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Breast Cancer in Women

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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Compliance rules:

- Guideline
- Conflict of interests

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1 Definition and Basic Information

Breast cancer is the most common malignant tumor in women. Histologically, the predominant form is invasive ductal carcinoma, followed by invasive lobular, tubular, mucinous and medullary carcinomas. Ductal Carcinoma In Situ (DCIS) and Atypical Ductal Hyperplasia (ADH) are precancerous lesions. The present chapter deals with invasive breast cancer in women. Male breast cancer will be treated in a separate guideline (Breast Cancer in Men).

1.1 Epidemiology

In Germany, the number of new cases is estimated to amount to about 72,000 / year and to account for 32% of all cancers in women [1]. In Austria, 4,500 new patients are diagnosed per year [2], the estimate for Switzerland is about 5,200 / year. Median age is 64 years [1]. Incidence had increased steadily from 1980 to 2000 in Germany, in Austria till 1997, in Switzerland till 2008. The lifetime risk to acquire breast cancer is 7% for girls born in 2008.

1.2 Risk Factors

The risk of breast cancer is increased by the following factors:

- Genetic factors (approximately 5 % of new cases) [3]
  - Increased incidence of breast and/or ovarian cancer on either side of the family (Criteria of the German Consortium for Familial Breast and Ovarian Cancer – *Deutsches Konsortium für Familiären Brust- und Eierstockkrebs*)
  - Hereditary breast and ovarian cancer with germ line mutations in the BRCA1 or BRCA2 gene
  - Peutz-Jeghers syndrome with germ line mutations in the STK11 gene
  - Ataxia telangiectasia with germ line mutations in the ATM gene
  - Cowden syndrome with germ line mutations in PTEN genes
  - Germ line mutations in the CHEK-2 gene
- Hormonal factors
  - Early menarche
  - Late menopause
  - Late gestation
  - Obesity, postmenopausal weight gain
  - Postmenopausal hormone replacement therapy (HRT)
- Toxic factors

- Radiation exposure of the breast during childhood or adolescence
- Smoking
- High consumption of alcohol (RR 1.46 with ≥45 g alcool / day) [4]
- Contralateral primary breast cancer

2 Prevention and Early Detection

2.1 Prevention

The general recommendations for prevention relate to the acquired risk factors so far identified:

- Avoidance of obesity and postmenopausal weight gain
- Regular physical activity
- No smoking
- No excessive alcohol consumption

Selective estrogen-receptor modulators (SERM, e. g. tamoxifen, raloxifen etc.) or the aromatase inhibitor exemestane reduce the of a hormone receptor-positive breast carcinoma [5]. The benefits depend on risk status, age and risk of side effects.

2.2 Early detection

Breast cancer by mammography can reduce the cancer-specific mortality [6]. The value of other screening methods (clinical and self exam, ultrasound) is not established. Magnetic resonance imaging is recommended in the screening of young women with hereditary predisposition. In the context of cancer screening in women, statutory health insurance providers in Germany pay for:

- Annual manual examination of the breast by a physician from the age of 30 years
- Biennial mammography between the ages of 50 and 69 years

The legal framework for the mammography screening program was created in 2002. In premenopausal women the timepoint within the menstrual cycle, i.e. day 7-14 within the first half, has to be observed for the planning of mammography.

3 Clinical Presentation

The focus is on local symptoms of the breast: Palpable node, skin changes above the tumor including the so-called peau d'orange (dimpled skin), retraction of the skin, contour changes, asymmetry of the breast, retraction of the nipple, secretion or bleeding from the nipple on the affected side, redness and hyperthermia in inflammatory breast cancer. The picture of locally very advanced cancer with spreading to the chest wall (cancer en cuirasse) and ulceration is rare. General symptoms are absent in the early stages of breast cancer. In advanced stages, there may be weight loss and cachexia. Symptoms of metastases include swelling of the arm due to lymphedema in patients with extensive involvement of axillar lymph nodes, bone pain in skeletal metastases, coughing and dyspnoea in pulmonary and / or pleural metastases, jaundice and hepatic failure in advanced liver metastases or neurological symptoms in CNS metastasis.

4 Diagnosis

4.1 Diagnostics

The first step is the confirmation of the tentative diagnosis based on clinical and / or imaging findings, see Table 1 [7].

Table 1: Diagnostics for newly occurred symptoms*

Examination	Recommendation	Comments
Mammography bilaterally	Method of first choice	
Biopsy (punch biopsy or vacuum biopsy)	for BI-RADS[1] IV or V	
Sonography of both breasts and axillae	Method of first choice for age < 40 years	
Magnetic resonance imaging bilaterally with contrast agent	Before surgery, whenever possibly	MRI[2] increases the detection rate of additional lesions and has an influence on the surgical procedure, but with prognostic impact

Legend:
*[1] BI-RADS – Breast Imaging Report and Data System of the American College of Radiology, [2] MRI – Magnetic resonance imaging; *see [7, 8]*

After diagnosis of breast cancer, staging for patients with tumors ≥ pT2 and with clinical symptoms is indicated, see Table 2. Distant metastases of breast cancer may occur in virtually all regions of the body. The most common localizations are skeleton, liver and lungs.

