Review article

Estrogen receptor, Progesterone receptor and Her-2/neu expression in breast cancer

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Abstract

Objectives : Now a day's estrogen receptors (ER), progesterone receptors (PR) and HER-2/neu are routinely evaluated in all breast cancer. Both hormone receptors are correlated with prolong disease-free survival and has increased response to endocrine therapy. Two different forms of estrogen receptor are α and ß, each encoded by a separate gene ESR1 (6q25.1) and ESR2 (14q23.2) respectively. ERα is found in endometrium, in breast cancer cells, in ovarian stromal cells and in the hypothalamus. Expression of ERß protein is found in kidney, brain, bone, heart, lungs, and intestinal mucosa, prostate and endothelial cells. Estrogen receptor bound to estradiol and to anticancer drug tamoxifen. Progesterone receptor (PR) is an intracellular steroid receptor which binds progesterone. PR is encoded by a single PGR gene on chromosome 11q22. Estrogen is necessary to induce activity to the progesterone receptors. HER-2/neu over expression is associated with increase disease recurrence, metastasis and shortens survival. HER-2/neu over expression has therapeutic implication in invasive breast cancer. Trastuzumab (Herceptin), a monoclonal antibody against the p185 protein has therapeutic efficacy in HER-2/neu over expressing tumours. HER-2/neu also known as Erb B2. HER-2 was named because it has a similar structure to human epidermal growth factor receptor or HER1. The oncogene neu is named because it was derived from a rodent glioblastoma cell line, which is a type of neural tumour. There is a wide variation of ER/PR and HER-2/neu expression in invasive breast carcinoma. In Sudan ER+, PR+ was 90% and 77.5% respectively on the other hand in Pakistan positive reactivity was ER(32.7%) and PR(25.3%). HER-2/neu over expression was found in India 46.3% and in Romania 37.3%. These immunohisto -chemical hormone receptor status and HER-2/neu reactivity should be routinely practiced in all laboratories, and this report should be supplied to the patient with the histopathological report of breast cancer which will reduce the patient's burden.

Key words : Estrogen receptors(ER), Progesterone receptors (PR), HER-2/neu, Immunohistochemistry (IHC).

Introduction

Analysis of estrogen receptor(ER) and progesterone receptor (PR) status has become the standard procedure for patient's care in breast cancer treatment. Particularly estrogen receptor(ER) content correlated more with prolonged disease-free survival rate and has increased response to endocrine therapy[1].

Biopsy specimen of breast cancer should be evaluated for hormone receptors status. If any of these two receptors are found, a response to hormonal therapy is expected. The more the estrogen or progesterone receptors present on those cells the more chance to result on effective hormonal therapy[2]. When a cancer shows few or no estrogen reactivity hormonal therapy is usually ineffective. But if there is progesterone receptor positive, hormonal therapy may sometimes be helpful. Women whose cancers are PR positive but ER negative has about a 10% chance of responding to hormonal therapy[2].

According to recently published guidelines, the estrogen receptor(ER) status and to lesser extent progesterone receptor status has been recommended as important prognostic and predictive markers for evaluation of breast cancer[3].

HER-2/neu over expression is associated with increase disease recurrence, metastasis and shortens survival. The over expression of HER-2/neu protein and amplification of the HER-2/neu gene is also associated with poor prognostic tumour characteristics such as high histological grade, high proliferative index, negative or lower ER expression and p53 mutation. HER-2/neu status along with ER/PR status are considered together to give any adjuvant systemic therapy[4].

HER-2/neu over expression has therapeutic implication in invasive breast cancer. Trastuzumab (Herceptin), a monoclonal antibody against the p185 protein has therapeutic efficacy in HER-2/neu over expressing tumours[5].

