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Treatment of Breast Cancer: New Approaches

Nadeem Sheikh*, Saba Shehzadi and Arfa Batool
Department of Zoology, University of the Punjab, Q-A campus, Lahore
Pakistan

1. Introduction

Breast cancer is the most common type of malignancy in the world and is also one of the major reasons of mortality among women worldwide. It exhibits a vast variety of pathological features and clinical signs and said to be a heterogeneous disease (Jemal *et al.*, 2009). It is also among the most studied cancers, but the biology of it is still not well understood (Fang *et al.*, 2011). Genetics, inheritance, aging are major risk factors for breast cancer, while hormonal factors, obesity (imitating in diet and exercise), and alcohol use presenting more diffident risk. Breast cancer mortality has been found to be decreasing gradually since 1990s, after the improvement of breast cancer screening techniques and the advancement of treatment approaches (Jatoi and Miller, 2003; and Tabar *et al.*, 2003).

1.1 Incidence of breast cancer in Pakistan

In Pakistan, breast cancer has maximum prevalence of all types of cancer, with frequencies similar to Western population. It affects mostly young women (45 or above) in Pakistan with a high frequency as compared to Caucasian women (Kakarala *et al.*, 2010), often presenting in advanced stage (Malik, 2002). The low socio-economic status and reproductive issues such as low parity and late first pregnancy may be responsible for higher incidence of breast cancer in Pakistan. It is described that patients with lower socio-economic status (SES) had larger, more aggressive tumors with worsened survival outcomes (Aziz *et al.*, 2010). The mutations of *BRCA1* and *BRCA2* genes are also considered as responsible factors for the greater numbers of breast cancer in Pakistan. As Pakistan has the maximum number of consanguineous marriages in the world (Hashmi, 1997), the transfer of these mutations after such marriages is supposed to be a vital factor in raising breast cancer cases in Pakistan (Shami *et al.*, 1991). The inheritance of recessive genes has been reported to increase the breast cancer risk in Pakistan (Liede *et al.*, 2002). But the exact reasons for high incidence of breast cancer in Pakistan are still to be detected.

All these risks put an emphasis on the development of better treatment strategies for breast cancer. Early finding of diseased condition, improvements in scientific methodologies and quality of care, with sufficient economic guidelines, need to be developed for countries with limited resources like Pakistan (Aziz *et al.*, 2008).

* Corresponding Author

2. Biological explanation of breast cancer

Breast cancer usually arises after menopause (age: 40+), but it can also arise before menopause in very rare cases. The ovarian-pituitary axis synchronizes the normal breast physiology during the reproductive cycle. The biological reason for it is that the glandular component of the breast gradually degenerates after menopause and the breast is mostly substituted by adipose tissue. Any problem in this process causes the development of breast cancer, whereas by epithelial cells of the breast ducts, uncontrolled growth and survival takes place, and in later stages the characteristics of neo-angiogenesis, invasion and metastasis occurs (Heldermon and Ellis, 2006).

3. Treatment and prevention

Breast cancer prevention is primarily made by pharmacoprevention using fenretinide and tamoxifen. The regular use of screening techniques for early detection of breast cancer is the best strategy to decrease death rates (Veronesi and Boyle, 1993). Better treatments include targeted chemotherapy, endocrine therapy, radiotherapy and surgery, inhibitors of certain proteins and more recently immune therapy (monoclonal antibodies) and miRNA therapy. Advancement in life style may also be a good treatment for breast cancer. Breast cancer threat may be reduced by physical activities or exercise (Eliassen *et al.,* 2010).

Many targeted genetic and molecular agents have been developed for efficient treatment of breast cancer, by keeping in view certain biomolecular characteristics of breast cancer, such as mutations of breast cancer susceptibility gene type 1, 2 (BRCA1/BRCA2) (Chen and Parmigiani, 2007), abnormal activation of human epidermal growth factor receptors (EFGR) (Wang and greene, 2007), overexpression of human epidermal growth factor receptor-2 (HER-2) (Ross *et al.,* 2003), and activation of vascular endothelial growth factor (VEGF) receptor (Bhinder and Ramaswamy, 2010). It is reported that more than half of the breast cancer cases are due to errors in hormone receptor proteins. For this reason, the primary concern of today's research is endocrine therapy. The development of targeting molecular agents is also among major goals of current research for efficient treatment of advanced breast cancer.

The major obstacles in treatment of breast cancer are resistance to therapeutic agents (Serrano-Olvera *et al.,* 2006). Women with breast cancer treatment and surgery have complaints of tension and depression. By using different treatment strategies including mastectomy, adjuvant chemotherapy, many women have shown incidence of nervousness and depression associated with cancer that puts unpleasant effects on the life status and emotional working.

