Breast Cancer: What You Need to Know About This Disease from the Western Medical Point of View + TCM

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Introduction

Breast cancer is the most common cancer and the second most common cause of death from cancer in women. Because of the high frequency of the disease and the esthetic and symbolic value invested in the breast, breast cancer has always been a source of severe distress to patients and their families. For the same reasons, breast cancer research has increased dramatically during the last two decades, resulting in extraordinary progress in our understanding of the disease and in new, more efficient, and less toxic treatments. Furthermore, the diffusion of knowledge, the medical advancements, and the increased public awareness have led to earlier diagnosis at stages usually amenable to complete resection and potential cure of the disease.

This article addresses the etiology, pathophysiology, clinical presentation, diagnosis, surgical and medical treatment, prognosis, and future directions of breast cancer in terms of Western medicine.

Frequency

The American Cancer Society estimated that 211,240 new cases of breast cancer (32.1% of all cancers in women) would be diagnosed in 2005 in the United States, making breast cancer the

most diagnosed cancer in women. Male breast cancer is a rare disease, and only 1690 cases were expected for 2005 in the U.S. The true incidence rates of breast cancer have been stable from 1987-1996 after a constant increase since 1979 (increase of 1% per year from 1979-1982; 4% per y from 1982-1987). The lack of decline of breast cancer incidence in the 1990s contrasts with a slight decline (decline of 1.3% per year from 1992-1997) of the incidence rate of cancer for all sites. Up to 40,870 cases of breast cancer-related deaths were expected for 2005 in the US.

Based on cancer cases diagnosed from 1995-1997, the probability of developing invasive cancer is 0.44% (1 in 225) for women younger than 39 years, 4.15% (1 in 24) for women aged 40-59 years, and 7.02% (1 in 14) for women aged 60-79 years. The estimated lifetime probability of developing breast cancer is 12.83% (approximately 1 in 8). The likelihood of developing breast cancer is higher in Caucasian women than in women of any other racial or ethnic group.

Although the death rate from breast cancer has decreased an average of 2.2% per year from 1990-1997, the recorded number of deaths from breast cancer has remained stable, at approximately 43,000 per year. Deaths dropped to 41,737 in 1998 after reaching the highest number, 43,844, in 1995. Among women aged 20-59 years, breast cancer is the leading cause of death from cancer. However, lung cancer remains the leading cause of death from cancer in women aged 60 years or older.

Etiology

Breast cancer is a heterogeneous disease with no single characterized cause.

Epidemiological studies have identified many risk factors that increase the chance for a woman to develop breast cancer:

• Factors with relative risk greater than 4

• Advanced age

• Being born in North America or northern Europe

• High premenopausal blood insulinlike growth factor (IGF)–1 level

• High postmenopausal blood estrogen level

• History of mother and a sister with breast cancer

• Factors associated with a relative risk of 2-4

• High socioeconomic status

• Age at first full-term pregnancy older than 30 years

• History of cancer in one breast

• Any first-degree relative with a history of breast cancer

• History of a benign proliferative lesion, dysplastic mammographic changes, and a high dose of ionizing radiation to the chest

• Factors associated with a relative risk of 1.1-1.9

• Nulliparity (i.e., never having given birth)

• Early menarche (age <11 y)

• Late menopause (age >55 y)

• Postmenopausal obesity

• High-fat diet/saturated fat-rich diet

• Residence in urban areas and northern United States

• White race - Older than 45 years

• Black race - Younger than 45 years

• History of endometrial or ovarian cancer

• Identified factors with a protective role against breast cancer

• Age at first period older than 15 years

• Breastfeeding for longer than 1 year

• Monounsaturated fat-rich diet

• Physical activity

• Premenopausal obesity

Genetic factors

As with other cancers, breast cancer is the result of multiple genetic changes or mutations. Early mutations may be inherited (e.g., mutations of breast stem cells) or acquired (e.g., somatic mutations due to ionizing radiation, chemical carcinogens, or oxidative damage).

Estrogens, by their proliferation-promoting effect on the breast epithelium layer, increase the chance of DNA replication errors leading to carcinogenic mutations. Indeed, the common denominator to many of these risk factors is their effect on the level and duration of exposure to endogenous estrogenic stimulation.

Early menarche, regular ovulation, and late menopause increase lifetime exposure to estrogens in premenopausal women, while obesity and hormone replacement therapy increase estrogen levels in postmenopausal women. Conversely, late menarche, anovulation, and early menopause (spontaneous or induced) are protective, owing to their effect on lowering the level or shortening the duration of estrogenic exposure.

Lactation and premenopausal obesity are associated with lower estrogen levels as a result of anovulation. For unknown reasons, pregnancy decreases breast tissue susceptibility to somatic mutations. Thus, the earlier the first pregnancy, the shorter the susceptibility period.

Hereditary breast cancers have been thought to represent a small proportion (5-10%) of all breast cancers. However, based on new data derived from the comparison of identical and nonidentical twins, up to 27% of breast cancers may be attributed to inherited factors. The mutated genes BRCA1 and BRCA2 are responsible for approximately 30-40% of inherited breast cancers.

The prevalence of BRCA1 in the general population is 0.1%, compared with 20% in the Ashkenazi Jewish population. The gene is encountered in 3% of the unselected breast cancer population and in 70% of women with inherited early-onset breast cancer. Up to 50-87% of women carrying a mutated BRCA1 gene develop breast cancer during their lifetime.

Risks for ovarian and prostate cancers are also increased in carriers of this mutation. BRCA2 mutations are identified in 10-20% of families at high risk for breast and ovarian cancers and in only 2.7% of women with early-onset breast cancer. The lifetime risk of developing breast cancer in female carriers is 25-30%. BRCA2 is also a risk factor for male breast cancer; carriers have a lifetime risk of 6% for developing the cancer. BRCA2 mutations are associated with other types of cancers, such as prostate, pancreatic, fallopian tube, bladder, non-Hodgkins lymphoma, and basal cell carcinoma.

Li-Fraumeni syndrome, characterized by a mutation of TP53, is associated with multiple cancers, including the SBLLA syndrome (sarcoma, breast and brain tumors, leukemia, laryngeal and lung cancer). Cancer susceptibility is transmitted by an autosomal dominant pattern, with penetrance approximating 90% by age 70 years. Li-Fraumeni syndrome is identified in 1% of women with early-onset breast cancer. Bilateral breast cancer is noted in up to 25% of patients.

Cowden disease is a rare genetic syndrome associated with papillomatosis of the lips and oral mucosa, multiple facial trichilemmomas, and acral keratosis. The prevalence rate of breast cancer in women with this disease is 29%. Benign mammary abnormalities (e.g., fibroadenomas, fibrocystic lesions, ductal epithelial hyperplasia, nipple malformations) are also more common. Other rare genetic disorders, such as Peutz-Jeghers and Muir-Torre syndromes, are associated with an increased risk of breast cancer.

Pathophysiology

In a normal state, cells proliferate in response to external proliferation-promoting signals to fulfill a function such as replacing lost cells or repairing injured tissues. Once the goal has been reached, a set of proliferation-repressing signals is activated. These signals allow the cells to exit the proliferation cycle (cell cycle) by returning to the dormant state (G0), by differentiating, or by dying (apoptosis). Each of these functions is carried out by a complex system of interacting proteins. Constitutive expression by mutation or another genetic change of any component of the proliferation-promoting system may result in uncontrolled proliferation. The constitutively expressed component is called an oncogene.

Conversely, the loss by mutation or deletion of a proliferation-repressing gene results in an inability to stop the cell cycle and, thereby, continuous proliferation, possibly leading to cancer. The lost gene is called a tumor suppressor gene. Likewise, constitutive expression of antiapoptotic genes may result in immortalization of the cell, paving the way for further genetic changes and eventually cancer formation. Loss of proapoptotic genes may lead to similar results. Thus, autonomous proliferation and immortality shared by all cancers are the final result of successive genetic changes, which may be different from one cancer to another.

Breast cancer is not an exception in that regard. It is the result of multiple genetic changes that are different from those of other malignancies and that confer to this cancer its characteristic phenotype.

Cell-cycle deregulation in breast cancer

Estrogen and progesterone induce cyclin D1 and c-myc expression. Although both sex hormones provide directionality by shifting the CDKI p21 from CDK2 to CDK4, progesterone promotes maturation by inducing p27, while only estrogen allows multiple cycles. Recent studies have reported common amplification of cyclin D1 (a third of breast cancers), inactivation of p16, and mutation of TP53 in breast cancer.

c-myc overexpression is one of the most common genetic alterations encountered in persons with breast cancer (a third of patients). Depending on the availability of its different partners, it may result in proliferation and chromosomal instability (Myc-Max) or differentiation (Myc-Mad), probably by sequestering Myc and reducing its availability. Amplification of the c-myc gene is associated with a poor prognosis and a high S-phase.

Estrogen receptor (ER)–positive breast cancer cells undergo apoptosis after withdrawal of estrogen, suggesting that this hormone functions not only as a mitogen but also as a survival factor. The antiapoptotic factor Bcl-2 is commonly overexpressed in ER-positive breast cancers.

ER negativity is observed in a third of primary breast cancers and a third of recurrences of ER-positive primaries. The ER gene is usually intact with no identifiable deletions or mutations. Although the exact mechanism of this lack of expression is not known, hypermethylation used normally by the genome to silence certain genes is a possible explanation. Methylation of cytosine-rich areas (called CpG islands) of the ER-gene promoter region has been described in the majority of ER-negative breast cancers and in a small fraction of ER-positive breast cancers. Demethylation of these areas with specific agents (eg, 5-azacytidine) restores ER expression and its function in vitro.

A progesterone receptor (PR) is present in approximately 50% of all ER-positive tumors. Its presence depends on the expression of functional ER, which explains its absence in almost all ER-negative breast cancers. The mitogenic effect of progesterone in breast cancer may depend on the induction of local growth hormone production in the hyperplastic mammary epithelium. However, high doses of progestins have proven inhibitory effects on breast cancer growth mediated by the down-regulation of G1-phase CDKs and cyclin D1 leading to cell differentiation.

Regarding adhesion-dependent cell regulation, the transmembrane glycoproteins, ie, epithelial cadherins (E-cadherins), mediate with their extracellular domain cell-to-cell interactions, thus stabilizing the cell in the epithelial tissue. Their intracellular domain interacts with and controls the transcription factors B-catenins. A mutation or the absence of E-cadherins results in cell detachment, increased motility and invasiveness, and release of B-catenins, which up-regulates c-myc expression.

Expression of E-cadherins is down-regulated in breast cancer. Another family of adhesion molecules, the integrins, is involved in cell-to-matrix interactions. Integrins signal through the Fak-Src pathway, which activates PI3K and AKT, resulting in enhanced survival, proliferation, and motility. The main components of this pathway (Fak, PI3K, and AKT) are inhibited by PTEN (ie, phosphatase on chromosome 10 gene product, mutated in Cowden disease), which results in the suppression of survival and apoptosis.

The epidermal growth factor (EGF) receptor family plays a critical role in mammary tumorigenesis. Other than the EGF receptor itself, three other members of this family have been described, including c-erb-B2 (HER2, HER2/neu), c-erb-B3, and c-erb-B4; the latter is called a kinase-dead receptor because it does not carry a kinase function on the cytoplasmic domain of the receptor, which is in contrast to the other members of the family.

These receptors interact with many ligands, including EGF, transforming growth factor (TGF)–alpha, hergulin (or Neu differentiation factor), heparin-binding EGF-like growth factor, beta-cellulin, and epiregulin. Upon binding of a ligand with its cognate receptor, a homodimerization or heterodimerization process occurs, followed by autophosphorylation of the intracellular

domain and activation of the intrinsic catalytic domain.

Transmission of the signal is operated via phosphorylation of adaptor proteins (GRB2-SOS, Shc, IRS-1/2, STAT) docked or recruited to the cytoplasmic domain of the receptor, followed by activation of the RAS-GTP protein, then 1 of 3 pathways to the nucleus (ie, Raf/MEK/ERK-1/2, MEKK1/MEK4/7/JNK, PI3K/AKT/GSK).

Transmission of the signal from adaptor proteins to the nucleus without mediation by RAS is possible through Fak/Src or Rho/Rac/CDC42 pathways. In addition, phospholipase C-gamma is activated by direct interaction with the phosphorylated c-erb-B-2; however, its intracellular pathway is not fully known. The final result is the induction of transcription factors (ie, Myc, NF-kB, ATF, Ets, AP-1, EIK, SRF) that drive the cell cycle by up-regulating cyclins and inhibiting CDKIs and proapoptotic signals.

Once the biological message has been executed, the complex ligand receptor is internalized and destroyed in the lysosomes. The pattern of heterodimerization, the intracellular pathway used, and the rate of internalization and destruction of the receptor depend on the specific ligand bound to the receptor.

Although c-erb-B2 does not have a specific ligand, its role in the signal transmission from the epidermal growth factor receptor is crucial. Cell lines lacking c-erb-B2 are resistant to the tumorigenic effect of EGF, while those with a kinase-deficient or carboxyl terminal–truncated EGF receptor with intact c-erb-B2 can still execute all the functions of the wild type.

The discovery of the role of HER2 in breast cancer was one of the landmarks in breast cancer research in the last 2 decades. HER2 is overexpressed in 20-30% of breast cancers. Tumor cells overexpressing HER2/neu may have up to 2 million copies of the receptor on their surface compared with 20,000-50,000 copies in normal breast epithelial cells. Because of this abundance of HER2/neu, many heterodimers contain HER2/neu, resulting in potent intracellular signaling and malignant growth.