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Hormone receptors

A hormone receptor is a protein on the surface of a cell or in its interior that binds to a specific hormone. Estrogen receptor is activated by the hormone 17ß-estradiol (estrogen). Two different forms of estrogen receptor are α and ß, each encoded by a separate gene ESR1 (6q25.1) and ESR2 (14q23.2) respectively. ERα is found in endometrium, in breast cancer cells, in ovarian stromal cells and in the hypothalamus. Expression of ERß protein is found in kidney, brain, bone, heart, lungs, and intestinal mucosa, prostate and endothelial cells. Estrogen receptor bound to estradiol and to anticancer drug tamoxifen. Estrogen receptor over expression is found in about 70% of breast cancer cases, referred to as "ER positive". Two hypothesis are explained in the causation of tumorigenesis are, binding of estrogen to the ER stimulates proliferation of mammary cells, with resulting increase in cell division and DNA replication leading to mutation and estrogen metabolism produces genotoxic waste. Both of these processes cause disruption of cell cycle, apoptosis and DNA repair and therefore tumour formation6.Figure-1 shows intracellular localization of estrogen receptor, estrogen and helper protein. Figure 2 shows intracellular mechanism of action of tamoxifan[2].

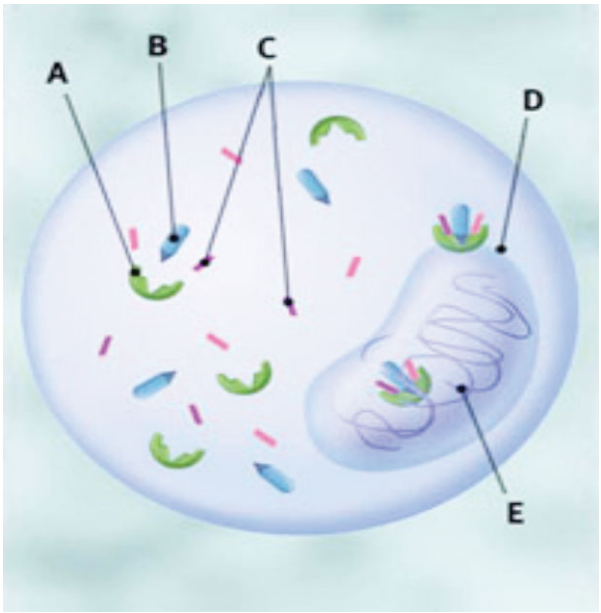

Figure-1 : Cell with estrogen receptors, estrogen, and helper proteins.

A : Estrogen receptor, B:Estrogen, C:Estrogen helper proteins, D:Nucleus E: DNA genetic material

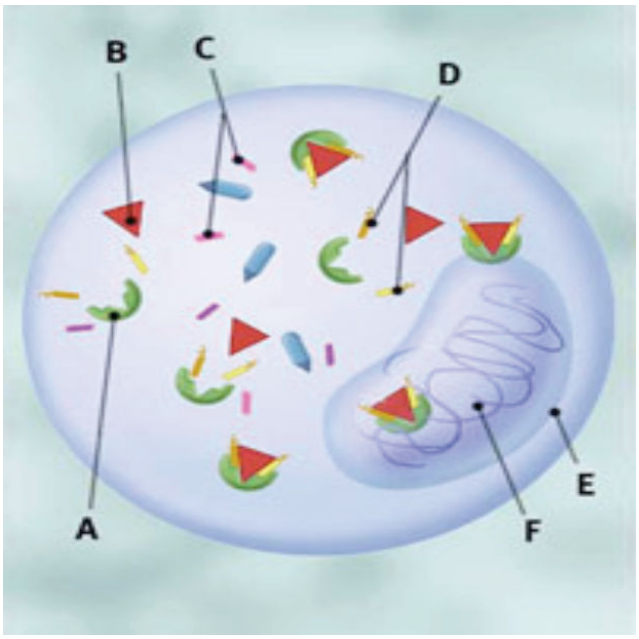

Figure-2 : Cell with estrogen receptors blocked by tamoxifen and helper proteins.

A : Estrogen receptor, B: Tamoxifen, C: Estrogen helper proteins, D: Tamoxifen helper proteins, E: Nucleus, F: DNA genetic material.

Progesterone receptor (PR) is an intracellular steroid receptor which binds progesterone. PR is encoded by a single PGR gene on chromosome 11q22. Estrogen is necessary to induce activity of the progesterone receptors. After progesterone binds to the receptor and restructure with dimerization, then this complex enters the nucleus and binds to DNA. These transcription resulting in formation of messenger RNA that is transmitted by ribosome to produce proteins[6].

