Targeted Therapy in Breast Cancer

Essay

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BY

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KEY WORDS AND ABSTRACT

Key words:
Breast cancer, targeted therapy, human epidermal growth factor, angiogenesis, PI3K\AKT pathway.

Abstract:
Targeted therapy for breast cancer is a reality at this time, and several new agents hold promise for expanding and refining the pool of patients likely to further benefit from this approach in the near future.

The ongoing significant improvements in understanding of the altered molecular events in cancer cells in general and breast cancer cells specifically, have led to an explosion of new targets and agents for clinical testing.

LIST OF ABBREVIATION

AC	Adriamycin, cyclophosphamide
ADCC	Antibody dependent cell mediated cytotoxicity
ALLTO	Adjuvant Lapatinib and/or Trastuzumab Treatmen Optimization
AML	Acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AVADO	Avastin and Docetaxel
17-AAG	17-allylamino-17-demethoxygeldanamycin geldanamycin
BC	Breast cancer
BETH	Bevacizumab and Trastuzumab Adjuvant Therapy in HER2-positive BC
BCIRG	Breast cancer International Research Group
b FGF	Basic fibroblast growth factor
CALGB	Cancer And Leukaemia Group B
CHF	Congestive heart failure
CISH	Chromogenic in situ hybridization
CML	Chronic myeloid leukemia
CMF	Cyclophosphamide, methotrexate, 5-florouracil
CNS	Central nervous system
CR	Complete response
CRC	Colorectal carcinoma
CREC	Cardiac Review and Evaluation Committee
DFS	Disease free survival
DLT	Dose limiting toxicity
EBCTCG	Early Breast Cancer Titlist Collaborative Group
EC	Endothelial cell
ECD	Extra cellular domain
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked Immuonosorbent Assay
ER	Estrogen receptor
FAC	5-Florluracil, adriamycin, cyclophosphamide
FC	Fragment crystallizable
FDA	Food and Drug Adminstration
FISH	Fluorescence in situ hybridization
FTI	Farnesyl transferae inhibitors
GIST	Gastrointestinal stromal tumors
HDAC	Histone deacetylase
HER	Human epidermal growth factor
HERA	Herceptin Adjuvant.
HsP	Heat shock protein
IBC	Inflammatory breast cancer
IGF-1	Insulin-like growth factor-1
LVEF	Left venricular ejection fraction
MoAb	Monoclonal antibody

MAPK	Mitogen-activated protein kinase
MBC	Metastatic breast cancer
MEK	Mitogen extracellular signal kinase
MPP	Matrix metalloproteinase
MVD	Microvessel density
m TOR	Mammalian target of rapamycin
NCCTG	North Central Cancer Treatment Group
NeoALTTO	Neoadjuvant Adjuvant Lapatinib and/or Trastuzumab Treatmen Optimization
NK	Natural killer
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PDGF	Platelet-derived growth factor
PIKK	Phosphoinositol kinase-related kinase
PI3K	Phosphatidylinositol 3-kinase
PI3K CA	Phosphatidylinositol 3-kinase catalytic subunit
PIP	Phosphatidylinositol-bis-phosphate
PLGF	Placenta growth factor
PgR	Progestrone receptor
PR	Partial response
ORR	Overall response rate
OS	Overall survival
RFS	Relapse free survival
RCC	Renal cell carcinoma
RR	Response rate
SABCS	San Antonio Breast Cancer Symposium
SD	Stable disease
SERM	Selective estrogen receptor modulator
TBP	Trastuzumab Beyond Progression
TEACH	Tykerb Evaluation After Chemotherapy
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
TGF	Transforming growth factor
TOPO-11	Topoisomeras-11
TTP	Time to disease progression
VEGF	Vasculoendothelial growth factor

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الملخص العربي

لقد أحدث العلاج الموجه للأورام السرطانية تغييراً كبيراً في السنوات الأخيرة ، على سبيل المثال لا الحصر عقار (ايماتنيب) وعقار (تراستوزوماب) اللذان أثبتا فعالية كبيرة في علاج أمراض الدم السرطانية وسرطان الثدي .