Table 2: Staging

Suspicion	Examination (first choice)	Examination for confirmation / in case of uncertainty
Skeletal metastases	Bone scan	X-ray, MRI
Liver metastases	Sonography of the abdomen	CT of the abdomen
Pulmonary metastases	Chest X-ray, PA and lateral	CT of the chest
CNS metastases	CT or MRI	

4.2 Classification

The size of the primary tumor and the metastases are classified on the basis of the TNM criteria. The classification of the Union Internationale Contre le Cancer (UICC) summarizes these criteria into stages, see Table 3.

Table 3: Classification of tumor stages (UICC)

Stage	Primary tumor	Lymph node status	Distant metastases
0	Tis	N0	M0
I	T1mic	N0	M0
	T1a (1 – 5 mm)	N0	M0
	T1b (6 – 10 mm)	N0	M0
	T1c (11 – 20 mm)	N0	M0
IIA	T0, T1mic, T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0, T1mic, T1, T2	N2	M0
	T3	N1	M0
IIIB	T4	N0 – 2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

4.3 Molecular Subtypes

Based on gene expression profiles, biologically distinct subtypes of breast cancer can be distinguished. The St. Gallen Consensus Conference 2011 recommended the identification of clinically relevant subtypes using histochemical surrogate parameters. They form the basis for therapeutic recommendations in the adjuvant setting, see Table 4.

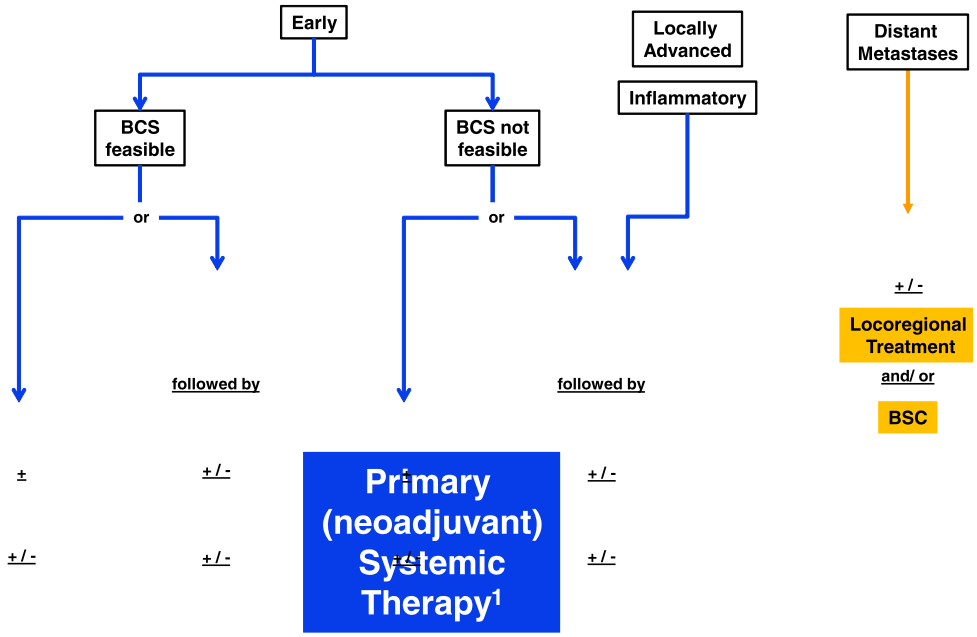
Table 4: Molecular Subtypes of Breast Cancer and Definition of Surrogate Parameters [8]

Molecular Subtype	Subgroup	Definition	Comments
Luminal A		• ER and / or PgR positive • HER2 negative • Ki67 low	
Luminal B	HER2 negative	• ER and / or PgR positive • HER2 negative • Ki67 high	
	HER2 positive	• ER and / or PgR positive • HER2 overexpressed or amplified • Ki67 low or high	
HER-2 enriched		• HER2 overexpressed or amplified • ER and PgR negative	
Basal like		• ER and PgR negative • HER2 negative	Approximately 80% overlap with triple negative carcinoma

5 Therapy

Treatment options for early breast cancer include surgery, radiotherapy and systemic therapy [7, 8, 9]. The treatment recommendation for the patient is based on quality-assured detection of the relevant risk factors. A therapy algorithm is shown in Figure 1.

Figure 1: Algorithm for Primary Therapy



Legend:
[1] *Systemic therapy includes endocrine therapy and / or chemotherapy and / or monoclonal antibodies*

5.1 Early Breast Cancer

Intensity of treatment is stage-adapted.

5.1.1 Surgery

5.1.1.1 Breast

The basis of the therapy is the extirpation of the tumor with a tumor-free resection border of at least 1 mm (R0). Breast-Conserving Surgery (BCS) with subsequent radiotherapy is equivalent to modified radical mastectomy in terms of overall survival [10].