Despite persistent controversy regarding certain aspects of its biology, prognostic value, and methods of evaluation, HER2 overexpression or amplification is generally accepted to be correlated with a high histologic grade, the absence of hormone receptor expression, aneuploidy, a high proliferation index, tumor size, and a poor clinical outcome. Its role as a predictor of response to chemotherapy and hormonal therapy (HT) is not clearly defined.

Certain clinical studies using tamoxifen showed not only a lack of response, but also a detrimental effect in the group of patients overexpressing HER2. Retrospectively reviewed chemotherapy data showed longer disease-free survival and overall survival in HER2 overexpressors who received high doses of doxorubicin-containing chemotherapy compared with HER2-negative patients. Available data concerning the interaction between cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy and HER2 overexpression are inconclusive and do not allow the formation of final conclusions. Taxanes

seem to have high efficacy in patients overexpressing HER2 (relative risk, 65%) compared with the HER2-negative group (relative risk, 35%).

The IGF family consists of IGF-1, IGF-2, IGF receptor-1, IGF receptor-2, and IGF-binding proteins. The members of this family play an important role in normal mammary development and tumorigenesis. Both IGF-1 and IGF-2 bind to IGF receptor-1, whose strong mutagenic effect is synergistic with estrogen. In breast cancer, IGF receptor-1 and IGF-1 and IGF-2 are overexpressed in epithelial cells and stromal cells, respectively. Paradoxically, this overexpression correlates with a good prognosis, perhaps reflecting simple hormone dependence or association. IGF receptor-2 plays a tumor-suppressing role by down-regulating IGF-2.

The TGF-beta family consists of 3 TGF-beta and 2 interdependent serine-threonine kinase receptors. In normal mammary epithelial cells, TGF-beta blocks the expression of cyclin A, an S-phase–promoting protein and (to a lesser degree) cyclins D and E involved in the G1 phase and induces the expression of the CDKI p15, which results in cell-cycle arrest and, potentially, apoptosis. This explains its role in postlactational mammary gland regression.

Expression of TGF-beta in breast cancer is increased and seems to correlate with disease progression rather than tumor suppression. Mutation of TGF-beta receptors (type I and II) or any of the downstream molecules (Smad4) involved in intracellular signal transduction renders breast cancer cells resistant to its suppressive effects. However, its role in promoting angiogenesis and invasion and in suppressing the immune system becomes advantageous for the cancer cells, which acquire a proliferative advantage by losing sensitivity to TGF-beta and developing a way to escape the host immunosurveillance.

Mutated BRCA1 and BRCA2, breast cancer susceptibility genes, are proven risk factors for breast cancer. More than 500 mutations have been described in the BRCA1 gene (band 17q21), and 250 have been described in the BRCA2 gene (band 13q12-13). The mutations occurring at either end of the BRCA1 gene are associated with more aggressive tumors; those occurring at the 5` extremity are associated with breast and ovarian cancers, while those closer to the 3` end are associated with only breast cancer.

The biological function of the BRCA1 gene product is not well known. Accumulated evidence suggests that BRCA1 is a nuclear protein involved in other genes' expression, in cell cycle progression, and in the response to DNA damage. DNA damage results in activation and interaction of BRCA1, BRCA2, RAD51, and TP53 with subsequent expression of p21, which leads to a cell cycle pause until the damage is repaired. The mutation or absence of BRCA1 results in failure to repair the damaged DNA, and the cell cycle continues to accumulate further mutations, eventually leading to tumorigenesis. BRCA2 seems to play a role similar to that of BRCA1 in the cell cycle, other genes' expression, and DNA damage repair.

Clinical manifestations

In the past, the great majority of patients presented with a painless palpable mass. Although more than 80% of palpable masses are benign, the decision to observe such lesions should be made only after careful clinical, mammographic, and pathologic workup. Cystic lesions identified clinically or on ultrasound images should be explored using fine-needle aspiration (FNA) biopsy. Nonbloody fluid and complete resolution of the cyst confirm its benign nature. If the fluid is bloody or the cyst does not resolve after aspiration or has a complex appearance on the ultrasound image, a biopsy is indicated.

Other symptoms, such as breast pain or deformity, nipple discharge, and erythema or skin ulceration, occasionally occur. Patients with Paget disease present with a long-standing eczematoid rash of the nipple-areola complex, itching, tenderness, burning, and occasional bloody discharge from the nipple. Skin dimpling, the result of shortening or retraction of the Cooper ligaments induced by the tumor, does not have prognostic value, while the ominous peau d'orange sign reflects the invasion of the subdermal lymphatic plexus and portends a shortened survival.

Symptoms related to distant metastases, such as bone pain, dyspnea, or meningitic syndrome, are encountered in some cases.

In current practice, increasing numbers of breast cancers are mammographically diagnosed in the preclinical stage. Screening mammography has resulted in earlier diagnosis of breast cancer, which has translated in recent years into a 25% improvement in the mortality rate related to breast cancer. Mammographic signs suggestive of cancer include architectural distortions, microcalcifications, or masses. These changes require further evaluation using diagnostic mammograms with or without ultrasound. Biopsies are indicated if these changes are confirmed. Features helpful in the evaluation of palpable breast masses are as follows:

• Malignant masses

• Hard

• Painless: Malignant masses are painful in only 10-15% of patients.

• Irregular

• Possibly fixed to the skin or chest wall

• Skin dimpling

• Nipple retraction

• Bloody discharge

• Benign masses

• Firm, rubbery mass

• Frequently painful

• Regular margins

• Not fixed to skin or chest wall, mobile

• No skin dimpling

• No nipple retraction

• No bloody discharge

• Cysts: No reliable features distinguish cysts from solid masses based on clinical data.

Nipple discharge may be spontaneous or induced, unilateral or bilateral, and have different colors and textures. If the discharge is associated with one or more of the suggestive features, further investigation is necessary. Clinical characteristics of nipple discharges are as follows:

• Malignant discharge

• Unilateral

• Spontaneous

• One duct orifice

• Bloody, serosanguineous, or serous

• Benign discharge

• Bilateral

• Spontaneous or induced

• Multiple duct orifices

• Thick green or yellow, induced and bilateral (duct ectasia)

Indications

Ductal carcinoma in situ

Mastectomy has been the criterion standard for many years, with significantly low local recurrence and mortality rates (0.75% and 1.7%, respectively). The idea of using BCS has gained acceptance after good success in women with invasive disease.

When BCS is used, RT is often a part of the treatment plan because the prevalence of ipsilateral noninvasive breast cancer was reduced from 13.4% to 8.2% and, for invasive cancer, from 13.4% to 3.9%, after using RT (National Surgical Adjuvant Breast Project [NSABP] B-17). Because most of the tumors in this study were smaller than one centimeter, a wise plan is to continue offering mastectomy to (1) patients with extensive multicentricity, (2) those with multifocality, and (3) those in whom negative margins cannot be obtained with wide excision. Axillary node dissection or adjuvant chemotherapy has no role in the treatment of this disease.

Patients with early-stage invasive breast cancer (TNM stage I and II) may benefit from BCS. BCS should be offered to patients with small tumors and adequate breast size. Family history, tumor location, and the presence of pathologically or clinically involved axillary lymph nodes are not contraindications to such a surgery. Absolute contraindications are two or more primary tumors in separate quadrants, previous RT to the breast, persistent positive margins, and pregnancy.

An extensive intraductal component within the index lesion and the surrounding tissue is not associated with a high risk of recurrence as long as clear margins can be achieved.

For Paget disease, mastectomy should be performed in patients with a tumor located beyond the central portion of the breast, while BCS may be considered in patients with disease limited to the retroareolar area, with excision of the nipple-areolar complex and complete excision of the mammographic abnormalities with a two centimeter cone of the retroareolar tissue. If surgical margins are negative, RT should complete the treatment; otherwise, mastectomy is the treatment of choice.

Indications for mastectomy include patient preference, an inability to achieve clean margins without unacceptable deformation of the remaining breast tissue, multiple primary tumors, previous chest wall irradiation, pregnancy, and severe collagen vascular diseases (e.g., lupus), which are considered absolute contraindications to BCS.

Simple mastectomy is used in the treatment of ductal carcinoma in situ (DCIS), after lumpectomy or axillary dissection with or without radiation, if the specimen shows positive margins, in frail patients in whom an axillary dissection is contraindicated, and as a prophylactic measure.

Modified RM is performed in the presence of contraindications to BCS or as a patient preference.

ALND remains the standard of care in the management of invasive carcinoma of the breast.

ALND is not indicated in carcinoma in situ, unless the presence of an invasive component is strongly suggested.

SLNB has recently emerged as a credible alternative to ALND, with comparable, if not better, staging results and much less morbidity. In expert hands, SLNB identifies the sentinel lymph node (SLN) in 85-98% of patients and correctly stages the axilla in more than 95% of patients, with a false-negative rate of less than 5%. The combined use of technetium colloid and blue dye techniques increases the detection rate of the SLN.

SLNB is usually offered to patients with early-stage breast cancer (stage I or II) who have no gross axillary lymph node involvement. SLNB is contraindicated in patients with clinically palpable axillary lymphadenopathy, multifocal disease, or locally advanced lesions. Patients with positive SLNB findings should undergo level I and II ALND. Because of the slow learning curve for this new procedure, the American Society of Breast Surgeons considers that an individual surgeon should perform at least 20 SLNB procedures with ALND to minimize the risk of false-negative results.

Relevant anatomy & contraindications

Relevant anatomy

The breasts are between the second and sixth ribs and are composed of breast tissue, skin, and subcutaneous tissue. The breast tissue is composed of parenchyma and stroma. The parenchyma is composed of 15-25 lobes, and each lobe contains 20-40 lobules. Each lobule consists of 10-100 alveoli. Fifteen to 25 lactiferous ducts provide separate drainage to the corresponding lobes. Before opening at the nipple, these ducts become dilated, forming the lactiferous sinuses. The breast tissue is enveloped superficially by the superficial pectoral fascia and deeply by the deep pectoral fascia, with the two layers connected by fibrous bands called Cooper suspensory ligaments.

The lymphatic drainage of the breast is unidirectional, from the superficial to the deep lymphatic plexus. The lymph then flows centrifugally to the regional lymph nodes after traveling through the lymphatic vessels of the lactiferous ducts. Ninety-seven percent of this flow is collected in the axillary lymph nodes, while only 3% goes to the internal mammary nodes.

Axillary lymph nodes are divided into apical lymph nodes, interpectoral (Rotter) lymph nodes, axillary vein lymph nodes, central lymph nodes, scapular lymph nodes, and external mammary lymph nodes. An arbitrary method divides these lymph nodes into three levels relative to their relationship with the pectoralis minor muscle. Lateral to the lateral border of this muscle lie the level I lymph nodes, and medial to it lie the level III lymph nodes. Level II lymph nodes are located between and behind the muscle.

Several structures, including vessels and muscles with their nerve supply, are related to the breasts and should be preserved during mastectomy or axillary node dissection. The pectoralis

minor muscle and the lateral portion of the pectoralis major muscle are innervated by the medial pectoral nerve. Preservation of this nerve is particularly important to prevent atrophy of the pectoral muscles if a submuscular implant reconstruction is planned.

Additionally, the serratus anterior muscle is innervated by the long thoracic nerve of Bell, whose preservation is crucial to prevent winging of the scapula. Resection of the thoracodorsal nerve supplying the latissimus dorsi muscle should be avoided whenever possible, although resection does not result in any cosmetic or functional sequelae. Exposure of the axillary artery and brachial plexus should be avoided.

Also, injury to certain sensory branches of the brachial plexus that occasionally pass superficially to the axillary vein may result in arm numbness extending to the wrist. Injury to the intercostobrachial nerve results in numbness over the triceps area. It can be identified by its large size (2 mm) and its location near the axillary vein. Occasionally, this nerve is composed of multiple, thin branches that cannot be preserved. In this case, the nerve should be sectioned with the knife to prevent postoperative causalgia related to the use of electrocautery.

Contraindications

• Absolute contraindications to lumpectomy/RT

• Pregnancy

• Prior irradiation to the breast

• Two or more gross foci of cancer in separate quadrants of the same breast

• Mammographic findings suggestive of diffuse areas suggestive of malignancy

• Failure to obtain negative margins despite several surgical attempts

• Collagen vascular diseases

• Relative contraindications to lumpectomy/RT

• Tumors larger than five centimeters

• Very large or very small breasts

Workup

Lab studies

• CBC (complete blood cell) count with differential and platelet count

• Chemistry and renal function studies

• Liver function tests

• Calcium and phosphorus evaluations

Imaging studies

• Mammography: Bilateral study is necessary for screening, diagnosis, and follow-up care. Malignant and benign breast lesions have the following mammographic characteristics:

• Malignant breast lesions

+ Irregular speculated mass

+ Clustered calcifications

+ Calcifications - Smaller than 0.5 mm in diameter

+ Architectural distortion

+ Focal asymmetric density

• Benign breast lesions

+ Solid- or lucent-centered spheres

+ Smooth and round calcifications

+ Calcifications - Larger than 1 mm in diameter

+ Architectural distortion - Usually not present

• Chest radiograph (x-ray)

• CT (computed tomography) scan of the brain, chest, abdomen, and pelvis: Obtain CT scans if the patient has neurologic symptoms, abnormal chest radiograph results, supraclavicular lymphadenopathy and hepatosplenomegaly, or abnormal liver function test results.

• Skeletal radiograph: Use this for symptomatic areas only.

• Bone scan: Perform a bone scan if any of the following conditions are present:

• Advanced local disease

• Lymph node metastases

• Distant metastases

• Bony symptoms

Other tests

• Pathologic study of tumor specimens: Three features are evaluated and given scores from 1-3, i.e., tubule formation, nuclear pleomorphism, and mitotic activity.

• Tubular grade is defined based on the degree of development of tubular formations.

