

## BACKGROUND INFORMATION FOR MEDICAL TRADE MEDIA

### **Breast Cancer**

Breast cancer is a malignant tumor emerging from glandular breast tissue. Accounting for 25 % of all malignant cancer cases, breast cancer is the most common type of cancer amongst women world wide. In industrial countries the incidence rates are very high, the exception being Japan: here breast cancer is the third most common type, after colorectal and gastric cancer. In the USA significantly decreasing incident rates were noted between 2001 and 2004. A possible cause for this might be a reduced prescription of hormone replacement therapies used for treatment of menopausal symptoms. The risk of developing breast cancer increases gradually from the age of 30 and reaches its peak between the ages of 60 and 70.

The exact cause of breast cancer is yet unknown. In approximately 5-10 % of cases there is an underlying genetic predisposition caused by a mutation of the DNA repair genes BRCA-1 and BRCA-2. This leads to a higher familial risk factor of between 50-85 %. Other factors which can lead to an increased risk of developing breast cancer are ethnic origin, age, early menarche and a late menopause.

#### **Diagnosis**

Breast cancer symptoms vary widely. Palpable lumps in the breast or axilla, swelling, erythema, inflammation or changes of the breast skin are possible symptoms of the disease. Other typical signs are the retraction of the nipple or an abnormal fluid secretion. Besides breast examination and breast self-examination the methods for breast tumor screening include mammography and ultrasound. If a tumor is suspected, the next step is a fine needle aspiration biopsy which then allows a histological investigation of the tissue.

#### **Therapy**

The primary treatment for breast cancer which has not affected other organs is the curative removal of the tumor and the affected axillary lymph nodes via surgery, possibly neo-adjuvant chemotherapy might have been applied before. Further options following surgery are radio, chemo, hormone or antibody therapy, whereby the latter is becoming increasingly significant.

Whereas in the past standard of the primary surgery used to be the complete removal of the breast (mastectomy), nowadays a breast preserving operation can be carried out in 70-80 % of cases. The surgical resection of the tumor includes the removal of the surrounding healthy tissue and of the axillary lymph nodes. The breast preserving surgery is followed by radiotherapy; other adjuvant measures are dependent upon the hormone receptor status and on the patient's individual risk to relapse or develop metastases. Patients are defined as high risk either with four or more affected lymph nodes or with 1-3 positive nodes and HER-2/new overexpression, respectively. As a rule patients with positive hormone receptor status are treated with hormone therapy, high risk patients receive chemotherapy first. In patients with HER-2/new overexpression (3+ or 2+/FISH-positive) a combination of these treatments with the antibody trastuzumab might be considered.

In the case of existing metastases breast cancer can no longer be treated curatively and has to be considered and treated as a chronic illness. Chemo- and antibody therapy are of particular importance in metastatic breast cancer and can offer an improvement in the patients quality of life and survival. The therapy protocols used here are usually considerably less aggressive as the main objective is a prolonged survival of the patient in combination with high quality of life. When metastases exist and the patient is hormone receptor positive, generally hormone therapy is administered; if the cancer continues to progress or the patient still has serious discomfort, chemotherapy can follow. If, however, the hormone receptor status is negative or the cancer progresses rapidly chemotherapy is indicated. Up to present day there is no data proving that a particular therapy sequence or regimen is more successful than others. The therapy in this situation is usually a series of mono therapies due to their good tolerability. In case of overexpression of HER2/new, the use of the monoclonal antibody Trastuzumab in combination with Paclitaxel, Docetaxel or in combination with an aromatase inhibitors as a first line therapy is also approved.

### **Immune biological approaches**

In approximately every fourth breast tumor a strong overexpression of the HER2/new gene (3+ or 2+/FISH-positive) can be found. The monoclonal antibody trastuzumab binds to the HER2 receptor and blocks the signal cascade which is responsible for the accelerated growth of the HER2 over-

expressed tumor. Patients with metastasized and early breast cancer can benefit from this target therapy.

Further improvement could be achieved with the administration of the trifunctional antibody ertumaxomab which is currently being examined in clinical trials. Like trastuzumab ertumaxomab binds to the receptor HER-2/new. In addition, preclinical data show that ertumaxomab also recruits T-lymphocytes and accessory cells, leading to their mutual stimulation. This results in a strong immune reaction against the Her-2/new expressing tumor cells. Therefore ertumaxomab is being evaluated in a phase II study (IV-ERT-BC-04) including patients with metastasized / advanced breast cancer whose disease is still progressing under, or after Trastuzumab therapy.

For patients whose tumor cells show HER-2/new low expression (1+/2+ FISH negative) treatment with trastuzumab is not indicated. The phase II studies with ertumaxomab FBT-IVREXBC 02 and IV-ERT-BC-03 investigate its efficiency and safety when administered to patients with hormone refractory, advanced / metastasized breast cancer, displaying a low to moderate HER2-expression (1+ or 2+/FISH-negative). Should these trials prove successful, a Her-2/new-based therapy would also be available to this group of patients.

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