Indications for breast-conserving surgery (BCS) are [7, 9]:

- Invasive carcinoma with favourable relation of tumor size to breast volume
- Invasive carcinoma with intraductal component, if an R0 situation is reached

Indications for modified radical mastectomy are [7, 9]

- Multifocality
- Diffuse, extensive calcification of malignant type
- Incomplete resection of the tumor in BCS (including intraductal component), even after secondary resection
- Inflammatory breast cancer

- Presumably unsatisfactory cosmetic result after BCS
- Clinical contraindications for adjuvant radiotherapy after BCS
- Patient preference

Reconstructive surgery can be performed immediately or delayed.

5.1.1.2 Axilla

Standard for the evaluation of axillary lymph nodes is the sentinel lymph node biopsy (SLNB). It includes the targeted removal and histological examination of one to three lymph nodes [11]. SLNB is equivalent to axillary dissection with regard to local control, but associated with lower morbidity. Thus far, axillary dissection with removal of at least 10 level and II lymph nodes was recommended in patients with positive sentinel node. This concept is currently under debate. In 2011, results from a multicenter study on the role of axillary dissection in patients with positive sentinel lymph nodes were published. After a median observation time of 6.3 years the oncological results for patients with or without axillary dissection were not significantly different, see Breast Cancer Study Results. Patients fulfilled the following criteria:

- T stage T1 or T2
- Sentinel lymph node positive
- Preoperative N stage cN0, i.e. no clinical axillary lymph node involvement
- Breast conserving surgery
- Postoperative radiotherapy of the breast with tangential whole-breast irradiation
- Adequate adjuvant systemic therapy

Standard for the analysis of sentinel lymph nodes is the histological examination. The detection of isolated tumor cells or the presence of micrometastases ≤ 2mm in a single lymph node has no impact on prognosis. It also has no influence on the therapeutic concept and is does not pose an indication for axillary dissection [7, 9].

In patients with primary (neoadjuvant) therapy the concept of SNLB is under debate. Primary systemic therapy offers the chance for reduction of positive lymph nodes and reduced extent of axillary dissection. On the other hand, it contains the risk of false negative results. An alternative is pretherapeutic SNLB. Results of large prospective clinical trials are pending.

In patients with distant metastases, surgical axillary staging is not recommended.

5.1.2 Radiotherapy

Postoperative radiotherapy lowers the risk of locoregional relapse by about half [12] and can contribute to prolongation of survival. It should be initiated 4 – 6 weeks after surgery or after completion of adjuvant chemotherapy.

5.1.2.1 Breast / Chest Wall

After breast-conserving surgery (BCS), adjuvant radiotherapy of the affected breast is indicated. The target volume includes the entire remaining breast and the adjacent chest wall. The optimal iadiation regimen is currently being discussed [13, 14]. The standard is conventional radiation with administration of 50Gy in 25 fractions during 5 weeks. In hypofractionated radia-

tion therapy, 40 – 42.5Gy are administered in 15 – 16 fractions during 3 weeks. An additional boost of the tumor bed with 10 – 16Gy leads to a further reduction of the local relapse rate.

Intraoperative partial irradiation of the breast leads to comparably low local relapse rates in patients with early breast cancer, see Breast Cancer Study Results. The overall radiation exposure is reduced. Data on long term oncological results are pending. Thus far, partial irradiation of the breast is not a standard therapy.

After mastectomy, irradiation of the chest wall for reduction of the local relapse rate and breast cancer-specific mortality is recommended in patients with positive lymph nodes, in particular with > 3 positive lymph nodes. The benefits of irradiation are also plausible in case of other risk factors present (age < 40, lymphangiosis or hemangiosis, pT2 > 3 cm, infiltration of the pectoral fascia, R1 / R2 situation) [7].

5.1.2.2 Regional Lymph Nodes

In the current German S3 guideline, irradiation is recommended for residual tumor tissue of the axilla, and if in the case of definite clinical involvement of the axillar lymph node an axillary dissection was not or only incompletely carried out. Recent data suggest that tangential whole-breast radiotherapy is adequate in patients with positive sentinel lymph node, see Chapter 5. 1. 1. 2..

Irradiation of the supra- and infraclavicular lymph vessels is recommended in case of ≥ 4 positive axillary lymph nodes, in case of involvement of the level III of the axilla and in other indications for the irradiation of the axilla.

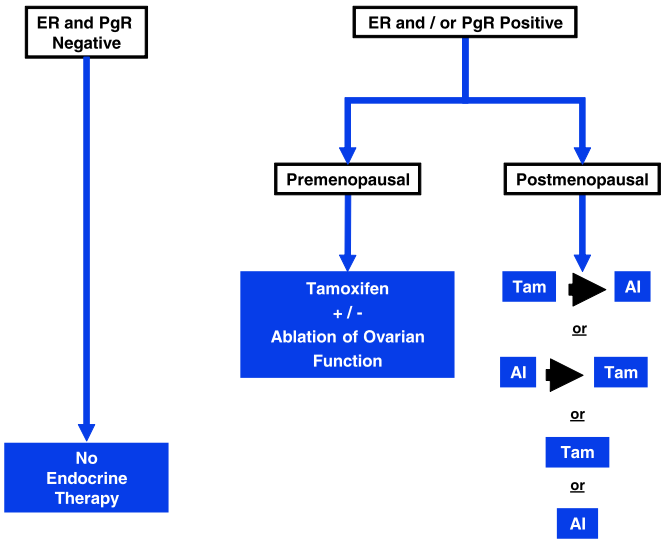
Publication of randomized trials on the additional radiotherapy of regional lymph nodes in patients stage II / III after breast conserving surgery and whole-breast irradiation are pending, see Breast Cancer Study Results.