+ Well differentiated if tubular structures occupy more than 75% of the tumor - 1 point

+ Moderately differentiated if tubular structures represent 10-75% of the tumor - 2 points

+ Poorly differentiated if the tubular structures represent less than 10% of the tumor - 3 points

• The nuclear grade is defined based on the nucleus size, stain density, and shape variations.

+ Small and uniformly staining nucleus, good prognosis - 1 point

+ Moderate variation in nuclear size and shape, intermediate prognosis - 2 points

+ Marked nuclear polymorphism with dark staining, poor prognosis - 3 points

• Determine the cycling fraction (mitotic index and S-phase). While the determination of the S-phase requires the use of flow cytometry, the mitotic index is the easiest and fastest way of assessing proliferation. Score the mitotic index as follows:

+ Low (0-3.3/mm2) - 1 point

+ Medium (3.3-7/mm2) - 2 points

+ High (>7/mm2) - 3 points

• The histologic grade is a composite index obtained by totaling the tubular, nuclear, and mitotic scores. Invasive breast cancer is graded as follows:

+ Well differentiated - 3-5 total points

+ Moderately differentiated - 6-7 total points

+ Poorly differentiated - 8-9 total points

• ER and PR evaluation: Two types of assays are used to quantitate ERs and PRs.

• For ligand-binding methods (e.g., dextran-coated charcoal assay), results are expressed in femtomoles of receptor protein per milligram of cytosol protein (fmol/mg). Cutoffs vary from 3-20 fmol/mg, depending on the laboratory. To ensure accuracy and reproducibility, specimens should be large and must be immediately fixed in liquid nitrogen. Results of this method may be affected by the presence of estrogens or tamoxifen in the specimen.

• With regard to monoclonal antibody–based methods (e.g., immunohistochemistry [IHC], enzyme immunoassay), IHC has 2 advantages. First, it can be performed on any type or size of specimen, including cell blocks from body fluids or those fixed or imbedded in paraffin. Second, it measures total protein; therefore, it is not affected by the presence of estrogens or tamoxifen. IHC is a semiquantitative technique that depends on the observer and the type of antibodies used. Enzyme immunoassay results are more objective because of the use of a spectrophotometer to quantitate the receptor protein; however, the technique is limited by the need for a sufficiently large fresh, frozen specimen.

• HER2/neu status: Several methods have been used to detect and quantitate HER2/neu.

• IHC methods have been extensively used. This method is a semiquantitative assay using a monoclonal antibody.

• Scoring of HER2/neu overexpression using the DAKO HercepTest (DAKO Cytomation; Carpinteria, Calif) follows. The cell membrane staining pattern, the interpretation, and the score are listed.

+ Strong complete membrane staining in more than 10% of tumor cells - Interpreted as strongly positive; score of 3+

+ Weak-to-moderate complete membrane staining in more than 10% of cells - Interpreted as weakly positive; score of 2+

+ Faintly perceptible membrane staining in more than 10% of tumor cells - Interpreted as negative; score of 1+

+ No staining or staining in 10% of tumor cells - Interpreted as negative; score of 0

+ Cytoplasmic staining of any intensity - Interpreted as negative; score of any

• Detection of gene amplification with fluorescence in situ hybridization (FISH) is highly specific

and has an 82% overall concordance rate with IHC. However, when FISH results are expressed in the function of the IHC scores, they are positive in 92% of 3+ and 39% of 2+ IHC specimens. Only 7% of 1+ IHC specimen results are FISH-positive.

• Certain authorities consider FISH to be the criterion standard for HER2/neu evaluation. However, because this test is not readily available in many laboratories, they recommend use of IHC as a first-line test; 3+ and 1+ IHC results correspond to positive and negative expression of HER2/neu, respectively, and a 2+ IHC result is considered borderline. In these cases, only FISH is performed because a significant number of true HER2/neu–positive patients may be identified in the 2+ IHC group.

Diagnostic procedures

• Surgical procedures for nonpalpable lesions

• Image-guided core-needle biopsy

+ This is the preferred method for needle biopsy of a nonpalpable lesion. Note that because of sampling error, it carries a higher risk of false-negative findings than open biopsy. Negative or equivocal results in the face of suggestive mammogram findings or residual calcifications should be followed by an open biopsy. False-negative results are encountered in 1-10% of biopsies, with the highest rates occurring with the least-experienced operators.

+ For the technique, ultrasound is the method of choice to guide the core-needle biopsy. Stereotactic mammographic guidance is used in lesions not visualized on ultrasound images. Stereotactic core-needle techniques have the advantages of lower complication rates and lower costs, although they cannot be used when the lesion is very close to the chest wall or areola, where open biopsy is the best approach. The radiograph should be compared with the mammogram to ensure that all calcifications are included within the core biopsy specimen.

• Open biopsy with needle localization

+ Invasive localization techniques with small radiopaque needles to guide a surgical biopsy are used more commonly than noninvasive techniques.

+ For the technique, local anesthesia with or without intravenous sedation is sufficient in most cases. A thin needle and a fine wire with a thickened distal segment are used for immediate preoperative localization of the lesion. The incision may include the wire entry site if the lesion is superficial. A core of tissue along and around the wire is excised (including the lesion easily identified by the previous placement of the thickened segment inside it) and sent en bloc for radiographic evaluation. However, when the wire entry site is located far from the lesion, the incision should be placed directly over the lesion; dissection is then performed to find the wire.

+ Once identified, the free end of the wire is pulled up through the incision. A core of tissue

around the wire is excised (including the lesion) and sent for radiographic evaluation. Closure should not proceed until radiographic confirmation that the entire lesion was excised.

• Surgical procedures for palpable lesions

• Fine-needle aspiration biopsy

+ In experienced hands, FNA biopsy may provide a high accuracy rate when combined with physical examination and mammography (sensitivity ~80-98%, specificity ~100%). However, negative results from a palpable lesion cannot exclude carcinoma. Lesions most suited for this procedure are T3 and T4 tumors and axillary or chest wall relapses.

+ Owing to the high false-negative rate with FNA in lesions smaller than 1 cm in diameter, another diagnostic procedure should be used. Because false-positive rates are extremely low (<2%), positive results are sufficient to plan surgery, without the need for further investigation. However, perioperative frozen sections are necessary to distinguish between invasive and in situ carcinoma and to determine the need for axillary dissection because FNA results cannot be used to make this distinction.

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Treatment

Medical therapy

Treatment of in situ disease

Ductal carcinoma in situ

Approximately 85% of DCIS is detected mammographically, and this represents 20-30% of mammographically detected breast cancer. The risk of developing invasive cancer is approximately 40% in the ipsilateral breast and 5% in the contralateral breast. Regardless of the initial treatment modality, 50% of recurrences are invasive carcinoma.

Mastectomy cures 98-99% of all types of DCIS, with a recurrence rate of only 1-2%. Most recently, lumpectomy with RT was shown to yield local recurrence rates of 7-13.4%, compared with 26.8-43% for local excision alone. Furthermore, the addition of tamoxifen resulted in a 44% decrease of invasive breast cancer in the ipsilateral breast and a 52% decrease of invasive breast cancer in the contralateral breast.

Predictors of recurrence in patients undergoing BCS for DCIS are as follows:

• Residual microcalcifications: Risk of relapse is 100%.
• Comedo necrosis

• Positive margins: For margins less than 1 mm, the recurrence rate is 25%. For margins of 1-9 millimeters, the recurrence rate is 15%. For margins greater than one centimeter, the recurrence rate is 3%.

• Age younger than 50 years

• Bloody discharge

Lobular carcinoma in situ

This lesion is usually an incidental finding in breast biopsy specimens. LCIS is not a cancer; it is an indicator for increased risk for breast cancer. This risk is estimated at 1-1.5% per year and 20-30% over a lifetime. Of invasive carcinoma developing in this setting, 50% is ductal carcinoma; the other 50% is lobular carcinoma.

Patients may be observed or offered participation in a chemoprevention trial. Bilateral simple mastectomy with immediate reconstruction is the recommended surgery should the patient elect a radical treatment. Chemotherapy and RT have no role in the treatment of this lesion.

Treatment of invasive disease

Modern treatment of breast cancer is based on a multimodality approach combining surgery, chemotherapy, HT, and RT. Treatment is tailored for an individual patient based on tumor size, axillary lymph node involvement, ER and PR status (the most important variables identified by many historical studies), histologic tumor type, standardized pathologic grade, and menopausal status. The 2000 US National Institutes of Health Consensus Conference updated adjuvant therapy guidelines for breast cancer.

Adjuvant hormonal therapy

Adjuvant HT is indicated only in the presence of hormone receptors (ER and/or PR) on cancer tissue assessed using IHC. Adjuvant tamoxifen has shown a 50% decrease in the risk of breast cancer recurrence and a 28% decrease in breast cancer mortality, while ovarian ablation produced benefits similar to certain chemotherapies (20-25%) in this population.

In two cooperative trials (NSABP 23, Intergroup trial 0102), the addition of tamoxifen to chemotherapy was not associated with improvement in disease-free survival and overall survival in patients with ER-negative tumors and was even detrimental in premenopausal patients with ER-negative tumors. Therefore, HT is indicated only in case of ER and/or PR positivity, regardless of age, menopausal status, lymph node status, or tumor size.

The goal of HT in breast cancer is to induce an estrogen deprivation state at the tumor level. This may be achieved by 1) receptor blockade using one of the selective estrogen receptor modulators, such as tamoxifen or toremifene; 2) suppression of estrogen synthesis by aromatase inhibitors (e.g., anastrozole, letrozole, exemestane) in postmenopausal women or by luteinizing hormone-releasing hormone analogues (e.g., goserelin) in premenopausal women; or 3) ovarian ablation by surgical oophorectomy or external beam radiation therapy in premenopausal women.

Tamoxifen has been the most common form of adjuvant HT used to date. It can be used both in pre and post menopausal women. However, the recent publication of the results of many large aromatase inhibitor (AI) trials (ATAC, BIG 1-98, examestene trial) has shown that AIs are superior to tamoxifen as adjuvant HT in postmenopausal women. Anastrozole and letrozol are approved for use in first line hormonal therapy for HR-positive postmenopausal women and examestene is approved for use sequentially after 2-3 years of tamoxifen. When tamoxifen is chosen, administer 20 mg/day for five years. In asymptomatic women, no special screening procedures (e.g., transvaginal ultrasound, endometrial biopsies) for endometrial cancer are recommended. The dose of anastrozole is 1 mg a day, of letrozol 2.5 mg and of examestene 25 mg per day.

The Early Breast Cancer Trialists' Collaborative Group's overview analysis suggests that ovarian ablation is effective as adjuvant HT for premenopausal receptor-positive breast cancer patients regardless of nodal status. Premenopausal patients who receive chemotherapy and maintain their ovarian function may benefit from ovarian ablation. If the patient is younger than 50 years and there is a question about her ovarian function, FSH/LH and estradiol should be checked to document her menopausal status.

Adjuvant chemotherapy

Combination chemotherapy is superior to single agents in the adjuvant setting. The body of knowledge about adjuvant chemotherapy for breast cancer has benefited from the serial updates of the Oxford Overview analysis and from other large randomized trials, which have shown slight but statistically significant superiority of anthracycline-containing regimens over traditional CMF. Adjuvant chemotherapy results in an approximately 25% decrease of breast cancer mortality. However, the determination of the anthracycline-containing regimen of choice is still under investigation.

Doxorubicin (Adriamycin) and cyclophosphamide (AC) has a threshold effect; thus, doses greater than 60 mg/m2 and 600 mg/m2, respectively, are of no additional benefit. The results of three large US trials (NSABP B22 and B25, Cancer and Leukemia Group B 9344) did not support any role for dose intensification of the AC combination. However, two other studies, one French (French Adjuvant Study Group -05) and the other Canadian, showed that when epirubicin was escalated in the fluorouracil-epirubicin-cyclophosphamide (FEC) combination, disease-free survival and overall survival were significantly improved in operable breast cancer

with positive axillary lymph nodes.

High-dose chemotherapy with stem cell or bone marrow support did not prove superior to standard chemotherapy and is best reserved for clinical trials.

Results from two trials (Cancer and Leukemia Group B 9344 and NSABP-B28) exploring the role of taxanes in the adjuvant setting were encouraging. CALGB-9344 had a 3x2 factorial design with patients randomized to receive doxorubicin at 60, 75, or 90 mg/m2 followed by paclitaxel at 175 mg/m2 or no additional therapy. NSABP-B28 had similar design except that the dose of doxorubicin was not escalated and the dose of paclitaxel was 225 mg/m2. From the first trial it was established unequivocally that doxorubicin dose escalation does not improve outcome while the addition of paclitaxel results in small but statistically significant improvement of both the risk of relapse and the risk of death. In NSABP-B28, relapse free survival was significantly improved by the addition of paclitaxel while the data about survival are not available yet.

In patients with node-negative, early-stage disease (stages I, IIA, and IIB), chemotherapy is not indicated if the tumor is smaller than 0.5 centimeter, regardless of the histologic subtype. In persons with invasive ductal and lobular carcinomas, tumors measuring 0.6-1 centimeter require chemotherapy only if they were associated with unfavorable features (e.g., angiolymphatic invasion, high S-phase, high nuclear grade, high histologic grade), while all tumors larger than one centimeter require adjuvant chemotherapy alone (hormone-receptor negative) or in combination with tamoxifen (hormone-receptor positive). In patients with other histologic types (i.e., tubular, colloid, medullary, adenoid), chemotherapy is indicated only for tumors larger than three centimeters. It may be considered in those from 1-2.9 centimeters, and it is not indicated for tumors smaller than one centimeter.