3.1 Chemotherapy

Chemotherapy is the most primitive method for treating breast cancer, if employed immediately after surgery, termed as adjuvant chemotherapy (AC), and administered before surgery, neoadjuvant chemotherapy (NAC) (Alvarado-Cabrero *et al.,* 2009). Chemotherapy is recommended for all women with invasive cancer greater than 1 centimeter (Ganz *et al.,* 2011). Adjuvant chemotherapy is associated with significantly more severe physical symptoms, including musculo-skeletal pain, vaginal and weight problems and nausea (Ganz *et al.,* 2011).

3.1.1 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy (NAC) has been a common approach for the management and treatment of locally advanced breast cancer (LABC). It is applied very effectively for treatment of patients with LABC before breast and axillary lymph node resection (Pusztai, 2008). The NAC is aimed to reduce tumor size subsequently aiding mastectomy and radiotherapy (Cleator *et al.,* 2002; and Pusztai, 2008). NAC is better treatment option because it averts adverse physiological reactions (Alvarado-Cabrero *et al.,* 2009).

Patients of LABC had showed complete clinical and pathological response to NAC, while those with pure micropapillary carcinoma (PMC) gave incomplete response (Alvarado-Cabrero *et al.,* 2009). Patient's therapy effect can be predicted by clinical & pathological responses (Jones *et al.,* 2006), and by biomarker levels in the patients, which have better prognostic influence in contrast to pathological and clinical response, multi-biomarker levels have showed better expressive power for treatment outcome as compared with single biomarker level (Nolen *et al.,* 2008).

Paclitaxel is a chemical agent applied before radiotherapy and surgery. It binds to tubulin resulting in cell cycle arrest at M-phase which enhances radiation sensitivity. In a report, Patients having 3 cycles of paclitaxel followed by simultaneous radiotherapy before specific surgery, showed better results as compared those without paclitaxel (Chakravarthy *et al.,* 2000). The most common approach for treating LABC in developed countries consists of NAC with anthracyclines and taxanes followed by surgery and radiation therapy (Osako *et al.,* 2007). HR-positive tumors are less chemosensitive so an anthracyline based NAC is developed without hormonal treatment to evaluate estrogen receptor (ER) and progesterone receptor (PgR) semi-quantitative expression in patients with HR-positive tumors (Petit *et al.,* 2010). Preoperative and postoperative marker studies in NAC might facilitate tumor analysis and to observe possible change in status respectively (Piper *et al.,* 2004).

3.2 Endocrine therapy

An understanding of the mechanism of action, pharmacology and clinical indications for various classes of endocrine agent is critical for the management of breast cancer (Heldermon and Ellis, 2006). Breast cancer is divided into three major molecular types which are diagnosed by routine histopathological tests: (i) hormone receptor-positive (ER/PR+), (ii) human epidermal growth factor receptor type 2 enriched (HER2+) and (iii) triple negative (ER-, PR-, HER2-) breast cancer (TNBC). HR+ breast cancers comprise about 60–70% of all the clinically positive breast cancers, while the other two types equally accounts for the remaining 30–40% of all breast cancer cases (Slamon *et al.,* 1989). Endocrine therapy has been used before surgery but Dittmer *et al.,* (2011) reported adjuvant endocrine therapy not so effective for breast tumor treatment because of its side effects (Dittmer *et al.,* 2011).

3.2.1 HER2+ breast cancer and targeted therapy

The HER2 overexpression due to gene amplification or transcriptional deregulation (Slamon *et* al., 1989) presents a poorer prognosis, with development of resistance to many chemotherapeutic and hormonal agents, and a rise in tendency of metastasis to brain (Serrano-Olvera *et al.,* 2006).

3.2.2 Monoclonal antibodies for endocrine therapy

The basic purpose of current therapeutic policies is to make overexpressed HER2 silent with certain targeted complexes e.g., trastuzumab, a monoclonal antibody prepared for humans against HER2 protein, reported to be a well accepted therapy for women with MBC (Vogel *et al.,* 2002). This antibody specifically hinders the HER2-mediated activation of intracellular kinases and other molecules (Valabrega *et al.,* 2007). The combination of chemotherapy and trastuzumab extends the life of patient in adjuvant and metastatic patterns, but most women with HER2+ metastatic tumor become resistant to trastuzumab; about 15–25% of women detected with early HER2+ disease have trastuzumab-resistant tumors (Bedard *et al.,* 2009).

The combinations of anti-HER2 agents should close to abolish acquired drug resistance, shorten the period of therapy, and potentially dole out with the need of coexisting chemotherapy, because the anti-HER2 therapies including drugs trastuzumab and lapatinib, targeted against the HER2 signaling network has gradually changed the natural history of early and metastatic HER2-overexpressing breast cancer (Abramason and Artega, 2011).