من أهم العوامل التي أدت إلى ذلك النجاح الكبير للعلاج الموجه هو التطور الذي حدث في العلوم البيولوجية والجزيئية التي بدورها تؤدي لحدوث الأورام . هناك العديد من العقاقير الحديثة تحن التجارب في المراحل الأخيرة . لذلك يحتاج ذلك إلى تكثيف الجهود والأبحاث وتجربة تلك العقاقير مصاحبة للأنواع الأخرى من العلاج الكيميائي والهرموني .

يهدف هذا العمل إلى التعرف إلى الأنواع المختلفة من العلاج الموجه المستخدم في أورام الثدي من حيث الفعالية والفائدة الإكلينيكية والمضاعفات والتأثير على مستقبل المرض.

Introduction and aim of work

Breast cancer is the most common female cancer in the world accounting for 32% of all female cancer. It is estimated that 180,000 American women will be diagnosed with breast cancer (BC) in the year 2007, with approximately 40,910 women expected to die from the disease (**Jemal et al, 2007).** Among Egyptian females BC is also the most common cancer, accounting for 35.7% of all female cancers, (**Garbia 2007).**

Early diagnosis and advances in systemic therapy have reduced BC mortality by 30% **(Baunm, 2005).** However, about 10% of newly diagnosed BC patients have locally advanced and/or metastatic disease **(Greenberg et al**, **2005).**

Treatment of BC includes surgical resection of the primary tumor, which remains the basis for cure of early BC. Adjuvant radiotherapy is given according to the tumor risk to help prevent local recurrence.

Systemic therapy, including chemotherapy and/or hormonal therapy, is an important part of successful treatment for patients in all stages of the disease, either in the neoadjuvant, adjuvant or metastatic setting. Without adjuvant therapy, up to 50% of patients with early BC and 80% of patients with advanced BC will develop metastasis and die (**Baunm, 2005).**

Hormonal therapy has been the most specific targeted therapy for BC for decades. In the adjuvant setting 5 years of tamoxifen reduces the risk of recurrent BC and improve survival for both premenopausal and potmenopausal patients with estrogen receptor (ER) positive BC. In the metastatic setting, objective responses range from 25% to 50%, and additional patients benefit with prolonged stability of disease **(Nabholtz et al, 2001).** Aromatase inhibitors have expanded the adjuvant endocrine treatment options for postmenopausal women with hormone-receptor positive BC and were

shown to be superior to tamoxifen in improving the disease-free survival (DFS) in several large, randomised controlled clinical trials (**Dixon, 2008)**.

Combination chemotherapy remains an important part in optimal therapy, anthracycline containing regimen has replaced cyclophosphamide, methotrexate, and 5-florouracil (CMF) as standard adjuvant therapy. From the Early Breast Cancer Trialist's Collaborative Group (EBCTCG) meta-analysis, it was shown that, anthracyclines provided an extra advantage in survival than CMF, especially in women younger than 50 years **(Bonneterr et al, 2005).**

Taxanes have emerged as powerful compounds in BC in several adjuvant clinical trials. The addition of taxanes was shown to improve the DFS and overall survival (OS) of patients with node positive breast cancer. **(Henderson et al, 2003),** however therapy of metastatic disease is still palliative with a very low probability to induce complete remission and definitive cure of disease.

Despite the important role of chemotheray, it is limited by toxicity, nonspecificity, and inevitable development of resistance. Cytotoxic therapy has not been considered a "targeted" therapy since many of its specific targets have not been identified, it is evident that to be effective against cancer, it has to target cellular pathways involved in growth regulation.

The relevant efforts of basic research to identify the key and selective molecular alterations, which sustain BC growth and progression allowed the possibility to develop specific molecular target treatments. The outcome of BC have improved dramatically in recent years with the advent of targeted therapy alone or combined with chemotherapy.

Trastuzumab has revolutionized BC treatment outcome, reducing the risk of recurrence and significantly increasing survival, at least for a subgroup of patients (**Hortobagyi, 2005).**

Other targeted therapies have been approved for BC treatment, and other have been developed in phase II and III clinical trials showing promising activity.

Aim of work

This work aims to focus on the role of molecular targeted therapy in the treatment of breast cancer, provide overview of the molecular pathways involved in BC development, and the selected targeted agents for each pathway, in addition to identification of several new agents that hold promise in the near future.