In patients with node-positive, early-stage disease, adjuvant chemotherapy with or without adjuvant HT is the mainstay of treatment. Anthracycline-containing chemotherapy, such as doxorubicin (Adriamycin) (60 mg/m2) and cyclophosphamide (600 mg/m2), administered for four cycles is the treatment of choice. Many oncologists consider this treatment insufficient and opt for two more cycles of the same treatment or 2-4 cycles of paclitaxel (175 mg/m2).

In persons with advanced-stage disease (stage IIIA and IIIB), the same regimen of AC for four cycles followed by at least two more cycles of the same treatment or 4 cycles of a taxane is recommended after surgical treatment. Neoadjuvant chemotherapy may be offered to patients with this stage.

The role of neoadjuvant chemotherapy is being intensively investigated. The NSABP B-18 trial compared the effect of preoperative AC for four cycles to the same regimen postoperatively in subjects with early-stage breast cancer. Pathologic node-negativity of 60% and BCS of 68% could be achieved in the preoperative AC group compared with 42% and 60%, respectively, in the postoperative AC group. Five-year disease-free survival and overall survival rates for those who achieved pathologic complete response were 84% and 87% compared with 72% and 78%,

respectively, in patients who had residual disease.

Based on these encouraging results, NSABP started its B-27 trial to address the question related to the role of four cycles of preoperative or postoperative docetaxel added to four AC cycles. The use of preoperative docetaxel almost doubled the pathologically confirmed complete remission rate compared with the AC arm (25.6% vs 13.7%).

Because the role of neoadjuvant therapy is not fully established, participation in clinical trials should be encouraged. In ER- and/or PR-positive tumors, neoadjuvant tamoxifen or letrozole may achieve the same magnitude of response as chemotherapy but with longer time to response. Although the neoadjuvant approach does not seem to prolong survival, its theoretical advantages include downstaging the tumor, in vivo testing of the chemosensitivity of the tumor, and allowing BCS.

The treatment of metastatic disease is mainly medical. In postmenopausal patients with ER- and/or PR-positive tumors, the use of tamoxifen or an aromatase inhibitor (e.g., anastrozole, letrozole, exemestane) is the standard of care for bone disease and limited visceral disease. In many cases, at least a partial response can be achieved. Patients who progress on first-line HT may still respond to second- or third-line HT, aromatase inhibitors, and megestrol acetate, respectively.

ER down-regulators are a promising new class of HT agents that may have some efficacy if the previous treatments fail. In premenopausal women with ER- and/or PR-positive breast cancer, ovarian ablation and tamoxifen are the mainstays of treatment. Ovarian ablation can be achieved by medical (e.g., luteinizing hormone-releasing hormone analogues such as goserelin, leuprolide, buserelin, and triptorelin), surgical (i.e., bilateral oophorectomy), or RT methods.

Chemotherapy is indicated for patients with advanced visceral disease (visceral crisis) and those with hormone-refractory or hormone-insensitive tumors. The goals of chemotherapy in this setting are palliative and include control of symptoms, control of disease progression, and prolongation of life. The best response rates are obtained with first-line therapy and combination regimens. However, regardless of the response rates achieved with these therapies (including high-dose chemotherapy with autologous stem cell support), survival is not affected in most cases.

In 2001, Slamon and Pegram reported a survival advantage for the combination of chemotherapy and trastuzumab over chemotherapy alone in women with HER2-positive metastatic breast cancer.

Predictors of poor response to chemotherapy in patients with metastatic breast cancer are poor performance status, multiple and/or visceral sites of disease, short disease-free intervals, and failure to respond to prior chemotherapy. Because the goals of chemotherapy in patients with metastatic breast cancer are palliative, many authorities recommend the sequential use of single chemotherapeutic agents rather than combinations in order to limit toxicity. Taxanes,

anthracyclines, oral fluoropyrimidines, vinorelbine, and gemcitabine are the most effective drugs used in this setting.

Trastuzumab, a monoclonal antibody directed against the extracellular domain of the HER2/neu receptor, has shown significant antitumor activity in patients with metastatic breast cancer overexpressing HER2/neu. Response rates of 30-35% have been observed in patients with metastatic breast cancer who are receiving single-agent trastuzumab as a first-line therapy. The relative risk of death was decreased by 20% with a median follow-up of 30 months when trastuzumab was used in combination with chemotherapy. However, when combined with doxorubicin, a significant increase in cardiotoxicity was noted. For this reason, the current recommendation is to avoid trastuzumab in combination with or after doxorubicin.

The mechanism of action of trastuzumab is still debated. Trastuzumab induces down-regulation of HER2/neu and prevents its heterodimerization, reestablishing breast cancer cell sensitivity to HT and chemotherapy. As a result of this down-regulation, p27 is induced, resulting in cell-cycle arrest in the G1 phase. Furthermore, trastuzumab binds to the receptor at a site where the extracytoplasmic domain (ECD) is usually cleaved by metalloproteinases. The ECD cleavage results in a constitutively active truncated receptor and a more aggressive phenotype; this would be prevented by binding to trastuzumab. Finally, trastuzumab may induce antibody-dependent cytotoxicity, resulting in cell death.

Four large multicenter trials were conducted with trastuzumab in the adjuvant setting in patients with HER2/neu-positive breast cancer (NSABP B31, NCCTG N9831, The HERA trial and BCIRG 06). A combined analysis of the first two trials showed dramatic improvement of DFS in the group randomized to receive trastuzumab with chemotherapy consisting of AC x 4 followed by T x 4.

Radiotherapy (RT)

Radiotherapy reduces the risk of local recurrence and has the potential to decrease long-term mortality from breast cancer. Although certain studies have shown that RT following chemotherapy results in better long-term survival rates than the opposite, recent updates from Bellon et al. and the Joint Center randomized trial showed no significant differences between the CT-first and RT-first arms in any endpoint studied. A reduction of approximately 20% in local recurrence correlates with an absolute reduction of approximately 5% in long-term mortality from breast cancer 10-15 years later.

Radiotherapy to the breast (with or without the supraclavicular area) is indicated after lumpectomy in persons with early-stage breast cancer as an integral part of the treatment plan, and it is indicated after mastectomy in the presence of a large tumor mass (>5 cm), positive margins, and four or more lymph nodes positive for disease.
The role of axillary RT after radical ALND is debated. Many experts believe that RT is best avoided after complete dissection of the axilla for level I, II, and III nodes (RM and modified RM). A 6- to 8-fold increase in the incidence of lymphedema in the ipsilateral arm was reported

with the combined modality.

Surgical therapy

Procedures

Radical mastectomy (RM) is the en bloc resection of the breast, the overlying skin, the pectoralis muscles, and all of the axillary contents (level I, II, and III dissection). Extended RM is RM with removal of the internal mammary nodes. Both procedures are rarely performed in current practice. In addition to their mutilating effects, they result in functional impairment as a result of neurologic and lymphatic vessel damage. Resection of the involved portion of the muscle is satisfactory even when the tumor abuts or invades the pectoral fascia or when the muscle fascia was violated at the time of biopsy.

Modified RM implies the removal of breast tissue, the underlying fascia of the pectoralis major muscle, and some of the axillary lymph nodes. The nipple-areola complex and the area around the biopsy incision must be removed, but the remainder of the skin of the breast can be preserved.

Total mastectomy removes the entire breast. Both pectoralis muscles and the axillary nodes are preserved.

Skin-sparing mastectomy removes the breast parenchyma, the previous biopsy site(s), and the skin overlying superficial tumors through a periareolar incision. Thus, the breast envelope is preserved, allowing immediate reconstruction with improved cosmetic results. Skin-sparing mastectomy can be coupled with SLNB.

BCS (lumpectomy) removes the tumor with 0.5-1 cm of normal tissue. It is often coupled with ipsilateral axillary lymph node sampling and, increasingly, with SLNB. Quadrantectomy is the removal of the quadrant containing the cancer with the overlying skin and underlying pectoral fascia.

ALND, when performed in a 2-cm primary breast cancer to levels I and II, reduces the probability for regional recurrence from 20% to approximately 3%.

Regarding SLNB, the combined use of a radionuclide and a blue dye increases the detection rate of the SLN. Isosulfan blue (Lymphazurin) is the most commonly used blue dye. Five mL of isosulfan blue are injected into the parenchyma, and the injection site is gently massaged for 3-5 minutes before the SLNB procedure is performed. Technetium sulfur colloid, the radionuclide of choice, is used at a dose of 0.1-1 mCi. The isotope is injected into the parenchyma 1-2 hours before the procedure. The SLN is preoperatively localized using a handheld gamma probe.

Postoperative reconstruction

Breast reconstruction may be offered immediately or be delayed to patients with breast cancer as an integral part of the multidisciplinary therapeutic approach.

Immediate reconstruction is offered to patients with stage 0, I, or II disease. Its psychological, esthetic, and practical advantages outweigh its disadvantages, which mainly include the need for a multidisciplinary team collaborating during the same operative time and the absence of final histology results during surgery. Complications are similar to those of ablative surgery alone. Immediate reconstruction can be combined with any type of ablative surgery, including modified RM. Delayed reconstruction can be performed in all breast cancer stages. It usually follows chemotherapy and RT.

Two reconstructive techniques are used: implant insertion and autologous graft. Implants are made of a silicone shell filled with silicone gel or saline. Although the surgical procedure itself is short and easy, long-term complications are common and include capsular contracture/wrinkling, skin necrosis, and leakage (33%, 8.5%, and 6%, respectively). Because of this high rate of problems, multiple revisions are required, which can add significantly to the total cost. Implants are indicated for small- to medium-sized breasts, in women with poor general health, and in those with short life expectancy. They are contraindicated in patients who require chest wall RT, owing to the high rate of complications.

Although breast reconstruction using autologous tissue is more complex, its advantages far outweigh those of the implant. Esthetically, breast reconstruction results in a warm, soft texture of the breasts with good imitation of natural ptosis. Results are long-lasting, with a low rate of complications and subsequent procedures. Breast reconstruction is probably the only valid option for patients with partial mastectomy and those who require RT.

The most commonly used flaps are the pedicled latissimus dorsi myocutaneous flap, the thoracodorsal artery perforator skin-flat flap, the pedicled or free transverse rectus abdominis myocutaneous flap, the free deep inferior epigastric perforator skin-flat flap, the superior and inferior gluteus myocutaneous flap, and the free superior gluteal artery perforator skin-flat flap. The choice of the donor site and type of procedure depend not only on local conditions at the donor and recipient sites but also on the surgeon's experience.

Complications

• Mastectomy

• Wound infection and abscess

• Necrosis of skin flap

• Paresthesia of chest wall

• Phantom breast syndrome

• Postsurgical pain syndrome

• Seroma

• Lymphedema

• Axillary lymph node dissection

• Injury to or thrombosis of the axillary vein

• Seroma formation

• Lymphedema: The reported prevalence rate of lymphedema is approximately 11%, with extremes ranging from 5-30%. Extensive surgery, RT, and advanced age are recognized risk factors for arm edema. Although the risk may decrease with time, it does not completely disappear.

• Impairment of shoulder movements: Depending on whether the patient has received RT to the axilla, the incidence rate varies from 12-15% (RT) and 7-8% (no RT). Symptoms include decreased range of motion of the shoulder, a problem that may be improved with early participation in a physical therapy program.

• Damage to the brachial plexus, with chronic pain and varying degrees of decreased grip strength occurring in up to 15% of patients and lasting for more than a year after surgery

• Chest wall pain

• Chemotherapy

• Cyclophosphamide: Adverse effects may include hemorrhagic cystitis, and amenorrhea.

• Methotrexate: Adverse effects may include liver toxicity, increased toxicity in the presence of pleural effusion, and ascites.

• Fluorouracil: Adverse effects may include mucositis, hand-foot syndrome, and cerebellar ataxia.

• Doxorubicin: Adverse effects may include myocardial dysfunction, alopecia, nausea, vomiting, mucositis, and neutropenia.

• Paclitaxel: Adverse effects may include myelosuppression, peripheral neuropathy (less common if <170 mg/m2 is used), hypersensitivity reaction (premedication with steroids, H1- and H2-receptor blockers), cardiac toxicity, alopecia, mucositis, nausea, vomiting, and typhlitis.

• Docetaxel: Adverse effects may include myelosuppression, mucositis, conjunctivitis, edema due to capillary leak syndrome (>80% of patients if not medicated; <10% if premedicated with steroids), hypersensitivity reactions, neurotoxicity (less frequent than with paclitaxel), nausea, vomiting, and alopecia.

• Radiation therapy

• Necrosis of the breast soft tissue, prolonged breast edema, rib fracture (low rates, 1-3%)

• Decreased shoulder mobility (low rates, 1-3%)

• Brachial plexopathy with paresthesia and arm pain (low rates, 1-3%)

• Lymphedema

• Angiosarcoma: The 30-year cumulative risk is lower than 1%, with a peak incidence at six years.

• Lung cancer: Ipsilateral lung cancer may occur, with an increased risk in persons who smoke.

• Coronary artery disease: The risk has significantly decreased with newer RT techniques.

• Symptomatic pneumonitis: It is relatively infrequent, affecting 3-6% of women treated with RT for breast cancer. Patients present 3-12 months after competition of RT with dry cough, dyspnea, and low-grade fever. Chest radiographs may reveal intersitial infiltrate in the ipsilateral lung, which can evolve to fibrosis.

• Adverse effects of tamoxifen

• Endometrial cancer: This rare complication occurs in two of every 1000 women receiving tamoxifen. Most of these cases are detected at an early stage and are easily cured by surgery. Other than yearly gynecologic examinations in asymptomatic women, the National Cancer Institute and the American Society of Obstetricians and Gynecologists recommend prompt evaluation with endometrial biopsy in women on tamoxifen who experience vaginal bleeding.

• Perimenopausal symptoms: Hot flashes and mood changes may occur in women on tamoxifen and occasionally are very severe, thus posing a serious threat to the woman's quality of life. Selective serotonin uptake inhibitors have been used with some success to treat these symptoms.