3.2.3 HR+ breast cancer and targeted therapy

Estrogen is a well-characterized growth factor in about 60–70% of breast cancer patients (Clemons and Goss, 2001). The malignant epithelial cells depend on reproductive hormones, specifically estrogen in ER+ tumors (Heldermon and Ellis, 2006). The initial endocrine therapy of breast cancer was removal of the ovaries (oophorectomy) (Taylor *et al.,* 1998). Many thriving remedies have been formulated to decrease or eradicate circulating estrogen or to obstruct its communication with genomic target objects. The specific ER antagonist tamoxifen is recommended as adjuvant endocrine therapy for the hormone receptor positive early breast cancer (Sehdev *et al.,* 2009). Endocrine therapies for ER+ patients include three types of agents that (i) directly target ER through molecules that bind ER and change ER function; (ii) estrogen deprivation through aromatase inhibition or ovarian suppression; and (iii) sex steroid therapies, including estrogen, progestins and androgens.

3.2.4 Selective Estrogen Receptor Modulators (SERM)

The rise of estrogen level in blood proposed the use of a therapeutic modulator to oestrogen, a selective oestrogen receptor modulator, or SERM (Jordan, 1999). The evidences from breast cancer treatment trials presented the ability of the first SERM, tamoxifen, to avoid tumors in the contralateral breast of women receiving adjuvant therapy (Ragaz and Coldman, 1998). Tamoxifen considerably lessens the rate of treatment failure in breast cancer patients, with lesser frequency of clinically obvious toxic effects. For tamoxifen, response rates range from 16 to 56%, and an improved toxicity profile than alternative therapies, for example large dosage of estrogen or adrenalectomy results in quick acceptance of tamoxifen as a selective cure for advanced disease (Muss *et al.,* 1994). The combination of ovarian suppression and tamoxifen is referred to as the first line therapy for HR+ advanced breast cancer in pre-menopausal women. Some examples of SERM comprise raloxifene and toremifine (Holli *et al.,* 2000; and Martino *et al.,* 2004).

3.2.5 Tyrosine kinase inhibitors

Lapatinib is an oral, selective, reversible small-molecule dual tyrosine kinase inhibitor of both the ErbB1 and ErbB2 signaling pathway that works by inhibiting growth and guiding to cell arrest and apoptosis. It is presented to be effective against HER-2+, LABC and metastatic breast cancer (MBC). The primary activity of lapatinib in breast cancer patients is mediated through HER-2 inhibition. In addition, lapatinib treatment inhibits the growth of ErbB2-overexpressing human breast cancer cells that showed resistance to trastuzumab. Clinically related antitumor activity has not been reported when lapatinib is used in the mixed population of LABC patients with distinct HER-2 negative or HER-2 untested tumors (Leo *et al.,* 2008). Patients with HER-2 negative or HER-2 untested MBC had not showed any advantage from lapatinib therapy. However, the first-line therapy with paclitaxel and lapatinib in combination expressed improved clinical outcomes in HER-2+ patients. Future assessment of the effectiveness and safety of this combination is constant in early and metastatic HER-2+ breast cancer patients. A combined targeted approach with letrozole and lapatinib has appreciably improved progression free survival in patients with MBC that coexpresses HR and HER2.

3.2.6 Triple-negative breast cancer treatment

CCN1, also known as Cyr61 (cysteine-rich 61), is a proangiogenic factor, increased CCN1 expression is associated with the development of tumors (O'Kelly *et al.,* 2008), e.g., in about 30% of invasive breast carcinomas, and particularly in triple-negative breast carcinomas (TNBC). TNBCs patients had been treated with bisphosphonate in combination to chemotherapy. Zoledronic acid (ZOL) is a bisphosphonate having direct antitumor activity in breast tumor cells by preventing independent growth, branching and morphogenesis by targeting CCN1 overexpressing cells through a negative regulation of CCN1 by FOXO3a; it is a new therapeutic approach for TNBC (Espinoza *et al.,* 2011).

3.3 Anti-angiogenic therapies

Angiogenesis is the mandatory step in tumor development, so anti-angiogenic agents can be developed for the better management and prevention of breast tumor. The monoclonal antibody to platelet/endothelial cell adhesion molecule (PECAM) has proved to be a sensitive and specific marker for endothelial cells; these antibodies might reduce the tumor size or hinder the development of metastatic tumors (Horak *et al.,* 1992).

3.3.1 Viral vector therapy

Expression of VEGF in several types of tumors is amplified, subsequently correlated with weak prognosis of several tumors. Im *et al* (2001) used transfection method to create a replication-deficient adenoviral vector containing antisense VEGF cDNA (Ad5CMV-αVEGF) to down-regulate VEGF expression. This therapeutic strategy notably repressed the growth of developed breast tumors (Im *et al.,* 2001). These viral vectors may be used in future for targeting the tumor vasculature in breast cancer therapy.