5.1.3 Adjuvant Endocrine Therapy

About 80 % of invasive ductal breast carcinomas express estrogen (ER) or progesterone receptors (PgR). The criterion for an endocrine sensitive carcinoma is the immunohistochemical detection of ≥ 1% ER positive tumor cells

Analysis should be performed according to the recent guidelines [5, 7, 8, 15]. For patients with oestrogen and/or progesterone receptor positive breast cancer, endocrine therapy is indicated. The therapy algorithm is shown in Figure 2.

Figure 2: Algorithm for systemic adjuvant endocrine therapy



Legend:
[1] ER – oestrogen receptor; [2] AI – aromatase inhibitor

In combined chemoendocrine therapy with tamoxifen, the endocrine treatment should be started only after the completion of chemotherapy.

5.1.3.1 Premenopausal

Menopausal status is determined by menstruation anamnesis and laboratory analysis of FSH and oestradiol (E2). Standard in endocrine therapy is tamoxifen, see Figure 2. It is not unequivocally resolved whether the additional ablation of ovarian function is beneficial. For ablationelimination of the ovarian function, three methods are equivalent [7, 8, 16]:

- GnRH analogues (GnRHa)
- Ovarectomy
- Radiomenolysis

Aromatase inhibitors are not recommended. The combination of GnRH analogues plus anastrozole was statistically equivalent in progression free survival, but had a potentially negative effect on overall survival, see Breast Cancer Study Results. Premenopausal women who turn postmenopausal within the 5 year treatment with tamoxifen, benefit from extended adjuvant therapy with aromatase inhihibitors.

5.1.3.2 Postmenopausal

For systemic adjuvant endocrine therapy of postmenopausal patients, aromatase inhibitors and tamoxifen are available, see Figure 2. Tamoxifen reduces the relapse risk by half and prolongs overall survival compared to patients without systemic adjuvant endocrine therapy [17]. In randomised studies, treatment with aromatase inhibitors decreased the relapse risk by further 3% [18]. There are several options for the time point when to start using the aromatase inhibitors:

- Switch after 2 – 3 years of tamoxifen therapy
- Switch after 5 years of tamoxifen therapy
- Monotherapy (upfront)

If used as first line therapy (upfront) aromatase inhibitors lead to a significant decrease of relapse rate within the first two years. In the pivotal trial with letrozole, mortality was also decreased. In the switch studies together with tamoxifen, AI decreased breast cancer specific mortality, see Breast Cancer Study Results.

5.1.3.3 Substances

GnRH (LHRH) analogues

GnRH analogues block the production of female and male sexual hormones by interaction with the release of the pituitary gonadotropins FSH and LH. They are active in the adjuvant and the palliative setting. Common side effects with potential impairment of quality of life are hot flashes, dryness of vaginal mucosa, reduction of libido and mood swings. GnRH analogues can be applied SC, IM as implant or liquid depot.

Tamoxifen

Tamoxifen is a selective estrogen-receptor modulator. It is a prodrug and converted into the active metabolite via cytochrome P450. Discussion about the clinical relevance of the CYP2D6 polymorphism for efficacy of tamoxifen is controversial. In breast cancer, tamoxifen is active in primary prevention, in the adjuvant setting, in secondary prevention and in the palliative therapy. Common side effects with potential impairment of quality of life are mild nausea, fluid retention and hot flashes. Severe side effects are venous thromboembolism, endometrial changes including endometrial cancer, and reduction of bone density in premenopausal patients.

Aromatase Inhibitors (AI)

AI block the enzyme aromatase, which converts androgens into estrogens. Chemically, steroidal (exemestane) and non-steroidal AI (anastrozole, letrozole) are available. AI are active in primary prevention, in the adjuvant therapy of postmenopausal patients, and in the palliative therapy. Common side effects with potential impairment of quality of life are arthralgia, arthritis, myalgia, hot flashes and reduction of bone density including osteoporosis. Monitoring of bone density and preventive treatment with Vitamin D and Calcium is recommended. Zoledronate and denosumab can prevent the bone loss.

5.1.4 Adjuvant Chemotherapy

Adjuvant chemotherapy reduces the risk of relapse [19]. The individual benefit depends on cancer biological risk factors, stage, type and intensity of the chemotherapy and comorbidity.

5.1.4.1 Adjuvant Chemotherapy – Indication

In Figure 3 the risk factors are grouped into three categories, depending on their value for the benefits of adjuvant chemotherapy, against the benefits of chemotherapy or as factors of unclear significance. The summary assessment forms the basis for the individual treatment recommendation.