• Cataracts: These have also been reported in women receiving tamoxifen, justifying a yearly eye examination.

• Adverse effects of trastuzumab

• Cardiac toxicity: In the phase III trial, trastuzumab alone resulted in cardiac dysfunction in 7% (class III/IV, 1.5%) of cases. The prevalence rate increased to 11% when trastuzumab was administered with paclitaxel (class III/IV, 0%). With the combination of anthracycline and cyclophosphamide, the prevalence rate increased to 28% (class III/IV, 6%). Apparently, the combination of an anthracycline and trastuzumab is particularly cardiotoxic. The mechanism of this dysfunction is yet to be defined.

Although HER2/neu is minimally expressed on the cardiomyocytes, trastuzumab-induced phosphorylation of HER2 has been documented in vitro and is associated with cytoskeletal infrastructure dysfunction, which seems to be the underlying mechanism. These abnormalities may be reversed by adding neuregulin to the culture milieu. Clinically, trastuzumab-induced cardiomyopathy is partly reversible by medical therapy.

• Fever, chills, nausea, vomiting, and pain with first infusion: These are relatively common but become infrequent with subsequent infusions.

Outcome & prognosis

Prognostic factors help predict the clinical outcome of the disease, while predictive factors are those that help predict the response to therapy. Certain factors are both prognostic and predictive.

Prognostic factors

Lymph node status is a significant prognostic factor. Axillary lymph node involvement and the number of lymph nodes involved remain the most important prognostic factors for invasive breast cancer. Although 75% of the lymphatic drainage from the breast goes to the axilla and 25% to the internal mammary lymph nodes, isolated metastasis to the internal mammary lymph nodes is extremely rare (~5%).

The prognosis depending on the number of axillary lymph nodes involved in patients who received adjuvant chemotherapy is as follows:

• With 0 positive nodes

• Recurrence rate at five years - Approximately 20%

• Survival rate at 10 years - 65-80%

• With 1-3 positive nodes

• Recurrence rate at five years - 30-40%

• Survival rate at 10 years - 35-65%

• With four positive nodes

• Recurrence rate at five years - Approximately 44%

• Survival rate at 10 years - Not available

• With more than four positive nodes

• Recurrence rate at five years - 54-82%

• Survival rate at 10 years - 13-24%

Additionally, tumor size is highly correlated with lymph node involvement and clinical outcome. Tumor size and the percentage of axillary node involved is as follows:

• Tumor smaller than 0.5 cm - Approximately 20%

• Tumor 0.5-0.9 cm - Approximately 20%

• Tumor 1-1.9 cm - 33%

• Tumor 2-2.9 cm - 45%

• Tumor 3-3.9 cm - 52%

• Tumor 4-4.9 cm - 60%

• Tumor larger than 5 cm - 70%

The 5-year survival rate based on tumor size and axillary lymph node status is as follows:

• Tumor smaller than 2 cm

• Negative nodes - 96%

• One to 3 positive nodes - 87%

• Four or more positive nodes - 66%

• Tumor 2-5 cm

• Negative nodes - 89%

• One to three positive nodes - 79%

• Four or more positive nodes - 58%

• Tumor larger than 5 cm

• Negative nodes - 82%

• One to three positive nodes - 73%

• Four or more positive nodes - 45%

Hormone receptor status helps predict the prognosis. The expression of ERs and/or PRs portends a good prognosis. It also helps predict the response to HT.

Finally, the histopathologic grade helps predict the patient's prognosis. This is a composite index based on nuclear differentiation (nuclear grade I, II, III; the higher, the worse), histologic differentiation (I, II, III; the higher, the worse), and mitotic index (I, II, III; the higher, the worse).

New prognostic or predictive factors

Cancers overexpressing HER2/neu are frequently poorly differentiated and lymph node–positive. HER2/neu overexpression correlates with more aggressive behavior and shortened disease-free survival and overall survival rates. HER2/neu overexpression is a marker of response to chemotherapy and HT, ie, relative resistance to tamoxifen and CMF and sensitivity to anthracycline- and taxane-containing regimens. HER2/neu overexpression predicts the response to trastuzumab and to monoclonal anti-HER2/neu antibodies in the metastatic setting. A few recent reports suggest that high serum HER2/neu levels predict resistance to HT. HER2 shedding may result in constitutive activation of its cytoplasmic domain and a more aggressive phenotype, with possible estrogen-independent activation of ER receptors, hence the resistance to tamoxifen.

Other predictive or prognostic factors include the EGF receptor family, the S-phase, and DNA ploidy. Overexpression of the EGF receptor family is inversely correlated with ER positivity and is usually associated with a poor prognosis. A high S-phase indicates a rapid proliferation rate and is associated with a worse prognosis. Because most breast cancers are aneuploid, the significance of aneuploidy awaits definition. However, diploid tumors are usually associated with a good prognosis.

Bone marrow micrometastasis is an area of current active research. Occult bone marrow micrometastasis has been discovered to help predict disease-free survival and overall survival of breast cancer patients with both lymph node–positive and lymph node–negative disease. The

presence of bone marrow micrometastasis is associated with larger tumor size, higher tumor grade, and lymph node involvement. Bone marrow micrometastasis is an independent prognostic indicator with a predictive value superior to axillary lymph node status, tumor stage, and tumor grade.

The last of the new predictive or prognostic factors includes angiogenesis, peritumoral lymphatic invasion and perineural invasion, cathepsin D, and obesity.

Future & controversies

Hormonal therapy

The selective estrogen receptor modulator family, headed by tamoxifen, has been enlarged by the addition of new members (i.e., toremifene, raloxifene, arzoxifene, lasofoxifene, idoxifene, EM-652, GW5638). Some have received approval for the same indications as tamoxifen (toremifene), and others are still the subjects of intense investigation. The introduction of aromatase inhibitors to the armamentarium of HT, first in the metastatic setting and more recently in the adjuvant setting, has opened new horizons for this modality. The new class of selective estrogen receptor down-regulators is being evaluated in clinical trials, and results are promising. Lastly, the rehabilitation of ovarian ablation with the use of luteinizing hormone-releasing hormone analogue has added another layer of complexity to modern HT for breast cancer.

The publication of the results of many aromatase inhibitor clinical trials including the ATAC, BIG 1-98 and the examestene trials evaluating the role or anastrozole, letrozol and examestene, respectively has announced the end of the tamoxifen domination era in the adjuvant setting. Furthermore, aromatase inhibitors have shown the capability to significantly reduce the prevalence of new contralateral breast primaries, paving the way for their use in chemoprevention trials. However, the following questions must be addressed.

• Which selective estrogen receptor modulators will be most effective in adjuvant and prevention settings?

• What is the role of selective estrogen receptor down-regulators?

• Which aromatase inhibitor is the best adjuvant therapy for breast cancer and if these agents are equivalent in terms of efficacy are they different in terms of toxicity?

• Using modern biotechnology (i.e., genomics, proteomics), will it be possible to predict the responsiveness to any of these hormonal therapies?

• Will prolonged treatment of aromatase inhibitors beyond five years be superior to five years of therapy (more than five years of tamoxifen is not superior to five year) ?

• What is the best sequence to provide these patients with the longest survival possible?

• What are the patterns of resistance to HT, and are there methods available to overcome them?

• Will long-term use of aromatase inhibitors result in an increased prevalence of skeletal or other complications?

The overview analysis from the Early Breast Cancer Trialists' Collaborative Group has shown that ovarian ablation results in significant improvement of disease-free survival and overall survival, similar to cytotoxic chemotherapy. Because chemotherapy itself results in ovarian failure in 30-40% of patients younger than 40 years and in 70-90% of patients older than 40 years, the relative contribution of chemotherapy and ovarian ablation is difficult to determine. Several ongoing adjuvant trials are examining the role of ovarian ablation versus chemotherapy, the role of combined chemotherapy and ovarian ablation, and, lastly, the role of total estrogen ablation using tamoxifen and ovarian ablation.

Chemotherapy

Several concepts are being explored in this area.

The precise role of taxanes in the adjuvant setting is still awaiting the results of completed (i.e., Breast Cancer International Research Group 001, Eastern Cooperative Oncology Group 2197) or ongoing trials. Three ongoing adjuvant trials are examining the role of sequential administration of taxanes following AC chemotherapy in early-stage breast cancer (Cancer and Leukemia Group B 9344, NSABP B-28, Eastern Cooperative Oncology Group 1199). Four other adjuvant trials are exploring the potential of doxorubicin/paclitaxel combinations (Breast Cancer International Research Group 001, Eastern Cooperative Oncology Group 2197, NSABP B-30, Breast Cancer International Research Group 005). Three trials are testing the effect of sequential anthracycline-containing regimens and paclitaxel in the neoadjuvant setting (NSABP B-27, M.D. Anderson Cancer Center, Aberdeen).

Many trials are addressing the role of trastuzumab in the adjuvant setting. The development of trastuzumab was a major triumph of transnational research into finding targeted therapy for cancer. Consequently, once this new drug proved its efficacy in the metastatic setting, it followed that researchers tried to include it in adjuvant regimens. However, to overcome its unexpected cardiac toxicity, new chemotherapy combinations and trial designs had to be sought.

Preclinical and clinical data have indicated dramatic synergistic interactions, with platinum salts and docetaxel forming the basis for an ongoing trial comparing sequential AC and docetaxel with or without trastuzumab to cisplatin or carboplatin with docetaxel and trastuzumab (Breast

Cancer International Research Group 006).

Two other trials are examining the efficacy of four cycles of AC followed by paclitaxel in different schedules with or without trastuzumab (NSABP B-31, North Central Cancer Treatment Group 9831). Vaccine trials are another type of trial targeting HER2/neu in the adjuvant setting. The theory that maximum efficacy of cancer vaccines is more likely to occur in minimal residual disease than in bulky disease is now accepted.

The success of bisphosphonates in reducing skeletal complications in persons with metastatic breast cancer has suggested a possible role for these noncytotoxic agents in the adjuvant setting. Previous trials have also shown a possible reduction of recurrences in sites other than bone and a survival benefit. To test the potential of this therapy in the adjuvant setting, 3 trials are underway (NSABP B-34, Southwest Oncology Group S9905, CLB-79809).

Postmastectomy radiotherapy

The 2000 National Institutes of Health Consensus Conference has recognized the benefit of postmastectomy RT in patients with breast cancer who have four or more positive lymph nodes, but participants could not make final recommendations for patients with 1-3 positive lymph nodes. Some benefit is probably derived in patients with 1-3 positive lymph nodes; however, because the absolute risk of failure is small, the demonstration of small absolute benefit requires a large clinical trial.
To lift the uncertainty surrounding this issue, the Southwest Oncology Group S9927 trial proposes to assess postmastectomy RT in women with stage II breast cancer with 1-3 positive lymph nodes. The impact of irradiating internal mammary and medial supraclavicular lymph nodes on survival, disease-free survival, metastasis-free survival, and cause of death in women with resected stage I/II/III breast cancer is being evaluated by European Organization for Research and Treatment of Cancer trial 10925. Another European study will compare complete ALND to axillary irradiation in SLN-positive women with operable invasive breast cancer (European Organization for Research and Treatment of Cancer 10981).

Therapy duration

Optimal duration of different breast cancer therapies is still the subject of discussion. The currently accepted theory is that in the adjuvant setting, 6 months of chemotherapy is equivalent to longer durations. However, controversy remains as to whether four months of chemotherapy (AC for four cycles) is equivalent to six months and, in the event that a longer regimen is used, whether a non–cross-resistant regimen should be implemented.

Adjuvant tamoxifen therapy for five years is superior to shorter durations, but whether longer durations are beneficial or detrimental remains to be determined. With the advent of aromatase inhibitors to the adjuvant arena, the question of their optimal duration will fuel the debate for the coming years.

Because of the absence of serious adverse effects, many oncologists tend to use trastuzumab in patients with metastatic breast cancer until progression. To date, whether the continuation of trastuzumab with a different cytotoxic agent is of any benefit to patients whose disease progresses while on combination therapy with trastuzumab and another cytotoxic agent remains unknown. The optimal duration of trastuzumab in the adjuvant setting has not yet been defined and will depend on knowledge gained regarding its mechanism of action. If trastuzumab is mainly a cytostatic drug, its prolonged use is justified; however, if it is found to be cytotoxic, a limited duration may be reasonable.

HER/neu as a predictor or prognostic factor

The role of tissue HER2/neu as a prognostic and predictive factor has not been resolved. Early reports on the prognostic significance of tissue HER2/neu levels based on human and animal research have suggested that HER2/neu overexpression is a poor prognostic factor, although later clinical studies could not confirm these results. Similarly, the role of HER2/neu as a predictive indicator of response to chemotherapy or HT was tempered by the retrospective nature of these studies.

A part of this discrepancy is also related to the lack of a validated measurement assay. Several large retrospective studies analyzing serum banks from HT trials have suggested that elevated serum ECD-HER2 levels are correlated with a poor prognosis and resistance to HT.

Other smaller retrospective studies found similar results regarding serum ECD-HER2, ie, a negative prognostic but not predictive role. Owing to its simplicity and the possibility to express the results quantitatively, serum ECD-HER2 measurements should be included in future prospective trials to determine their exact value.

Patient selection

Controversy remains regarding the test of choice to select patients who may benefit from trastuzumab. Because this is a targeted therapy, reliably identifying patients who carry the overexpressed target, HER2/neu, is important. Early trials have used IHC, which is a semiquantitative method with high rates of false-positive and false-negative results compared with the more precise method, ie, detection of gene amplification by FISH.

Retrospective analysis of the FISH status of patients with metastatic breast cancer treated with trastuzumab as first-, second-, or third-line therapy showed that FISH was by far superior to IHC in predicting response to this agent. Response to therapy in patients with FISH-negative tumors was close to zero, while all the patients who experienced a clinical response had FISH-positive tumors.

