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List of Abbreviations

ABCSG	Austrian Breast and Colorectal Cancer Study Group
ADCC	antibody dependent cell mediated cytotoxicity
ADCC	antibody dependent cell mediated cytotoxicity
AJCC	The American Joint Committee on Cancer
ASCO	The American Society of Clinical Oncology
ATAC	Arimidex, Tamoxifen, Alone or in Combination
BCT	Breast conservative therapy
BIG1-98	Breast International Group
CAM	complementary and alternative medicine
CAP	College of American Pathologists
COX-2	cyclooxygenase 2
DCIS	Ductal carcinoma insuto
DFS	Disease free survival
EOD- E	Extent of Disease – Extent
EOD-S	Extent of disease-s
EREG	Epiregulin a member of the epidermal growth factor family.
FDA	Food and Drug Administration
FISH	fluorescence in-situ hybridization
Flk-1	Fetal liver kinase1
FTIs	Farnesyltransferase Inhibitors
GnRH	gonadotropin-releasing hormone
H&E	Haematoxilin and Eosin
HD-CT	high-dose chemotherapy
HDI	HER-dimerization inhibitors
IBC	Inflammatory breast cancer
IES	Intergroup Exemestane Study
ITA	the Italian Tamoxifen Arimidex
Ki67/MIB1	the cell proliferation marker
LABC	Locally advanced breast cancer
LHRH	Lutinizing hormone releasing hormone

MHz	Mega hertz
MMP-9	matrix metalloproteinase-9
MRI	Magnetic Resonance Imagining
MTD	Maximum Tolerated Dose
MTT	Molecular targeted therapy
MTT	Molecular targeted therapy
MUC1	a transmembrane mucin that is highly expressed in various cancers
MVD	Microvessel density
MYCN	V-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian), also known as MYCN, is a human gene.
OFS	Ovarian function suppression
OS	overall survival
ORR	overall response rate
PAI-1	plasminogen Activator Inhibitor
PET	Positrone emission tomography
PEV	Poussee Evolutive
PEV	Pousee Evolitive
PTEN	The tumour-suppressor phosphatase with tensin homologue (PTEN
RhoC-GTPase	Ras homolog gene family, member C) guanosine triphosphate .
Rt-PCR	Polymerase chain reaction
SEER	Surveillance, Epidemiology, and End Results
SERMs	Esteron receptor modulator
SHH	Sonic hedgehog protein precursor
TKI	tyrosine kinase inhibitor
TNF	Tumor Necrosis Factor
ULABC	Unresectable Locally advanced breast cancer
uPA	urokinase plasminogen activator
VEGF	Vascular Endothelial Growth Factor
VEGFR1	vascular endothelial growth factor receptor1/Flt-1

INTRODUCTION

Inflammatory breast cancer is a rare but aggressive subtype of breast cancer, which historically was considered uniformly fatal, it is accounts for about 5% of all cases of breast cancer ***(Levine et al., 2003).*** In general, women with inflammatory breast cancer present at a younger age are more likely to have metastatic disease at diagnosis, and have shorter survival than women with non-inflammatory breast cancer ***(Levine et al., 2003).*** According to the latest revision of the American Joint Committee on Cancer staging guidelines, inflammatory carcinoma is classified at T4d, which makes all patients with inflammatory carcinoma stage IIIB, IIIC, or IV depending on the nodal status and presence of distant metastases ***(Singletary et al., 2002).***

Clinically, inflammatory breast cancer is characterized by the rapid onset of breast warmth, erythema, and edema (peau d'orange) often without a well-defined mass. Along with extensive breast involvement, women with inflammatory carcinoma often have early involvement of the axillary lymph nodes. The rapidity of growth can be used to distinguish true 'primary' inflammatory carcinoma from neglected locally advanced breast tumors that have developed inflammatory features ('secondary' inflammatory carcinomas) ***(Taylor et al., 1998).*** The mammographic appearance of inflammatory breast cancer differs from other

breast tumors because less than half will show a discrete mass ***(Kushwaha et al., 2000).*** However, other abnormal findings such as skin thickening, trabecular thickening, and axillary adenopathy are present in the majority of patients ***(Ueno et al., 2007).***

