, for proper diagnosis, to start early treatment.

Efforts for early detection in the US

Several collaborative and proactive efforts by multiple organizations like The American Cancer Society (ACS), The AstraZeneca Healthcare Foundation, The American College of Obstetricians and Gynecologists (ACOG), The American College of Radiology (ACR), The American Medical Women's Association (AMWA), CancerCare, Conquer Cancer Foundation (CCF), Susan G. Komen Foundation, Breast Cancer Research Foundation (BCRF), National Breast Cancer Foundation Inc. (NBCF), National Cancer Institute (NCI) of the National Institutes of Health (NIH), etc., has improved the overall rate of detection, and early diagnosis of breast cancer in the US. Other examples are the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) by the Centers for Disease Control and Prevention (CDC) which is an on-going program for over 2 decades to provide low cost screening and diagnostic services for breast and cervical cancer, including mammogram, clinical breast examination and pap smear test, among underprivileged and uninsured women across the US; free or low cost detection support (mammogram) provided by NCI and ACS. These efforts have revolutionized breast cancer treatment modalities and cure rates significantly over the last 2 decades in the US.

Methods for early detection

The 2 simplest methods of early detection are self-examination and regular screening.

Self-examination

This is the most effective method for early detection of changes in an individual's breast tissue. These include identifying changes in breast size and/or shape, nipple tenderness, lumps, skin thickening near breast or underarms, change in skin color and/or texture, redness, itchiness, inflammation, discharge, etc.

Regular screening

This is achievable by performing mammograms for maximum number of individuals on an annual basis, aged above 40 years. In developed countries and urban areas this can be achieved by incorporating mammograms during annual health check-ups, while in developing or under-developed nations and rural areas, low-cost health camps or schemes can be introduced based on the model systems mentioned in section 2.1.

Diagnostic methods and advances

The common methods of clinical diagnosis include mammogram, ultrasonography and MRI. Advanced technologies have enhanced the ease and access to identification of molecular characteristics of the tumor.

Mammogram

This is the most reliable and effective screening method using X-ray imaging for detection of dense mass of tumor or benign tissue. 2D and more advanced 3D images may be obtained during the process and can be compared to subsequent imaging.

Ultrasound and Magnetic Resonance Imaging (MRI)

These imaging tools are generally utilized if something abnormal is identified during mammography, as a follow-up. While ultrasound imaging (sonography) utilizes high-frequency sound waves, MRI uses radio waves in a magnetic field, to provide 3D images of the breast tissue.

Biopsy

This is a microscopic detection method where cells are removed from the breast tissue and examined/evaluated microscopically.

Molecular methods

These are beneficial in detecting specific biomarkers to provide more information for personalized treatment options. Some of the criteria that can be assessed include the hormone receptor status like the presence or absence of ER, PR and HER2/neu; oncogenic markers like BRCA1, BRCA2, PI3K, Akt, mTOR, NOTCH, etc.; tumor suppressors like p53, PTEN, etc.; microRNAs like miR21, miR10b, miR206, etc. Common techniques that are in use include immunohistochemistry (IHC), ligand binding assay (LBA) for ER and PR, fluorescence in-situ hybridization (FISH), quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and gene expression based arrays like Mammaprint, OncotypeDX, Theros H/I, MGI, etc., and more advanced Next Generation Sequencing (NGS) and Single-cell based screening techniques.

Treatment options

Treatment procedure is generally designed personally based on the tumor size, location, stage, type, molecular characteristics, age and condition of the patient, family history, etc. It is very important to understand that there is no best treatment option, instead the best strategy is combination therapy, where either surgery is combined with radiation and chemotherapy or hormonal or targeted therapy, or even several targeted agents can be used in combination to get the best outcome.

Surgery

This is the first option for early stage detection. This may include lumpectomy or mastectomy. In lumpectomy only the lump and minimal area of normal tissue around the rim of the lump is removed, while in mastectomy the entire breast is removed. Surgery is often followed by radiation or chemotherapy and radiation.

Radiation therapy

This treatment option is available for patients at all stages of breast cancer. It utilizes high energy radiation in the form of X-rays, protons or other particles. Radiation therapy may be used externally to expose the affected breast, or internally, where a radiation-delivering device is placed near the tumor site, post-surgery. Proton therapy is generally used for early stage locally advanced cases.

