Targeting Tyrosine Kinase and Mammalian Target of Rapamycin inhibitors in the Treatment of Breast Cancer.

Essay
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Introduction

The American Cancer Society consider breast cancer the most commonly diagnosed type of cancer among women in 2009 .Breast cancer alone is expected to account for 27% of all new cancer cases among women**(Jemal A. et al.,2009).**

In Egypt, Breast cancer representing 18,9%of total cancer cases (35,1% in women among the Egypt national Cancer Institute (NCI) series of 10556 patients during the year 2001**(Elatar I.,2004).**

Breast cancer account for 25% of total cancer cases during 2009 in Ain Shams Cancer Institute.

Breast cancer is no longer considered a homogeneous disease. This has led to shift breast cancer treatment to targeted therapies **(Perou M. et al., 2000).**

Despite advances in early detection of breast cancer, adjuvant therapy of localized disease, and palliative therapy of metastatic disease, breast cancer remains a significant public health problem. Cytotoxic chemotherapy remains an important part of optimal therapy for patients in all stages of disease, but it is limited by toxicity, nonspecificity, and inevitable development of resistance **(Timothy J. et al., 2005).**

The question of whether to offer adjuvant chemotherapy to patients with early-stage breast cancer continues to challenge clinicians on a daily basis .These patients could be spared the trauma of receiving

chemotherapy, but more reliable prognostic markers are still needed to aid our therapy decision making **(Piccart-Gebhar M. et al.,2007).**

By understanding molecular profiling of tumors, the field of personalized medicine will expand and will lead to more effective treatment of cancer **(Chustecka Z., 2009)**.

"The Hallmarks of Cancer," provide a framework for approaching these novel therapies by targeting growth factor pathways, inhibiting angiogenesis, evading apoptosis, and targeting mTOR (mammalian target of rapamycin) **(Hanahan D. et al.,2000).**

Cell growth, metabolism, death, differentiation, movement, and invasion are all controlled by intracellular signaling pathways. These pathways are initiated by ligands binding to, and activating, their receptors **(Sara A. , 2008).**

Tyrosine kinase family (ErbB1/EGFR, ErbB2/Her2, ErbB3, and ErbB4), which regulates cell growth and differentiation **(Burgess W. et al.,2003).**

HER signaling pathways are extremely complex, they can be targeted using several different strategies.Ligands that bind to HER receptors, the extracellular ligand-binding domain of a HER family receptor, the intracellular tyrosine kinase domain of the receptor, and downstream molecular signals can all be targeted**(Sliwkowski X. et al.,2004).**

Binding of soluble epidermal growth factor ligands to their cognate ErbB receptor induces homodimerization or heterodimerization of ErbB2 and autophosphorylation downstream growth and survival signaling networks **(Hynes E. et al.,2005)**.

Trastuzumab and lapatinib are effective in patients with breast cancer that overexpresses ErbB-2. The anti-vascular endothelial growth factor-A mAb bevacizumab is approved for treatment of patients with metastatic breast cancer. In addition, preclinical data suggest that signaling inhibitors can prevent or overcome resistance to endocrine therapy in estrogen receptor positive breast cancer (**Normanno N. et al.,2009).**

Targeting the epidermal growth-factor receptor (EGFR) family is a main strategy for drug development in the treatment of metastatic breast cancer. One approach is to inhibit the cross-talk among different EGFRs by inhibiting multiple receptors at once **(Kellie J. et al.,2009).**

A tumor cell's survival is determined not only by the rate of proliferation but also by the rate of cell death. Apoptosis is a physiologic response of normal cells to stressors. The success of cancer cells, in part, is attributed to acquired resistance to apoptosis (**Campbell E.et al.,2004).**

One strategy includes alteration of the phosphoinositide 3- kinase (PI3K)/AKT signaling pathway which is involved in mediating cell growth and proliferation.

Signaling through this pathway regulates the serine-threonine kinase (mTOR) which is important for regulation of the cell cycle **(Chow Y. et al., 2007).**

(mTOR) inhibitor, inhibiting transduction of prolifrative and survival signals. Rapamycin causes a well-documented arrest of the cell cycle in G1 phase in many cancer cell lines including cancer breast **(Leung B. and Hye Choi J., 2007)**.

Based on the clinical and preclinical data, inhibitors of mTOR are promising candidates for breast cancer therapy and should be studied in combination with HER inhibitors as well as endocrine therapy, based on cross-talk between the ER pathway and the PI3K/Akt/mTOR pathway **(Baselga J. et al, 2004).**

(mTOR) pathway is involved in the development of tumor resistance to endocrine therapy in breast cancer cell lines and represents an attractive target for pharmacologic intervention **(Generali D. et al.,2008).**

Aim of the work

The aim of this study is to review the different tyrosine kinase inhibitors and m TOR inhibitors; their mechanism of action and their evolving role as targeted therapy in the treatment of breast cancer.