Figure 3: Criteria for the Recommendation of Adjuvant Chemotherapy

	Not in Favor of Chemotherapy	Unclear	In Favor of Chemotherapy
Prognostic			
Primary Tumor	≤ 2 cm		
Nodal Status	N0	N1a	≥ N1a
Histological Grading[1]	G1	G2	G3
Infiltration of Blood Vessels	Absent		Extensive
Predictive and Prognostic			
ER Status[2]	Positive ≥ 50 %	Positive < 50 %	Negative
HER2 Status[3]	Negative	Negative	Positive
Molecular Subtype[4]	Luminal A		Luminal B
			HER2 enriched
			Basal like (triple negative)
Others			
GeneSignature[5]	Low		High
Proliferation (Ki67)[6]	Low		High
uPA / PAI[7]	Low		

Legend:
[1] G – Grading; [2] ER – Estrogen receptor; [3] HER2 - Human Epidermal growth factor Receptor; HER2 negative - no overexpression or amplification of HER2; HER2 positive – overexpression or amplification or HER2; [4] molecular subtypes – definition see Chapter 4.3.; [5] Gene signature – based on the transcription of prognostic genes, see Chapter 5.1.4.1.; [6] Proliferation - conventional methods are the Ki67 labelling Index or the mitotic rate, see Chapter 5.1.4.1.; [7] uPA / PAI-1 – Urokinase-Type Plasminogen Activator and Plasminogen Activator Inhibitor Type 1, see Chapter 5.1.4.1.;

The inclusion of the genetic signatures into the algorithm is new. The result of this molecular analysis of the tumor material is expressed in terms of a risk score. Retrospective studies suggest that patients with ER-positive breast cancer and a low risk score will not benefit from adjuvant chemotherapy. Results of large prospective studies with commercially available tests are pending.

The proliferation rate is an important prognostic factor. However, the microscopic count of Ki67positive cells is not standardized. A threshold value for the clinical benefit of chemotherapy has not been validated.

The relevance of uPA/PAI-1 activity was validated in prospective studies. It is commonly used in Germany. Internationally it is not recognized as standard procedure, also because of the lack of unfixed tumor material.

Chemotherapy is indicated in patients with triple-negative breast cancer, i.e. without expression of hormone receptors and of HER2. This excludes rare forms of breast cancer such as medullary, apocrine and the adenoid-cystic breast cancer – these are triple-negative but have no increased relapse risk. In patients with triple negative breast cancer stage pT1a pN0, the benefit of adjuvant chemotherapy has not been validated.

Adjuvant chemotherapy is also indicated in HER2-positive carcinomas, since the studies for demonstration of the effectiveness of trastuzumab were only carried out in this combination.

5.1.4.2 Adjuvant Chemotherapy – Drugs

In the adjuvant chemotherapy of breast cancer, at least two, often three cytostatic drugs are combined. These can be administered simultaneously or sequentially. A wide variety of combinations and application regimens has been evaluated. Currently there is no definitive, standardized assignment of any specific chemotherapy regimen to any specific risk constellation

[7, 8, 9]. The published results of randomised clinical trials are compiled under Breast Cancer Study Results and can be summarized as follows:

Anthracyclines

- Anthracycline-containing combinations are more effective than CMF. An exception is the similar efficacy of 4xAC and 6xCMF, given in three-weekly intervals.
- The dosage of doxorubicin should be ≥ 20 mg/m² / week, and that of epirubicin ≥ 30 mg/m² / week. (Anthracyclines are administered in two or three-weekly interval; for purpose of comparability the dosages are calculated per week.)
- In case of contraindications for anthracyclines, CMF is more effective than no chemotherapy. In patients > 65 years, CMF is more effective than monotherapy with capecitabine.
- Combination of docetaxel with cyclophosphamide represents a further alternative in case of contraindications for anthracyclines.

Taxanes

- In patients with increased relapse risk, combinations of anthracyclines and taxanes are more effective than regimens comprising anthracyclines only, e.g. for node-positive breast cancer or node-negative breast cancer with additional risk factors. The effect is independent from age, menopausal status, number of affected lymph nodes and hormone receptor status.
- The sequential application of 4 cycles of docetaxel after 4 cycles of doxorubicin / cyclophosphamide is equivalent to the simultaneous application of these three substances, see Breast Cancer Study Results. The simultaneous risk is associated with a higher risk of infections.
- Docetaxel and paclitaxel have turned out to be equivalent. In the sequential application after EC the weekly administration of paclitaxel or the administration of docetaxel every third week were more active than the administration of paclitaxel every three weeks.
- Application once a week instead of every third week alters the side effect spectrum and increases efficiency.

Dosage-dense therapy / dose escalation / high-dose therapy

- Escalation of the cytostatics dosage, reduction of the therapy intervals and / or high-dose therapy with autologous stem cell transplantation may improve disease-free survival, but does not consistently result in extension of survival times, see Breast Cancer Study Results.
- Intensication of chemotherapy followed by autologous stem cell transplantation does not lead to an improvement of overall survival and is not recommended in adjuvant therapy [20].

