

# Acknowledgment

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## List of Abbreviations

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

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