HER-2/neu

HER-2/neu also known as ErbB2. HER-2 was named because it has a similar structure to human epidermal growth factor receptor or HER1. The oncogene neu is named because it was derived from a rodent glioblastoma cell line, which is a type of neural tumour. For this reason 'neu' is added to the name. ErbB2 was named for its similarity to ErbB (avian erythroblastosis oncogene B), the oncogene later code for EGFR. Gene cloning showed that neu, HER-2 and ErbB are the same. It is also designated as CD340 (cluster of differentiation 340) and p185. HER-2 is a

cell membrane surface-bound receptor tyrosine kinase and is normally involved in the signal transduction pathways leading to cell growth and differentiation. HER-2 gene is a proto-oncogene located at the long arm of chromosome 17(7q 21 -22)[7].

Approximately 15-20 % of breast cancers have amplification of the HER2/neu gene or over expression of its protein product. Over expression of this receptor in breast cancer is associated with increased disease recurrence and worse prognosis[7]. Figure 3(a) shows normal breast epithelium expressing HER-2/neu and figure 3 (b) shows HER-2/neu protein over expression and gene amplification in breast cancer[8].

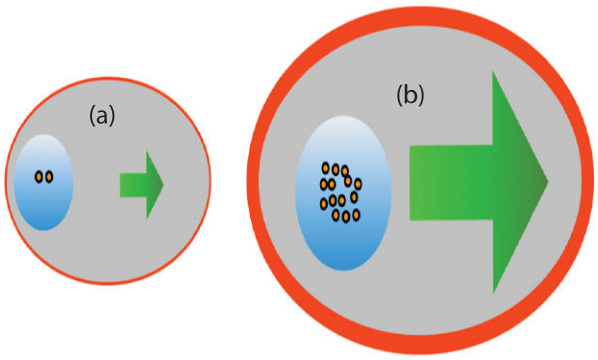

Figure-3 (a) and 3 (b): Relationship of HER2 DNA (orange dots), mRNA (green arrows), and protein levels (red peripheral band) in normal breast epithelium (left) compared with HER2-positive (over expression) breast cancer (right). Note that the vast majority of HER2-positive tumors show parallel marked increases of DNA, mRNA, and protein, but HER2 protein is present at low levels in normal breast epithelium.

Molecular classification of invasive ductal carcinoma (NOS)

Recently a new molecular classification of invasive ductal carcinoma (NOS) is given based on gene expression profiling, which measures the relative quantities of mRNA for every gene. These molecular classes correlate with prognosis and response to therapy, and thus have clinical importance. This molecular technique has identified five major patterns of gene expression: LuminalA, Luminal B, Normal breast-like, Basal-like, and HER2 positive[9].

Luminal A : This type constitutes 40% to 55% of NOS cancers. This largest group of cancers is estrogen receptor (ER) positive and HER2 /neu negative. These are generally slow growing and respond well to hormonal therapy and only a small number respond to standard chemotherapy.

Luminal B : This type constitutes 15% to 20% of NOS cancers. This group of cancers also expresses estrogen receptor (ER) but is generally higher grade, has a higher proliferative rate and often over expresses HER2/neu. They are sometimes referred to as triple-positive cancers, have lymph node metastases may respond to chemotherapy.

Normal breast-like : This type constitutes 6% to 10% of NOS cancers. This group is well-differentiated ER-positive and HER2 /neu negative cancers.

Basal-like : This type constitutes 13% to 25% of NOS cancers. These cancers are estrogen receptor (ER), progesterone receptor (PR) and HER2/neu negative. This is also known as triple-negative cancers. Many cancers arising in women with BRCA1 mutations are of this type. This cancer is generally high grade and have high proliferative rate. Theses cancers are associated with aggressive course, frequent metastasis to viscera and brain, and have a poor prognosis.

HER2/neu positive : This type constitutes 7% to 12% of NOS cancers. This group is ER-negative and HER2/neu positive cancers. These cancers are usually poorly differentiated, have a high proliferative rate and are associated with a high frequency of brain metastasis[9].