5.1.4.3 Adjuvant Chemoendocrine or Endocrine Therapy?

The decision between endocrine or chemoendocrine therapy in patients with hormone-receptor positive breast cancer is not yet resolved [21]. The published results of randomised clinical trials are compiled under Breast Cancer Study Results and can be summarized as follows:

Premenopausal

- Adjuvant endocrine therapy with goserelin and tamoxifen results in disease-free survival rate of > 90% after 5 years, see Breast Cancer Study Results.

- Retrospective studies suggest a benefit for chemoendocrine therapy in patients with ER expression < 90%, lack of PgR expression, and in patients < 40 years.
- In patients with HER2 positive breast cancer chemoendocrine treatment sequences are recommended, combined with anti-HER2 substances.
- In patients with the desire to have children, fertility-preserving measures should be extensively prior to the start of chemotherapy, see Onkopedia Guideline Adolescents and Young Adults (AYA).
- Endocrine therapy is an option in patients with contraindications for chemotherapy.

Postmenopausal

- The decision is based on general health status, comorbidity and biological risk factors, not on the chronological age.
- The overall survival is improved by chemoendocrine therapy only in patients with a presumed life expectancy ≥ 10 years.
- Patients with luminal A type breast cancer generally require endocrine therapy only.

5.1.5 Adjuvant Anti-HER2 Therapy

About 20 % of invasive ductal breast carcinomata express the human epidermal growth factor receptor 2 (HER2). The HER2 status should be analysed using an accurate and validated procedure. HER2-positivity is defined by:

- Immunohistochemistry: Score 3+
- Fluorescence In-Situ hybridisation (FISH): HER2/Centromere 17 Ratio > 2
- Chromogenic In-Situ hybridisation (CISH): > 6 HER2 signals / nucleus

As a drug, the monoclonal antibody trastuzumab is available. Adjuvant therapy with trastuzumab reduces the relapse risk compared to exclusive chemotherapy and extends overall survival [7, 8, 9], see Breast Cancer Study Results.

Patients with HER2-positive carcinomata should receive adjuvant therapy with trastuzumab over the period of 1 year. Patients with node-negative breast cancer and a tumor size < 0.5 cm may be an exception, as no adequate data are available for these. The large randomised studies on the effectiveness of trastuzumab were carried out in combination with chemotherapy. Trastuzumab can be administered simultaneously with taxanes, and sequentially after anthracyclines. It has not been clarified yet whether sub-groups of patients with high endocrine sensitivity will also benefit from an exclusive combination of endocrine therapy with trastuzumab.

5.1.6 Adjuvant Therapy with Bisphosphonates

Bisphosphonates and RANKL antibodies reduce the risk of osteoporosis and have potentially anti-neoplastic properties. Results of randomized studies are not unequivocal. Several studies had demonstrated a positive effect of bisphosphonates on the disease-free survival in postmenopausal patients. Recently, a large randomized study in pre- and postmenopausal patients found no significant benefit for zoledronate. In premenopausal women, an improvement of disease-free and overall survival was seen in premenopausal patients with simultaneous adequate endocrine therapy, see Breast Cancer Study Results.

One indication for bisphosphonates and the RANKL antibody denosumab is osteoporosis under adjuvant therapy with aromatase inhibitors.

5.2 Locally Advanced Stages

Locally advanced carcinomata comprise stages IIIA and B.

5.2.1 Primary (neoadjuvant, pre-operative) systemic treatment

Primary (neoadjuvant, pre-operative) systemic chemotherapy is indicated in the following situations:

- locally advanced breast cancer
- primarily unresectable breast cancer
- inflammatory breast cancer
- reduction (downsizing) of the primary tumor in order to avoid mastectomy
- alternative to postoperative adjuvant chemotherapy, which is indicated based on the pre-operative results (clinical, imaging, biopsy)
- HER2 positive carcinoma
- triple negative carcinoma
- clinical trial

In randomized clinical trials, disease-free and overall survival after primary or adjuvant systemic therapy is equal [22]. In patients without hormone sensitivity, pathohistological complete remissions (pCR) can be achieved in 40%. Patients who do not respond to primary systemic chemotherapy have an unfavourable prognosis. The regimens used correspond to those of adjuvant therapy with administration of anthracyclines and taxanes for a treatment of > 18 weeks.

In patients with HER2 overexpression / HER2 gene amplification, administration of trastuzumab is additionally indicated.

Primary endocrine therapy is an option for postmenopausal patients with ER-positive tumors where surgery or chemotherapy are contraindicated or refused by the patient.

Primary (neoadjuvant) therapy requires close monitoring including imaging of the primary tumor. In patients with small primary tumors, clip marking is recommended in order to identify the tumor site for surgery also in patients with pCR after primary therapy. Early breast surgery is recommended in patients with progressive disease.

5.2.2 Multimodal Therapy

Primary systemic chemotherapy is part of a multimodal treatment approach and to be continued with surgery, radiotherapy and systemic endocrine therapy according to the indications in early breast cancer.