The problem with FISH testing is the need for expensive equipment and consequent limited availability in pathology laboratories. To mitigate these deficiencies, effort was directed toward quantitation of the shedding of HER2/neu in the serum. Although a good correlation exists

between serum HER2 levels and HER2/neu expression in the tumor, this test, critics argue, does not accurately reflect the HER2/neu tumor status and cannot register single-cell expression, both required for clinical decision-making processes. The Breast Cancer International Research Group 006 trial is comparing peripheral levels of shed HER2 with FISH for predicting outcome, while the North Central Cancer Treatment Group N9831 trial is examining whether pretreatment levels of shed HER2 and HER1 and their autoantibodies are prognostic.

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(Part Two) Traditional Chinese Medicine in the Treatment of Breast Cancer

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Abstract

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Traditional Chinese medicine (*TCM*)is becoming increasingly popular in many medical contexts, particularly among patients with cancer. TCM encompasses a range of modalities including herbal medicine, acupuncture, medical qigong, dietary recommendations and meditation (*daoyin*). In contrast to standard chemotherapeutic and hormonal regimens used for the adjuvant treatment of early stage breast cancer, very little data from controlled clinical trials has been generated using TCM modalities in relationship to the outcomes of recurrence or survival,or even overall quality of life and safety. As we previously reported , the objectives of TCM modalities are manifold - the reduction of therapeutic toxicity, improvement in cancer-related symptoms, improvements in the immune system, and even a direct anti-cancer effect. The primary basis of TCM rests upon empirical evidence and case studies, as well as its

theoretical principles.In some cases, laboratory or clinical data lend support to these modalities. Although TCM practices are based on ancient medical tenets founded on centuries of experience, and documented through oral and written texts, its direct relationship to breast cancer treatment in an integrative setting is very young. There is still a paucity of evidence in the clinical setting, which limits firm conclusions about the effectiveness or safety of most TCM approaches to breast cancer. This review will summarise the application of certain TCM modalities in the therapy of early stage breast cancer.

Introduction

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Cancer affects one in three individuals in the Unites States and most patients seek initial evaluation and therapy in the modern conventional setting. Most oncologic therapies are based on evidence from randomised trials showing improvements in outcomes, particularly survival. However the use of TCM is becoming increasingly prevalent both where few conventional therapeutic or ameliorative options exist and also because standard oncologic therapies have side effects that can significantly affect patients' short and long term quality of life. A review of surveys of cancer patients from around the world showed the average prevalence of complementary and alternative medicine (*CAM*) use was 31%, with the most common types cited being dietary treatments, herbs, homoeopathy, hypnotherapy, imagery/visualisation, meditation, megavitamins, relaxation and spiritual healing. In China many hospitals that have cancer wards offer TCM treatments alongside Western treatments, although there is no formal study addressing the use of TCM among cancer patients. Colleagues in China estimate that in rural areas almost all patients take herbal medicine when treated for cancer,while in urban areas that number is estimated to be 50%-60%, with increase of use in more advanced stages of the disease. A population-based study conducted in San Francisco, California showed that 72%of women with breast cancer used at least one form of complementary or alternative medicine,and one third used two forms. The types of approaches used included dietary therapies (*26.6%, including megavitamins*), spiritual healing (*23.7%*), herbal remedies (*12.9%*),physical methods (*14.2%*),and psycho- logical methods (*9.2%*). The use of herbal medicine among women with ovarian cancer was 51% while only 12% of the women used trained herbalists for guidance. Use of CAM was more common in younger women, more educated individuals, and among women with advanced stages of cancer; about half of the patients reported the usage of CAM modalities to their physicians. The complete abandonment of conventional therapy accompanying the use of alternative approaches is not very common despite the fact that conventional and alternative medicine in the Western world are almost never administered in a coordinated fashion. Most formally trained medical oncologists tend to avoid making recommendations in the areas of alternative medicine and are generally reluctant to integrate their treatment plan with a discipline that is foreign to their training and not represented in the scientific literature. Yet at the same time, increasing awareness of CAM,coverage by the lay press and intense presence through electronic media, especially via the internet, has amplified cancer patients' interest in and pursuit of CAM. A recent analysis of over 1,000 CAM studies for

breast cancer published in the mainstream biomedical literature however revealed few controlled,well designed studies with adequate endpoints.
Several TCM modalities have been highlighted for discussion of their potential study and applicability in the area of adjuvant therapy for early stage breast cancer. Of these, special emphasis is placed on herbal medicine and acupuncture given their prevalent use in China and by Western practitioners.

Traditional Chinese Medicine

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Traditional Chinese Medicine (*TCM*) serves as a useful yet complicated model of CAM therapy in a variety of medical settings.TCM consists of herbal medicine that is usually administered as a combination or formula,as well as acupuncture. Therapy is typically individualised on the basis of a TCM diagnosis of imbalance of the body measured by various parameters including yin,yang,qi,blood and body fluids. TCM diagnoses generally do not follow standard Western pathophysiologic classifications of disease. The tradition of TCM has evolved and been passed down for centuries and several well recognised texts and training institutions exist; hence, there is a fair degree of standardisation of diagnostic and therapeutic practice. Furthermore, TCM practice is licensed and regulated in most US states. Given the widespread use of TCM on the West coast of the United States, our research program has focused on this modality for clinical investigation in several settings for breast cancer. Although a significant body of research has been conducted in China into the ability of TCM to treat cancer, many of the studies are of poor quality, lack proper control groups, fail to describe the specific methods of the study and omit information about the statistical significance of the results. An overview of both acupuncture and herbal medicine studies in specific cancer-related settings is presented here as it applies to the potential for the study of TCM in early stage breast cancer in conjunction with and following chemotherapy or radiation therapy.

TCM intervention for surgery

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Surgery is by far the most effective treatment for early breast cancer and all women diagnosed with early breast cancer will undergo surgery as the main treatment for the disease. Currently women face several surgical options when encountering breast cancer diagnosis: lumpectomy with or without axillary lymph node excision (*axillary clearance*) or sentinel node excision,or modified radical mastectomy. Surprisingly there is no significant survival benefit to mastectomy over lumpectomy followed by locoregional radiotherapy. In recent years women who are diagnosed with large breast tumors, for whom lumpectomy is impractical for cosmetic reasons, have undergone neo-adjuvant chemotherapy, prior to surgery, in order to attempt to reduce the tumour size and conserve the breast. There is no significant difference in survival between

women who undergo neo-adjuvant chemotherapy followed by surgery and women who undergo modified radical mastectomy . .
From a TCM point of view surgery is considered as an externally inflicted wound that results in damage to the smooth flow of qi and blood, gives rise to qi deficiency and blood stasis and results in both accumulation of blood in the vessels and in inability of the Spleen qi to contain qi and blood. Anaesthesia disturbs the functions of the hun (*ethereal soul*) and po (*corporeal soul*) in commanding the distribution and correct response of qi and blood. While under normal circumstances the body would have reacted with pain and strong survival response elicited by a combination of voluntary and involuntary reactions, the artificial disturbance of anaesthesia on the the hun and po results in irregularity in the normal course of the flow of qi, resulting in shen disturbance, qi deficiency and blazing of yin fire. The resulting symptoms such as pain, bruising, immobility, nausea and vomiting are part of that syndrome.
Although chemotherapy may induce nausea and vomiting as well, the type of symptoms and the duration of the symptoms encountered by women will be different. Post operatively the symptoms of nausea and vomiting tend to be shorter in duration: from a few hours to 3 days. The mechanisms of nausea and vomiting induction are not very clear. Many brain areas seem to be affected (*area postrema, nucleus tractus solitarius and central pattern generator*)and they are all mediated by abdominal vagal afferents.

Pre-operative acupuncture

Several issues can be addressed by TCM pre-and post- operatively.In preparation to surgery,acupuncture has been shown to reduce nausea and vomiting and pain. Simple points like Hegu L.I.-4, Taichong LIV-3, Zusanli ST-36 and Neiguan P-6 have been used successfully for this purpose.

Contraindicated herbs with anaesthesia

Several anecdotal reports can be found in the literature of suspected negative interaction between anaesthesia control and herbs and suggest that some caution should be practised.The following pharmacological categories are recommended to be used with caution:

Anticoagulants

Bai Zhu (*Rhizoma Atractylodis Macrocephalae*)
Dan Shen (*Radix Salviae Miltiorrhizae*)
Chuan Xiong (*Radix Ligustici Wallichii*)

Antithrombics

Dang Gui (*Radix Angelicae Sinensis*)
Hong Hua (*Flos Carthami Tinctorii*)
Jiang Huang (*Rhizoma Curcumae*)
Yi Mu Cao (*Herba Leonuri Heterophylli*)

CNS stimulating effect

Jin Yin Hua (*Flos Lonicerae Japonicae*)
Ma Huang (*Herba Ephedrae*)

Ren Shen (*Radix Ginseng*)

Coronary vasodilating and flow increasing
Bai Guo Ye (*Folium Ginkgo Bilobae*)
Bai Shao (*Radix Paeoniae Lactiflorae*)
Bu Gu Zhi (*Fructus Psoraleae Corylifoliae*)
Ji Xue Teng (*Radix et Caulis Jixueteng*)
Hypertensives
Sheng Jiang (*Rhizoma Zingiberis Officinalis Recens*)
Chen Pi (*Pericarpium Citri Reticulatae*)
Wu Yao (*Radix Linderae Strychnifoliae*)

Platelet aggregation inhibitors
Ge Gen (*Radix Puerariae*)
Shan Zhu Yu (*Fructus Corni Officinalis*)
Yan Hu Suo (*Rhizoma Corydalis Yanhusuo*)
Yin Yang Huo (*Herba Epimedii*)

Post-operative acupuncture

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Therapeutic and reconstructive surgeries bring on a variety of unwelcome conditions, including pain, anaesthesia-induced nausea,short-term diminished mobility, bruising and fatigue. TCM can be used to accelerate wound healing, increase peripheral blood circulation to aid the supply of nutrients and blood cells to the wounded area, aid nerve regeneration, reduce scarring, enhance the immune system and prevent lymphedema (*swelling of the arm that can occur after the lymphatic vessels are severed by surgery*).
A preliminary study of post surgical nausea,vomiting and pain,conducted at Duke University showed that acupuncture is slightly more effective than the most commonly used antiemetic, ondansetron (*Zofran*).40 women undergoing breast surgery (*augmentation, reduction or mastectomy*) requiring general anaesthesia were studied. The surgery lasted 2-4 hours. The results can be summarised as follows:

Symptom	Placebo	Zofran	Acupuncture
Incidence of nausea at 2 hrs. post-op	69%	36%	23%
Incidence of vomiting at 2 hrs. post-op	23%	7%	7%
Incidence of nausea at 24 hrs. post- op	61%	57%	38%
Incidence of vomiting at 24 hrs. post-	46%	28%	23%

op			
Incidence of pain at 2 hrs. post-op	77%	64%	31%

On the surface the results seem more than slightly better for the acupuncture treatment, but the number of women treated in this study was too small to derive a statistically significant conclusion.
Other than postoperative nausea,vomiting and pain, acupuncture is very useful to relieve postoperative constipation. Points like Shangjuxu ST-37,Xiajuxu ST-39, Yanglingquan GB-34,Zhigou SJ-6,Neiguan P-6,Tianshu ST-25, Qihai REN-6 and Qihaishu BL-24 seem to be very effective, especially when stimulated strongly. Acupuncture can be complemented with some herbs that stimulate bowel motility like Da Huang (*Rhizoma Rhei*)and Huang Lian (*Rhizoma Coptidis*). Gui Zhi Jia Shao Yao Tang (*Cinnamon Twig Decoction plus Peony*)may also be used.
Post-operative herbal interventions to help wounds heal and stimulate platelet aggregation herbs such as Huang Qi (*Radix Astragali*) are used , whilst herbs that inhibit granulation,such as Ba Ji Tian (*Radix Morindae Officinalis*) , should be avoided.
The application of herbal medicine after surgery takes into consideration the post-surgical syndrome, as described above, as well as the disease itself and the opportunity to initiate prevention of recurrence. Strengthening qi and fluids,regulating blood and reducing heat and toxins are the therapeutic principles employed.

Breast Cancer Post-Operative Formula	
Herb name	**Dose in grams**
Xia Ku Cao (*Spica Prunellae Vulgaris*)	15
Dang Gui (*Radix Angelicae Sinensis*)	10
Zhu Ling (*Sclerotium Polypori Umbellati*)	15
Shan Ci Gu (*Bulbus Shancigu*)	6
Jin Yin Hua (*Flos Lonicerae Japonicae*)	12
San Qi (*Radix Pseudoginseng*)	1.5
Huang Qi (*Radix Astragali*)	15
Tai Zi Shen (*Radix Pseudostellariae Heterophyllae*)	15
Gua Lou (*Fructus Trichosanthis*)	20
Fu Ling (*Sclerotium Poriae Cocos*)	15
Zi He Che (*Placenta Hominis*)	12

Bai Shao (*Radix Paeoniae Lactiflorae*)	10
Tian Men Dong (*Tuber Asparagi Cochinchinensis*)	15
Bai Hua She She Cao (*Herba Oldenlandiae Diffusae*)	15
Ren Shen (*Radix Ginseng*)	5
Zhi Mu (*Radix Anemarrhenae Asphodeloidis*)	12

TCM and radiation treatment

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Radiation is another prevention method for early breast cancer.The application of high energy beams through the breast tissue and local lymph nodes reduces the probability of local recurrence. Radiation exerts its cell inhibitive effect through the creation of a high concentration of free radicals that create high local oxidative stress. The oxidative stress causes irreparable DNA damage and results in cell death. Since the cell death caused by radiation is not selective to cancer cells the whole radiated area is affected and the body responds to it with strong inflammatory reaction. The main side effects of radiation are fatigue accompanied by agitation and insomnia. TCM views radiation as an extreme external attack of heat and dryness which,as with sun exposure, damages the yin fluids and the Spleen qi, with local accumulation of heat, fire and toxins. Inhibition of the Spleen's ability to transform pure from impure and to propel the vapour from food results in a complex picture of heat-fire dryness above,stagnation of heat toxins locally and deficient damp-heat below.
In order to increase the cell killing effect of radiation and control its local side effects,one needs to increase oxygenation to cells,and promote peripheral blood flow .