Inflammatory breast carcinoma is not associated with a particular histological subtype and can occur in association with infiltrating ductal or lobular, small cell, medullary, and large cell carcinomas The characteristic pathologic finding is dermal lymphatic invasion by carcinoma, which can lead to obstruction of the lymphatic drainage causing the clinical picture of erythema and edema ***(Jaiyesimi et al., 2002).***

The most significant prognostic factor for women with inflammatory breast cancer is the presence of lymph node involvement. Patients with lymph node involvement have shorter disease-free and overall survival than patients with node-negative disease ***(Ueno et al., 2007).*** Extensive erythema, the absence of estrogen receptor, and the presence of mutations in the *p53* gene have also been associated with poorer outcomes in patients with inflammatory carcinoma of the breast ***(Riou et al., 2003).*** Because most women with inflammatory carcinoma do not have discrete masses, tumor size does not have the same prognostic value as in women with non-inflammatory carcinoma.

Inflammatory carcinoma of the breast has distinct biological characteristics that differentiate it from non-inflammatory carcinoma. These tumors more often have a high S-phase fraction, are high-grade, are aneuploid, and lack hormone receptor expression ***(Aziz et al., 2001).*** In addition to having different rates of expression of many standard prognostic markers, inflammatory breast cancers can also be differentiated by their highly angiogenic and vascular characteristics. The high levels of members of the VEGF family might account for tumor neovascularization and the lymphotactic process in inflammatory breast cancer. Inflammatory breast cancers might also be more likely to express E-cadherin, a trans-membrane glycoprotein that mediates cell-cell adhesion, and may contribute to the aggressive lymphovascular invasion seen in inflammatory cancers ***(Tomlinson et al., 2001).***

Van Golen and colleagues reported that the overexpression of *RhoC GTPase* and the loss of expression of *LIBC* (lost in inflammatory breast cancer) were highly correlated with an inflammatory carcinoma phenotype .These genes remain a promising avenue for future investigation ***(Van Golen et al.,2002).***

The treatment of inflammatory breast cancer requires careful coordination of care between the medical, surgical, and radiation oncologists because most patients will be treated with a combination of these therapeutic modalities.

The initial component of therapy should be induction chemotherapy. Many different regimens have been used, most of which are anthracycline-based. Ueno and colleagues found that 71% of all patients had a response to anthracycline-based induction chemotherapy, with 12% of patients achieving a complete response In addition; initial response to induction chemotherapy was an important predictor of survival ***(Ueno et al., 2007).***

After induction chemotherapy, patients should proceed with definitive local therapy with radiation, surgery, or both. Considerable controversy still exists as to the optimal local treatment ***(De Boer et al., 2000).*** Even after induction chemotherapy and local therapy, the rates of relapse remain very high. Thus, further adjuvant chemotherapy with either an Anthracycline or a Taxane after local treatment. Finally, patients with estrogen or progesterone receptor-positive tumours should receive 5 years of adjuvant hormonal therapy with either tamoxifen or anastrazole. The role of high-dose chemotherapy followed by autologous stem cell transplantation remains experimental ***(De Boer et al., 2000).***

AIM OF THE WORK

The aim of this essay is to revise the recent advances and multi-disciplinary approaches in the management of inflammatory breast cancer aiming at improving survival and quality of life.

EPIDEMIOLOGY

Breast cancer is the second most common cause of death in all cancer female patients in USA; It is estimated that 184,450 new cases of invasive breast cancer will be diagnosed among women, of which approximately 40,930 women are expected to die from it in the year 2008 ***(Jemal et al.,2007).***

The crude incidence of breast cancer in Europe is 109.8/100.000 women per year and it is responsible for 38.4 out of 100.000 deaths per women annually ***(Pestalozzi et al., 2005).***

In Egypt, breast cancer is the most common cancer in females, it represents 37.6% of all cancer cases in Gharbia cancer registry 1999 and 37.5% of all cancer cases presented to the NCI between the year 2002 and 2004 ***(NCI, 2005).***

IBC is rare in the United States and Western Europe, accounting for only 2.0% of all breasts with an overall incidence of 2.5 per 100,000 women per years ***(Hance et al., 2005).***

Possibly because of varying case definitions, population-based estimates for IBC incidence range widely, from <1% to 10%. For example, using codes from the Surveillance, Epidemiology, and End Results (SEER)