5.3 Loco-Regional Relapse

The incidence of loco-regional relapses amounts to 5 – 10 % after breast-conserving surgery (BCS) and radiotherapy. In about 90 % of cases, they arise in the breast (intramammary relapse), less frequently in the chest wall or in the axilla. In loco-regional relapses, therapy strives to achieve cure, see Figure 4. The prognostic factors are the same as for the primary tumors. An additional negative factor is an interval of < 2 years between initial diagnosis and relapse. The primary goal is local control by surgery and/or radiotherapy. The value of systemic

adjuvant therapy in this situation has not been demonstrated. Options for systemic therapy are:

- endocrine therapy: switch of tamoxifen to aromatase inhibitors, or vice versa
- chemotherapy in patients with no chemotherapy or no chemotherapy containing anthracyclines and / or taxanes

5.4 Distant Metastases

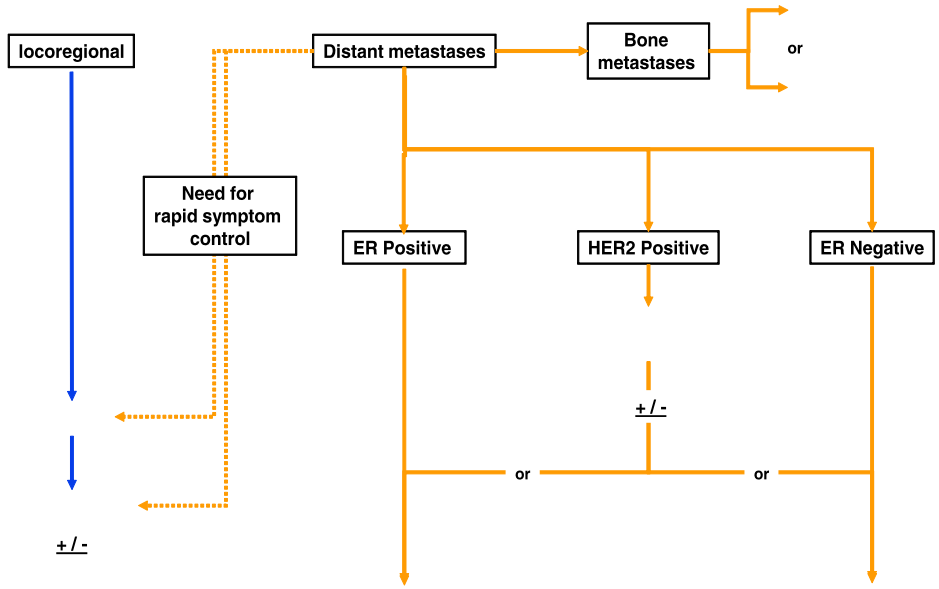
Despite effective primary therapy and advances in adjuvant treatment, in about 20 % of the patients distant metastases do occur. In this situation, the therapy will usually be palliative. The following factors are associated with above-average life expectancy:

- Good general condition
- Exclusive infestation of skeleton and / or skin
- ER positivity
- No HER2 overexpression / no HER2 gene amplification
- Relapse-free interval > 2 years
- No adjuvant therapy
- No previous therapy in the metastatic stage

Palliative therapy addresses physical and mental needs in multidisciplinary teams. The need for and options in palliative therapy should be discussed early and comprehensively with all persons concerned. The diagnostics are geared towards symptoms and therapy, see Table 2. If possible, a biopsy should be taken to confirm the relapse and analyze the current ER and HER2 status.

The selection of causal therapy is guided by the biology of the disease. An algorithm is shown in Figure 4.

Figure 4: Algorithm for the treatment of loco-regional relapse and distant metastases



Legend:
[1] ER – oestrogen receptor; [2] HER2 – human epidermal growth factor receptor; HER2-positive – HER2 overexpression / HER2 gene amplification

Additionally to systemic therapy, symptom-orientated procedures are important.

In patients with metastastic manifestation in one single site (e. g. liver, lungs, CNS, sternum), local treatment (e. g. surgery, radiotherapy) with or w/o systemic can result in 5 year survival rates above average. Randomized studies on the specific of local therapies are pending. It is recommended to start treatment in these patients with systemic therapy followed by additional local procedures.

A small group of patients initially presents with metastatic disease. In these patients primary systemic therapy is recommended. Retrospective analyses suggest further improvement of long term results by resection of the primary tumor. Indication and optimal timepoint of surgery are currently investigated in clinical trials, see Chapter 9

5.4.1 Palliative Endocrine Therapy

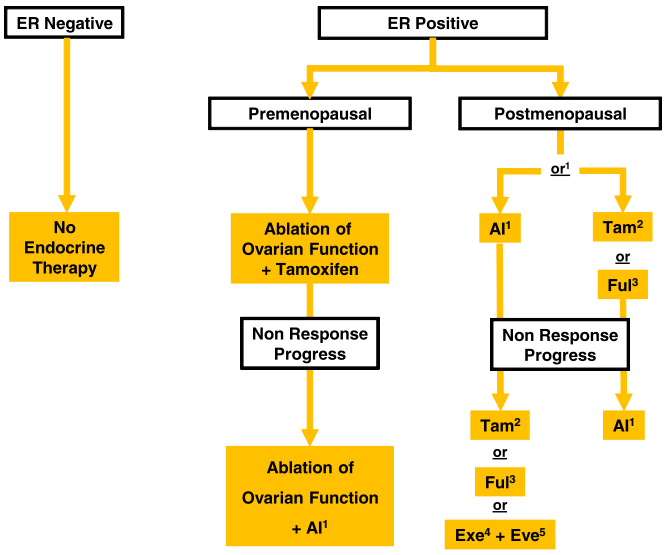
In patients with ER-positive breast cancer, endocrine therapy is the method of choice [23], see Figure 4. An exception is a life-threatening situation or danger to organ functions caused by the metastasis, see Figure 4. The remission rates of endocrine therapy are approximately 60 %. In comparison to chemotherapy, the side effects are lower and the remission duration longer. In HER2-positive carcinomas, endocrine therapy is administered in combination with anti-HER2 therapy. The palliative endocrine therapy is to be continued until disease progression.