Molecular Biology of Breast Cancer

Invasive breast cancers are heterogeneous group of tumors that show a wide variation as regard their clinical presentation, behavior, and morphological spectrum. At least 18 different histological breast cancer types (ie pathological entities) are described by the World Health Organization (WHO) **figure (1) (Tavassoli F. et al., 2003) .**

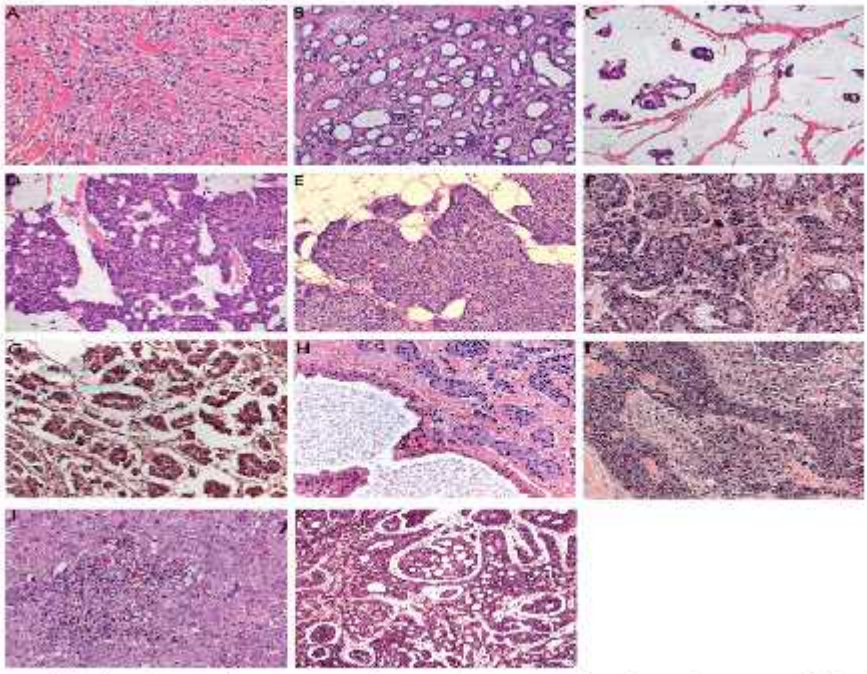

Fig 1. Histology of invasive breast carcinomas. Representative micrographs of special type breast cancers: (A) invasive lobular carcinoma, (B) tubular, (C) mucinous A, (D) mucinous B, (E) IDC with osteoclastic giang cells, (G) micropapilliary, (H) apocrine, (I) metaplastic, (J) medullary, and (K) adenoid cystic carcinoma**(Weigelt B et al,2008)**

Current classification systems are descriptive, based on morphological entities that have been shown to have prognostic implications, **Table(1).**

Table (1): frequency and outcome of histological types of invasive breast carcinoma**(Weigelt B et al,2008)**

Histological type of invasive breast carcinoma	Frequency	10-year overall survival rate
Invasive ductal carcinoma not otherwise specified (IDC NOS)	50-80%	35-50%
Invasive lobular carcinoma (ILC)	5-15%	35-50%
Adenoid cystic carcinoma	0.1%	90-100%
Apocrine carcinoma	0.3-4%	Like IDC NOS
IDC with osteoclastic giant cells	Unknown	Like IDC NOS
Medullary carcinoma	1-7%	50-90%
Metaplastic carcinoma	<5%	Unknown
Micropapillary carcinoma	<3%	Unknown
Mucinous carcinoma	<5%	80-100%
Neuroendocrine carcinoma	2-5%	Unknown
Tubular carcinoma	1-6%	90-100%

For the success of targeted therapies and individualised medicine. Anew classification system is required **(TomasC. et al,2010).**

Refinement of breast cancer classification by

1. Molecular characterization of histological special types:

Results of the Kruskal – Wallis test revealed comprehensive characterization of a series of 11 different histological special-type breast carcinomas by immunohistochemistry and gene expressieon profiling in an

attempt to refine breast cancer classification and improve patient stratification shown in **Table(2). (Tavassoli F. et al.,2003)**

Table 2. Results of the Kruskal – Wallis test : refinement of breast cancer by IHC**(Weigelt B et al,2008)**

	Histological Subtype										
Antibody	Apocrine	Mucinous A	Mucinous B	Neuroendocrine	IDC Grad	Microcap	Apocrine	Medullary	Metaplastic	ILC	Tubula
ER	42	71	81	81	81	81	29	23	23	67	68
E-cadherin	59	69	96	69	69	63	69	69	65	17	68
CK 19	54	74	57	69	54	74	27	33	24	70	69
CD117	47	47	47	47	47	47	100	01	72	47	47
AR	67	65	81	67	47	63	29	28	29	68	67
EMA	50	43	61	47	82	104	12	82	31	63	63
CK 8/18	66	60	66	66	66	66	33	33	35	65	66
PR	34	72	62	64	96	64	34	34	34	63	63
Vimentin	45	55	45	56	45	45	69	74	78	45	45
S100	36	54	36	36	36	36	70	68	74	62	61
Synaptophysin	51	62	86	69	51	51	51	51	51	53	51
GCDFP-15	36	34	86	53	34	40	34	34	34	36	52
CK 14	67	69	48	48	48	48	78	84	78	62	48
CK 5/6	52	48	43	43	54	64	85	82	65	53	43
P63	51	56	51	51	51	51	61	62	69	51	51
Chromogranin	55	55	67	61	55	55	55	56	55	55	55
CEA	66	69	53	66	70	67	47	47	48	53	53
CDX6	47	52	53	59	47	47	47	83	66	51	59
P53	70	45	46	53	71	68	59	47	56	68	53
EGFR	54	55	55	55	55	55	55	60	62	55	55
CD10	51	52	56	52	52	52	52	57	62	50	52
HER2	52	50	50	53	53	53	53	53	53	53	53

- The immunohistochemical staining patterns and gene expression profiles of the ER-positive tumors :apocrine,mucinous,neuroendocrine,micropapillary and invasive ductal carcinoma with osteoclastic gaint cell tumors were highly similar. Gene networks of invasion and proliferation to be down-regulated in these carcinomas, which may explain the low incidence of metastasis in such patients **(Schnitt S. and Guidi A., 2004).**