3.4 Surgery

Mastectomy is total removal of one or both breasts; it is frequently used in treatment of invasive breast cancers in early stages (Veronesi *et al.,* 2002). Bilateral mastectomy is

effective therapeutic approach for breast cancers with BRCA1 and BRCA2 mutations (Meijers-Heijboer *et al.,* 2001). Lumpectomy or breast conserving surgery (i.e., surgical removal of discrete tumor from breast) may be used alone or in combination with subsequent radiotherapy, later is reported to be more appropriate therapy for invasive breast cancer; because the risk of ipsilateral recurrence of breast cancer is very low in lumpectomy with irradiation as compared with mastectomy and lumpectomy alone (Fisher *et al.,* 2002). For hormone receptor positive breast cancer, initial treatment option was surgical removal of ovaries, oophorectomy (Taylor *et al.,* 1998).

3.5 Radiotherapy

Radiotherapy is applied after surgery, i.e., adjuvant radiotherapy. Cardiovascular disease continues to be chief problem of radiotherapy in breast cancer patients, but a little is known about it yet; It raises the enduring threat for cardiovascular mortality, predominantly in women treated for left-sided breast cancer; the mortality rate due to cardiac disease may boost to double in left-sided breast cancer survivors as compared to right-sided breast cancer patients (Foody, 2011). In women (aged 70+) with tumors larger than 5 cm, minor local regional recurrence (LRR) was observed through radiotherapy following mastectomy than those lacking radiotherapy (Truong *et al.,* 2005); Post-mastectomy radiotherapy (PMRT) might be helpful in the managing breast cancer with high-risk features (Lee *et al.,* 2005). Adjuvant radiotherapy is proved to be a breast conserving therapy (BCT) in younger women, it is not frequently recommended for patients with older age (Nagel *et al.,* 2002). Postoperative radiotherapy is normally in use for treating patients with positive surgical margins following mastectomy but a little data is present to sustain this approach (Truong *et al.,* 2004).

3.6 miRNA therapy

Each tumor type seems to have a unique miRNA marker, and such markers are being oppressed to recognize the tissue of origin of metastatic tumors and to distinguish between different cancer subtypes (Lu *et al.,* 2005). Furthermore, miRNA expression markers are linked to numerous clinicopathological features for instance tumor stage, receptor status and patient survival. Eventually, it is likely to make profiles that characterize a probable link between circulating miRNAs, disease status, basic subtype and HER2+ status, therapeutic response and metastatic risk. As miRNA expression is vanished during MBC, the renovation of these miRNAs' expression may suppress MBC; for example, miR-126 renovation reported to decrease in general tumor growth and propagation, and miR-335 presented to inhibit metastatic cell invasion (Tavazoie *et al.,* 2008).

3.7 Male breast cancer and treatment

Breast cancer is recently described to exist in males too. Tamoxifen, aromatase inhibitors and GnRH analogues targeting on HER2-directed therapies, PARP inhibitors, and angiogenesis inhibitors are reported endocrine therapeutic strategies for treating male breast cancer (Onami *et al.,* 2010).

4. Conclusion

Breast cancer is a heterogeneous disease and has become the most common cancer in women throughout the world. Known risk factors include age, dietary features,

reproductive hormonal imbalance, genetic predispositions, alcoholism, and breast adipose tissue density. Breast cancer is major cause of mortality of women worldwide. Keeping in view the above discussion, here is a need of developing better therapeutic plans for hampering breast cancer risks and reducing mortality due to breast cancer. Research investigating cultural, environmental, and genetic issues of breast cancer should be taken into consideration for development of better treatment plans and to present additional details for the clinical and pathological features. The molecular, endocrine and genetic means should be the major goals of today's efforts for treatment of breast cancer.

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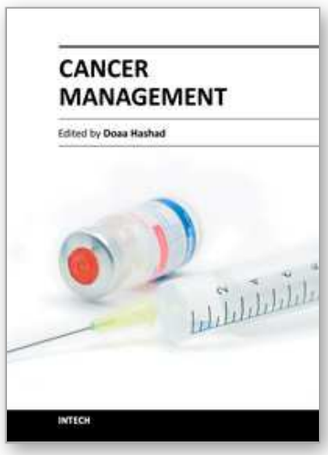

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Cancer remains a major clinical challenge as a cause of death due to its frequent poor prognosis and limited treatment options in many cases. Cancer management book addresses various cancer management related topics including new approaches for early cancer detection and novel anti-cancer therapeutic strategies. This book is a collection of studies and reviews written by experts from different parts of the world to present the most up-to-date knowledge on cancer management.

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