Herbs that are commonly used during radiation

Anti-hypoxic effect (*increase cell oxygenation*):
Dang Shen (*Radix Codonopsis Pilosulae*), Hong Hua (*Flos Carthami Tinctorii*), Bai He (*Bulbus Lilii*), Yin Yang Huo (*Herba Epimedii*).

Microcirculation improving effect:
Chuan Xiong (*Radix Ligustici Wallichii*), Dang Shen (*Radix Codonopsis Pilosulae*), Pu Huang (*Pollen Typhae*), Yi Mu Cao (*Herba Leonuri Heterophylli*).

Antihistaminic effect (*can reduce itching ,anti inflammatory effect can reduce swelling and redness in the breast and skin*):
Bai Zhi (*Radix Angelicae*),Qin Jiao (*Radix Gentianae Macrophyllae*), Jin Yin Hua (*Flos Lonicerae Japonicae*), Huang Qin (*Radix Scutellariae Baicalensis*).

Radiation sensitising effect:

Ren Shen (*Radix Ginseng*), Ling Zhi (*Ganoderma Lucidum*), Gui Pi Tang (*Restore the Spleen Decoction*), Hong Hua (*Flos Carthami Tinctorii*).

Two herbs [Shu Di Huang (*Radix Rehmanniae Glutinosae Conquitae*)and Rou Gui (*Cortex Cinnamomi assiae*)]can inhibit radiation effect; when given to animals they increase their survival.

Burns and skin protection

To prevent radiation burns and rashes apply Aloe-Vera gel (*fragrance-free,above 96%pure; fresh Aloe juice or leaf is superior*) on the skin 2-3 times a day. If an itchy, red, rough sensation starts to develop apply Ching Wan Hung ointment, once or twice a day. Beware that it stains everything. For more severe burns apply the following formula externally: Da Huang (*Rhizoma Rhei*)30, Di Yu (*Radix Sanguisorbae Officinalis*)30, Hong Hua (*Flos Carthami Tinctorii*)20, Chuan Xiong (*Radix Ligustici Wallichii*)15, Long Kui (*Herba Solani Nigri*)20, Han Shui Shi (*Calcitum*) 12, Shi Gao (*Gypsum*)12. In cases of blistering and pus add Huang Bai (*Cortex Phellodendri*).

Grind the above ingredients to very fine powder and mix with boiling water to make a light paste. Apply to burns with gauze, twice a day and leave on the skin for 30-60 minutes.

Fatigue

From the TCM perspective, radiation-induced fatigue is due to accumulation of heat toxin causing dryness and therefore disturbing the yin fluids. This in turn causes yin vacuity blazing fire. The symptoms are extreme fatigue accompanied by agitation and insomnia. This usually does not start until the third week into radiation therapy. Weekly acupuncture treatment relaxes this sort of agitation and comprehensive herbal therapy attempts to counter the damage to the fluids and the inflammation.

Scarring

Scarring from radiation is different from that of surgery. Since the radiation exposure covers a large area, the beams pass through and scatter to areas in the interior of the body, mainly the lungs and, if the cancer was in the left breast, to the heart. Though radiation technology has improved significantly in the last decade, preventing heart and lung fibrosis is important. Again the herbs we use are those that increase microcirculation, decrease collagen activity and promote the breakdown of scars, protecting the body from pulmonary fibrosis caused by radiation: Dan Shen (*Radix Salviae Miltiorrhizae*),Yu Jin (*Tuber Curcumae*) and Ji Xue Teng (*Radix et Caulis Jixueteng*).

About the Authors

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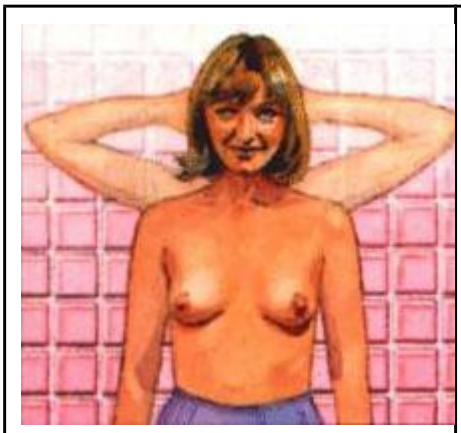
(Part Two) Traditional Chinese Medicine in the Treatment of Breast Cancer

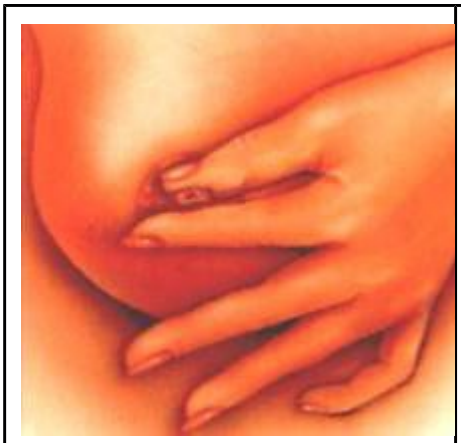
THREE STEPS TO BREAST HEALTH

1. Breast Self-Examination (BSE)

Look for Changes

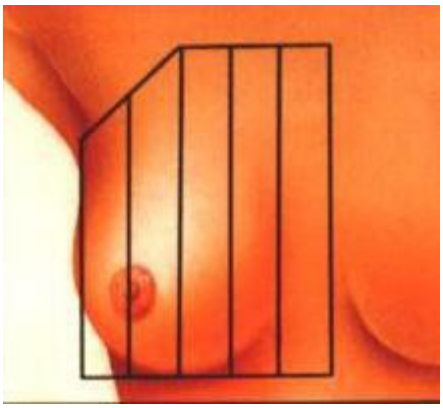
Changes in the way your breasts look may reveal a lump that cannot be felt. A hidden lump could cause a dimpling of the breast or, in some cases, a puckered nipple. A rusty-colored or puslike discharge from the nipple may indicate a blocked duct or other problem.

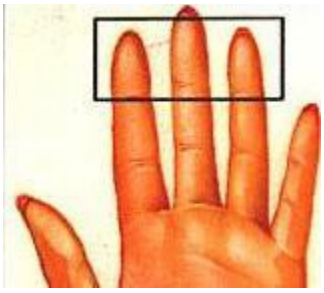
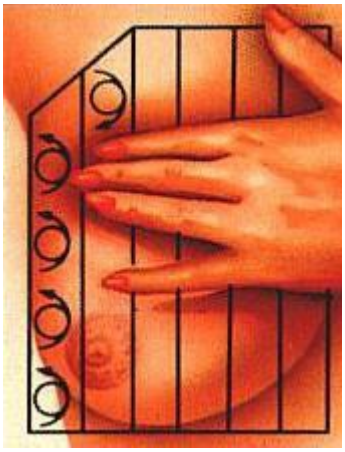
	Look for changes in your breasts while holding your arms at your side. Then, raise your arms above your head, clasp your hands behind your neck, and check again.		
	Press your hands on your hips to flex your chest muscles. Look for changes in the appearance of your breasts.		

	Squeeze your nipple between your thumb and forefinger to check for discharge. (A drop or two of clear or whitish fluid is normal.)		

Feel For Changes

To recognize changes in the way your breasts feel, *do a thorough breast self-exam (BSE) at the same time each month.* Once you know how your breasts feel normally, you can detect even minor changes. Perform BSE while lying down or while showering. (Hands glide easily over wet, soapy skin.)

	Lie down and place a pillow under the shoulder of the breast you're examining. Keep the arm on that side raised as shown.
	Mentally divide the breast area into strips or circles. The area should include your collar bone to your bra line and your breast bone to your underarm.

	Feel with the sensitive pads of your three middle fingers held flat.
	Use small circular motions to cover each area of the strip or circle. Go over each area three times using varying degrees of pressure as shown.
	1) Use light pressure to feel for changes below the skin.
	2) Use deeper pressure to feel for changes in breast tissue.

2. Professional Breast Exams

Contact your doctor immediately if you note any changes in your breasts. In addition, professional exams are recommended *at least* every 1-3 years for women between the ages 20 and 40, and annually thereafter. Ask your doctor or nurse any questions you may have about breast health or self-examination techniques.

3. Mammography

Mammography is a safe, low-dose x-ray technique that creates images of the inside of the breast. Mammography can detect lumps before they can be felt, so it is a particularly valuable screening procedure. Have a screening mammogram by age 40. From age 40 to 49, have one every 1-2 years, then annually from age 50 on.

About Risk Factors

We don't know what causes breast cancer, but some factors may be linked with a higher risk of developing it. If you're over 40 or have a history of breast cancer in your family (such as breast cancer in your mother or sister), you may be at greater risk. Being at risk does *not* mean you will develoop breast cancer. The purpose of knowing your risk factors is to help devise a breast health program suited to your individual needs. Although breast cancer may not be prevented, early detection is the best means possible for ensuring prompt, successful treatment and, in many cases, total cure.

***Bu Zhong Yi Qi Tang* & Adjunctive Chemotherapy in Breast Cancer**

abstracted & translated by
Bob Flaws, Lic. Ac., FNAAOM (USA), FRCHM (UK)

Keywords: Chinese medicine, Chinese herbal medicine, oncology, chemotherapy, breast cancer, *Bu Zhong Yi Qi Tang* (Supplement the Center & Boost the Qi Decoction)

On pages 33-34 of issue #1, 2005 of the *Hu Nan Zhong Yi Za Zhi (Hunan Journal of Chinese Medicine)*, Xu Jiang-li and Wu Jun published an article titled, "*Bu Zhong Yi Qi Tang* (Supplement the Center & Boost the Qi Decoction) Combined with Adjunctive Chemotherapy in the Treatment of 48 Cases of Breast Cancer)." A summary of that article is presented below.

Cohort description:

Altogether, there were 96 patients enrolled in this two-wing comparative study. All were female patients with breast cancer seen at the Hunan Chinese Medical Cancer Hospital from February 2000 to February 2002. These patients ranged in age from 28-60 years, with an average age of 51.2 years. Based on ultrasonography of lymphnode metastases, all these patients were stage II-III. These 96 patients were randomly divided into two groups, a treatment group and a comparison group that were statistically comparable in terms of their disease diagnosis and clinical staging.

Treatment method:

All members of the comparison group received the CEF chemotherapy protocol. This consisted of 500mg/m2 of cytoxan on days 1 and 21, 70mg/m2 of epirubicin on days 1 and 21, 200mg/m2 of formyl tetrahydrofolic acid on days 1 and 21, and 600mg/m2 of 5-FU on days 1 and 21. The course of chemotherapy lasted from day 1-24. In addition, 40mg of leucogen plus 100mg of batyl alcohol were administered orally three times per day.

All members of the treatment group received the same CEF protocol. In addition, they received the following Chinese medicinals:

Huang Qi (Radix Astragali Membranacei), 40g
Ren Shen (Radix Panacis Ginseng), 10g
Dang Gui (Radix Angelicae Sinensis), 15g
Chen Pi (Pericarpium Citri Reticulatae), 10g
Sheng Ma (Rhizoma Cimicifugae), 6g
Chai Hu (Radix Bupleuri), 10g
Bai Zhu (Rhizoma Atractylodis Macrocephalae), 10g
Yi Mu Cao (Herba Leonuri Heterophylli), 15g
Gou Qi Zi (Fructus Lycii Chinensis), 15g
Tu Si Zi (Semen Cuscutae Chinensis), 15g
Yi Yi Ren (Semen Coicis Lachryma-jobi), 20g
Bai Hua She She Cao (Herba Oldenlandiae Diffusae Cum Radice), 30g

One packet of these medicinals was decocted in water and administered per day warm in two divided doses.

Study outcomes:

Prior to chemotherapy and on days 14, 21, and 24 of chemotherapy, patients' blood was examined in terms of white blood cells (CBCs), platelets, and hemoglobin. After chemotherapy, patients were checked for digestive tract side effects and any changes in electrocardiogram. The following table shows mean blood analysis in the two groups.

Treatment group Comparison Group
WBCs Platelets Hemoglobin WBCs Platelets Hemoglobin
Before chemo. 5.45 1.05 X 109 /L 181.24 48.23 X 109 /L 116.24 21.28 g/L 5.64 1.32 X 109 /L 172.53 51.24 X 109 /L 116.02 19.23g/L
Day 14 4.32 4.12 180.12 41.36 112.04 19.23 2.84 0.98 146.78 52.06 96.42 16.12
Day 21 4.56 1.32 181.04 52.06 114.28 15.86 3.86 1.04 145.64 46.23 94.56 17.89
Day 24 4.10 0.35 168.28 58.23 110.46 66.24 3.56 0.64 44.36 38.02 92.18 24.28

This table shows that mean reductions in WBCs, platelets, and hemoglobin due to chemotherapy were all significantly less in the treatment group than in the comparison group.

The following table shows the incidence of fatigue, nausea and vomting, EKG changes (such as bradycardia, premature beat, and changes in the ST and T portions) in the two groups.