Chemotherapy

Chemotherapy regimen has to be determined based on certain conditions such as stage of the disease, size of tumor, genetic characteristics, health status and age of patient, prior treatments, etc. Accordingly, chemotherapy can be administered post-surgery and prior to radiation for early stage cases (adjuvant chemotherapy) or before surgery (neoadjuvant chemotherapy). This helps in minimizing recurrence and metastasis, and in shrinking larger tumors. The most common chemotherapeutic agents used for adjuvant and neoadjuvant chemotherapy are anthracyclines like Doxorubicin and Epirubicin, taxanes like Paclitaxel and Docetaxel, 5-fluorouracil, platinum-based Carboplatin, cyclophosphamide, etc. In addition to these agents, Cisplatin, Gemcitabine, Vinorelbine, Methotrexate, etc. are also used for advanced breast cancers.

Hormone treatment

The most common hormonal therapies include selective estrogen receptor (ER) modulators (SERMs) like Tamoxifen; the ER degrader Fulvestrant (Faslodex); and aromatase inhibitors like Anastrozole, Exemestane and Letrozole. These are effective in hormone receptor positive cases, but treatment often fails due to acquired resistance as a result of signaling crosstalks and bypass pathways.

Targeted molecular therapy

Targeted therapy is generally designed as recombinant antibodies against specific receptors or small molecules which act as antagonists or inhibitors. Examples of antibody-based agents are Trastuzumab and Pertuzumab, while Lapatinib and Palbociclib are examples of small molecule inhibitors. Trastuzumab (Herceptin), a monoclonal antibody against HER2/neu receptor was first approved by USFDA in 1998 for HER2 positive breast cancer patients. This is generally used alone or in combination with chemotherapy to treat early, late and metastatic stages of breast cancers. Pertuzumab (Perjeta) is another monoclonal antibody targeting HER2. Lapatinib (Tykerb), a dual tyrosine kinase inhibitor, targeting both HER2/neu and EGFR is used when metastatic cases become resistant to Trastuzumab and chemotherapy. PARP inhibitors like Olaparib (Lynparza) and Talazoparib (Talzenna) are effective in most breast cancer patients, as they harbor BRCA1/2 mutations showing impaired DNA damage repair ability. These are also effective in hormone non-responsive and hormone receptor negative (TNBC) patients. Some conjugated antibodies have also been effective, as for example, T-DM1 (Ado-trastuzumab emtansine or Kadcyla), where Trastuzumab is tagged to the microtubule inhibitor DM1. Another viable target in breast cancer are CDK4/6, and some inhibitors against these kinases are Palbociclib (Ibrance), Ribociclib (Kisqali), and Abemaciclib (Verzenio). mTOR inhibitors Everolimus and Temsolimus have shown promise in clinical tri-

als in combination with hormonal therapy. Since angiogenesis is a significant problem in controlling advanced breast cancer, anti-angiogenic agents have shown promise, as for example, anti-VEGF antibody Bevacizumab (Avastin).

Immunotherapy

Immunotherapy is the latest avenue of research in the field of breast cancer therapeutics. Although it has shown promising results in solid tumors like melanoma and lung cancer, the benefits in breast cancer are yet to be explored. Recently the USFDA has approved 2 agents: Atezolizumab (Tecentriq) for TNBC and PD-L1 positive breast cancer patients, and Pembrolizumab (Keytruda) for metastatic cancer that cannot be treated with surgery and harbor either high microsatellite instability or DNA mismatch repair deficiency.

Conclusion

Some of the most effective methods to combat breast cancer are increased awareness, so that women can perform self-examination. Similarly, very simple and adaptable changes in lifestyle like avoiding alcohol and smoking, maintaining a daily moderate exercise regime, and consuming low-fat, high-protein and green vegetable-rich diet are effective measures to reduce risk of incidence to a higher degree. Some factors that have been found to be associated with increased risk of breast cancer are early onset of menstruation (before 12 years of age), late menopause (after 55 years of age), no biological children or first childbirth at more than 30 years of age, etc. Family history accounts for about only 5–10% cases. Hence, it is important to start monitoring such individuals much earlier for any signs of disease onset. Another important aspect is to focus on counseling and support from physicians and social organizations, after diagnosis and/or treatment for betterment of quality of life.

Conflict of Interest

The author declares no conflict of interest.

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