ER, PR & HER-2/neu status in invasive breast cancer in different country : Hormone receptor status and HER-2/neu reactivity are routinely practiced in breast cancer now a day in Western countries. Several works related to it have been performed by different investigators in different parts of the world. There is a wide variation of ER/PR and HER-2/neu expression in invasive breast carcinoma. In Sudan ER+, PR+ was 90% and 77.5% respectively on the other hand in Pakistan positive reactivity was ER (32.7%) and PR(25.3%). HER-2/neu over expression was found in India 46.3% and in Romania 37.3%. Both of these values are higher than the reference range. ER/PR and HER-2/neu expression variation in different countries are shown in table-I and table-II.

Table-I : ER/PR status in invasive breast cancer in different countries

Name of the institute	Investigator/year	Country	ER+	PR+	ER(+)/ PR(+)	ER(-)/ PR(-)
University of Miami/Jackson Memorial Hospital	Nadji et al 2005[1]	USA	75%	55%	55%	25%
Aga Khan University Hospital	Azizun-Nisa et al,2008[10]	Pakistan	32.7%	25.3%	-	-
University of Peradeniya Faculty of Medicine, Department of pathology	Ratnatunga & Liyanapathirana 2007[11]	Sri Lanka	53.2%	50%	44.5%	41.1%
Oncology Institute of Vojvodina, Sremska Kamenica	Ivkvic-Kapicl et al 2007[4]	Serbia	73%	66%	-	-
Khartoum teaching hospital	Ahmed et al 2007[12]	Sudan	90%	77.5%	-	-
Habib Bourguiba University Hospital, Sfax, Department of pathology.	Ayadi et al 2008[13]	Tunisia	59.4%	52.3%	-	-
Leuven University Hospital	Huang et al 2005[14]	Belgium	81.1%	64.2%	-	-
"Victor Babes" University of Medicine and Pharmacy, Timisoara.	Narita et al 2006[15]	Romania	82%	73.6%	-	-
Ninewells Hospital and Medical School, Dundee, Department of Surgery and Molecular oncology	Thompson et al 2010[16]	UK	79.6%	62.0%	-	-
ArminPathobiology Laboratory Tehran University	Farzami et al 2009[17]	Iran	62.4%	61.5%	-	-
National cancer institute surveillance, American cancer society	Grann et al 2005[18]	USA	-	-	63.53%	20.40%
Bangabandhu Sheikh Mujib MedicalUniversity (BSMMU)	Hossain et al 2014[19]	Bangladesh	74.71%	74.71%	57.47%	8.05 %

Table-II : HER-2/neu status in invasive breast cancer in different country.

Name of the institute	Investigator/year	Country	HER-2/neu over expression
Aga Khan University Hospital	Azizun-Nisa et al 2008[10]	Pakistan	24.7%
Memorial Sloon-Kettering Cancer Centre, New York	Lal et al 2005[20]	Newyork	Grade-II 10.7% Grade-III 27.84%
University of Peradeniya, Faculty of Medicine, Department of pathology	Ratnatunga & Liyanapathirana 2007[11]	Sri Lanka	14.6%
Armin Pathobiology Laboratory,Tehran University	Farzami et al 2009[17]	Iran	21.7%
Country hospital,Timisoara	Benohr et al 2005[21]	Germany	34.0%
Banaras Hindu University, Institute of Medical Sciences, Department of pathology and surgical oncology	Kumar et al 2007[22]	India	46.37%
Oncology Institute of Vojvodina, Sremska Kamenica	Ivkvic-Kapicl et al 2007[4]	Serbia	20 %
Habib Bourguiba University Hospital, Sfax, Department of pathology.	Ayadi et al 2008[13]	Tunisia	18.1%
Leuven University Hospital	Huang et al 2005[14]	Belgium	10.9%
"Victor Babes"University of Medicine and Pharmacy, Timisoara.	Narita et al 2006[15]	Romania	37.3%
Bangabandhu Sheikh Mujib Medical University (BSMMU)	Hossain et al 2014[19]	Bangladesh	32.18 %

Conclusion

Histopathological examinations of breast cancer are done in many laboratories in our country. But ER, PR and HER-2/neu are evaluated only in a limited number of laboratory. These immune-histochemical hormone receptor status and HER-2/neu reactivity should be routinely practiced in all laboratories, and this report should be supplied to the patient with the histopathological report of breast cancer which will reduce the patient's burden.

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