Treatment group Comparison group
Fatigue Nausea & vomiting EKG changes Fatigue Nausea & vomiting EKG changes
Week 1 12 36 2 32 36 4
Week 2 14 38 4 30 34 24

This table shows that the incidence of nausea and vomiting due to chemotherapy was the same in the two groups. However, the treatment group had significantly less fatigue at both one and two weeks. Additionally, although the number of adverse EKG changes at week 1 were not hugely significantly different, at week 2, six times more patients in the comparison group (half the total group) had such reactions. Thus the Chinese herbal protocol seemed to have some cardio-protective ability from the toxicity of the chemotherapy.

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Er Xian Tang (Two Immortals Decoction) as the Main Treatment of Menopausal Syndrome As a Sequela of Breast Cancer Treatment

abstracted & translated by
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Keywords: Chinese medicine, Chinese herbal medicine, gynecology, menopausal syndrome, breast cancer, *Er Xian Tang* (Two Immortals Decoction)

In issue #2, 2004 of the *Zhe Jiang Zhong Yi Za Zhi (Zhejiang Journal of Chinese Medicine),* Liu Long and Zou Zhi-feng of the Shanghai Changzheng Hospital published an article titled, "*Er Xian Tang* (Two Immortals Decoction) as the Main Treatment of 35 Cases of Menopausal Syndrome As a Sequela of the Treatment of Breast Cancer." This article appeared on page 75 of that journal. Because one in 10 North American women are predicted to develop breast cancer in their lives and because *Er Xian Tang* contains Dang Gui (Radix Angelicae Sinensis), a summary is given below.

Cohort description:

All 35 women in this study were seen as out-patients at the authors' hospital in Shanghai. They were 25-56 years of age, with a median age of 47.23 3.51 years. Eight cases had noninfiltrative cancer, 28 had early stage infiltrative (or invasive) cancer, and nine cases had infiltrative cancer. All had undergone surgery. After surgery, 15 cases had undergone chemotherapy with the CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) protocol and 20 had used the CMF (cyclophosphamide, methotrexate and 5-fluorouracil) protocol. In addition, 18 cases had also undergone treatment with triphenylamine, nine cases had been treated with megestrol, and eight cases had been treated with another unidentifiable chemotherapeutic agent. Subsequent to this chemotherapy, 20 had developed hot flashes and sweating, 23 had developed vexation, agitation, and irritability, 16 had developed fear of cold and dread of wind, 20 had developed vexatious heat in the five hearts, 15 had developed psycho-emotional unrest, 25 had developed dizziness and tinnitus, 23 experienced low back and knee soreness and limpness, and 18 experienced heart palpitations and insomnia. Eight cases had previously used Chinese medicinals, while 27 had not.

Treatment method:

All the patients in this study were orally administered the following basic formula:

*Xian Mao (*Rhizoma Curculiginis)
Ba Ji Tian (Radix Morindae Officinalis)
Zhi Mu (Rhizoma Anemarrhenae)
Huang Bai (Cortex Phellodendri)
Dang Gui (Radix Angelicae Sinensis)
Sheng Di (uncooked Radix Rehmanniae), 15g each
Xian Ling Pi (Herba Epimedii), 30g.
If there was qi vacuity, 30 grams each of *Huang Qi* (Radix Astragali) and *Dang Shen* (Radix Codonopsis) were added.
If yang vacuity was marked, the dose of *Xian Ling Pi* was increased up to 60 grams.
If yin vacuity was marked, 15 grams each of *Bei Sha Shen* (Radix Glehniae), *Tian Men Dong* (Tuber Asparagi), and *Mai Men Dong* (Tuber Ophiopogonis) were added.
If there was constipation, 30 grams of stir-fried *Lai Fu Zi* (Semen Raphani) and nine grams of stir-fried *Zhi Ke* (Fructus Aurantii) were added.
If there was poor appetite, 15 grams of stir-fried *Ji Nei Jin* (Endothelium Corneum Gigeriae

Galli) and 30 grams of stir-fried *San Xian* (Three Immortals) were added.
If there was low back and knee soreness and limpness, 15 grams each of *Du Zhong* (Cortex Eucommiae), *Xu Duan* (Radix Dipsaci), and *Sang Ji Sheng* (Herba Taxilli) were added.
If there was qi depression, nine grams of *Chai Hu* (Radix Bupleuri) and 15 grams of *Yu Jin* (Tuber Curcumae) were added.
Then, on top of the above basis, a selection of the following anti-cancer medicinals were selected: *Quan Xie* (Scorpio), *Wu Gong* (Scolopendra), *Ge Ke* (Concha Meretricis), *Qi Ye Yi Zhi* Hua (Rhizoma Helminthostachydis), *Di Long* (Pheretima), *Xia Ku Cao* (Spica Prunellae), and *Shan Ci Gu* (Bulbus Shancigu) to suppress the cancer.
One packet of the above medicinals was soaked in water for one hour. Then it was boiled twice to obtain 300ml of medicinal liquid. This was administered in two divided doses, morning and evening. Fifteen days equaled one course of treatment and 2-3 successive courses were administered.

Study outcomes:

Marked effect was defined as a disappearance of clinical symptoms and no recurrence within three months of stopping the above medicinals. Some effect was defined as disappearance of clinical symptoms. However, within three months of stopping the above medicinals, the symptoms returned. No effect meant that, although a part of the symptoms disappeared, after stopping the above medicinals, the symptoms that had been eliminated returned even worse than before. Based on these criteria, 16 out of 35 patients were deemed to have gotten a marked effect, 12 got some effect, and two got no effect. Therefore, the total effectiveness rate was reported as 94.28%.

Discussion:

The main thing I would like to draw readers' attention to is the fact that the above formula contains *Dang Gui* (Radix Angelicae Sinensis), a herb which contains phytoestrogens. Breast cancer is regarded as an estrogen-dependent cancer. Therefore, women with or who have had breast cancer are advised to stay away from any exogenous sources of estrogen. Based on this, many Western MDs have advised their breast cancer patients to stay away from any herbal preparations that contain *Dang Gui.* This opinion is entirely theoretical and unfounded. As the above study shows, Chinese doctors in China routinely prescribe *Dang Gui* (as part of a polypharmacy formula based on the patient's pattern discrimination) to women with or who have had breast cancer and other estrogen-dependent cancers. There is absolutely no suggestion of which I am aware within the professional Chinese medical literature, including the Chinese medical oncological literature, that *Dang Gui* is contraindicated to such women. I hope this article may help put this Western medical myth to rest.

Late Stage Breast Cancer & Xiao Chai Hu Tang

abstracted & translated by Bob Flaws, Lic. Ac., FNAAOM (USA), FRCHM (UK)

Keywords: Chinese medicine, Chinese herbal medicine, oncology, breast cancer, *Xiao Chai Hu Tang* (Minor Bupleurum Decoction), chemotherapy

Breast cancer is the second leading cause of cancer deaths in women today (after lung cancer) and is the most common cancer among women, excluding non-melanoma skin cancers. According to the World Health Organization, more than 1.2 million people will be diagnosed with breast cancer this year worldwide. The American Cancer Society estimates that in 2004, approximately 215,990 women in the United States will be diagnosed with invasive breast cancer (stages I-IV). Another 59,390 women will be diagnosed with in situ breast cancer, a very early form of the disease. Though much less common, breast cancer also occurs in men. An estimated 1450 cases will be diagnosed in men in 2004. A woman's lifetime chance of developing breast cancer is now listed as one in eight. The are four types of Western medical treatment for breast cancer currently considered standard: surgery, radiation, chemotherapy, and hormone therapy. Which treatment a woman will receive depends on her particular condition and person wishes. However, treatment in most last-stage cases will include chemotherapy. Because chemotherapy is a systemic treatment affecting the cells in the entire body, it typically causes side effects, such as nausea and hair loss to name the two most infamous. In China, Chinese herbal medicinals are routinely used to manage and mitigate such chemotherapy side effects as well as to improve outcomes and increase length of life. In issue #5, 2004 on pages 270-272 of the *Shan Dong Zhong Yi Za Zhi (Shandong Journal of Chinese Medicine)*, Wang Xing-chun et al. published an article titled, "A Clinical Study on the Treatment of Late Stage Breast Cancer with *Xiao Chai Hu Tang* (Minor Bupleurum Decoction) Combined with Chemotherapy." Because this study is indicative of how Chinese doctors are integrating traditional Chinese and modern Western medicines in the treatment of breast cancer, a summary of its main points is presented below.

Cohort description:

Altogether, there were 60 patients with late stage breast cancer enrolled in this study. These 60 patients were randomly divided into two groups, a so-called treatment group and a control or comparison group. All had been treated with surgery and had distant metastases. After surgery, all experienced recurrence or metastasis. These women's Karnvosky score was 60 points or more, and all had a three month or more projected survival time. Diagnosis and follow-up studies were carried out by x-ray, ultrasound, MRI, CT scan, and bone ETC. In the four weeks prior to the commencement of this study, none of the women had had any chemotherapy. Blood signs and liver and kidney function were normal, EKG was normal, and heart enzymes were basically normal. In terms of Karnovsky scores, pathology staging, TNM staging, sites of metastases, and whether the woman was receiving initial or repeat therapy, the women in both groups were statistically quite comparable. (These statistics were all included in the original Chinese article.)

Treatment method:

Members of both groups received the CAF protocol. This consisted of 400mg/m2 of cytotoxin (CTX) from days 1-8, 40mg/m2 of adriomyacin (ADM) day one, and 300mg /m2 of 5-flourouracil (5-FU) on days 2-5, with 21 days equaling one round of treatment. One week before the commencement of this protocol, the members of the treatment group also received *Xiao Chai Hu Tang* was continued through the length of this study. *Xiao Chai Hu Tang* consisted of:

Chai Hu (Radix Bupleuri)
Huang Qin (Radix Scutellariae)
*Ban Xia (*Rhizoma Pinelliae)
Dang Shen (Radix Codonopsis)
Da Zao (Fructus Jujubae)
Sheng Jiang (uncooked Rhizoma Zingiberis)
Gan Cao (Radix Glycyrrhizae)

Seventy-eight point two grams of herbal medicinals were used to make each 200ml of medicinal liquid, and 200ml of this liquid were administered orally each time, two times per day (i.e., BID). Treatment was continued for three whole courses for both groups of patients.

Study outcomes:

Study outcomes were based on WHO criteria for cancer. CR meant complete remission, i.e., complete disappearance of lesions within the area treated. PR meant partial remission or a more than 50% decrease in lesions within the treated area. NC meant no change, i.e., less than a 50% decrease or less than a 25% increase in lesions within the treated area, and PD meant a more than 25% increase of a lesion in treated area or new lesions within treated area. Based on these criteria, outcomes were divided between treatment and comparison groups and between those receiving initial treatment and repeat treatment. There were seven patients in the treatment group who received initial treatment. Of these, there were two CRs, four PRs, one NC, and no PDs, with a CR + PR rate of 85.7%. In the comparison group, there were nine cases receiving initial treatment. Among these, there was one CR, five PRs, one NC, and two PDs, with a Cr + PR rate of only 66.7%. In the treatment group, there were 23 patients who received repeat therapy. Of these, there were five CRs, 11 PRs, five NCs, and two PDs, for a CR + PR rate of 69.6%. In the comparison group, there were 21 cases who received repeat treatment. Among these, there were two CRs, eight PRs, six NCs, and five PDs, with a CR + PR rate of only 47.6%. Therefore, the combined Chinese-Western medical protocol was judged more effective than the chemotherapy alone (P 0.05). Further, the mean remission time in the treatment group was 9.7 months as compared to only 6.9 months in the comparison group.

There were also significant differences in side effects from the chemotherapy between the members of these two groups. Thirty-three point three percent of the treatment group experienced decrease in number of red blood cells compared to 40% in the control group. Seventy-three point three percent in the treatment group experienced decreases in white blood cells compared to 83.3% in the control group. Forty-six point seven percent in the treatment group experienced decreases in platelets compared to 50% in the control group. Nausea and

vomiting occurred in 36.7% of the treatment group, but 70% of the control group, and hair loss was 76.7% in the treatment group; 83.3% in the comparison group. None of the members of either group experienced nephro-, hepato-, or cardiotoxicity, nor did any experience ulceration of the oral mucosa. Thus, overall, we can say that those who received chemotherapy plus *Xiao Chai Hu Tang* had less side effects than did those who only got the chemotherapy.

Discussion:

In their concluding remarks, Drs. Wang et al. cite Japanese research showing that *Xiao Chai Hu Tang* promotes the production of both interleukin-1 and 2 (IL-1 & IL-2) as well as strengthens the activity of natural killer (NK) cells. Other Japanese research has shown that a liquid extract of *Xiao Chai Hu Tang* is able to kill KIM-1 liver cancer cells and KMC-1 bile duct cancer cells without disturbing the surrounding normal cells. *Xiao Chai Hu Tang* is one of the most famous and commonly prescribed harmonizing formulas within Chinese medicine. It courses the liver and rectifies the qi, fortifies the spleen and supplements the qi, clears heat and transforms phlegm. This formula can easily be modified for each patient's personal presenting pattern. Most professional practitioners would then assume that its therapeutic effect should be even better than the unmodified form used in this protocol. For instance, hair loss due to chemotherapy is usually ascribed to spleen damage resulting in non-production of blood. By adding *Ji Xue Teng* (Caulis Spatholobi) and *He Shou Wu* (Radix Polygoni Multiflori), one should both increase red blood cells and decrease hair loss. While *Xiao Chai Hu Tang* already gets a good effect on nausea and vomiting, its effect should be even better where *Chen Pi* (Pericarpium Citri Reticulatae) and *Fu Ling* (Poria) added. Likewise, it is possible to add to this formula other ingredients from the *kang ai* (anti-cancer) category of Chinese medicinals to more effectively treat the cancer itself, such as *Xia Ku Cao* (Spica Prunellae) and *Pu Gong Ying* (Herba Taraxaci).

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