The incidence of adverse effects is monitored in intervals of approximately 4 weeks by anamnesis, clinical examination, laboratory analysis and, if necessary, diagnostic imaging. The response to the systemic therapy is controlled every 2 – 3 months using clinical examination and targeted, diagnostic imaging.

5.4.1.1 Premenopausal

The therapy of choice in premenopausal patients is the ablation of ovarian function (GnRH analogues, ovarectomy or radiomenolysis) in combination with tamoxifen. In case of disease progression, tamoxifen can be replaced with aromatase inhibitors. The algorithm for palliative endocrine therapy is shown in Figure 5.

Figure 5: Algorithm for palliative endocrine therapy



Legend:
[1] AI – aromatase inhibitor; [2] Tam – tamoxifen; [3] Ful – fulvestrant; [4] Exe – exemestane; [5] Eve – Everolimus;

5.4.1.2 Postmenopausal

The therapy of choice in postmenopausal patients is administration of steroidal or non-steroidal aromatase inhibitors, see Figure 5. Tamoxifen and toremifene are the alternatives. However, the studies on the higher activity of aromatase inhibitors were performed before the introduction of AI into adjuvant therapy. In case of non-response or disease progression, second- and third-line treatment with fulvestrant is recommended. Further forms of endocrine therapy include administration of gestagens (progestogens), estrogens, androgens or switch between non-steroidal and steroidal aromatase inhibitors.

Recently, the combination of exemestane plus everolimus lead to significant prolongation of progression-free survival in women after failure of non-steroidal AI, see Breast Cancer Study Results.

5.4.2 Palliative Non-Endocrine Systemic Therapy

Chemotherapy is active in metastatic breast cancer, but hampered with more side effects than endocrine therapy. After balancing benefits and risks, chemotherapy is indicated in patients after failure of an endocrine therapy and in patients with ER-negative carcinomas. It is also indicated if, on the basis of advanced organ function-threatening metastases or very rapidly progressive disease, a response must be achieved quickly, see Figure 4. In HER2-positive carcinomas, chemotherapy is administered in combination with anti-HER2 therapy.

Alleviation of symptoms and remission can be achieved with a large variety of substances and combinations. There is no definitive, standardized assignment of any specific chemotherapy regimen to any specific risk constellation [24, 25]. The selection of the drugs is determined by the treatment goal, previous adjuvant chemotherapy and comorbidity. After intervals >12 months, drugs of the previous chemotherapy regimen can be used again. Here the cumulative toxicity must be taken into account.

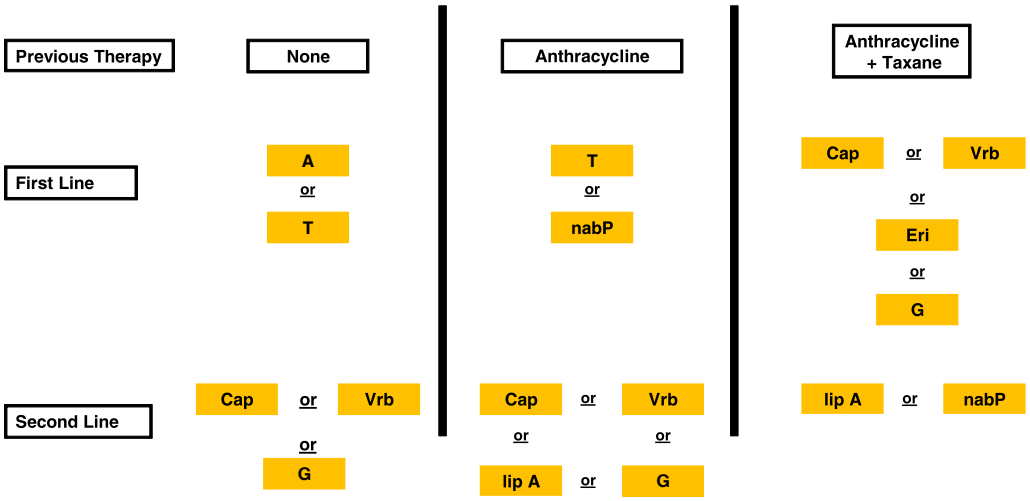
Biological testing procedures for selection of the optimal therapy, e.g. genetic signature or in-vitro sensitivity, have not undergone sufficient prospective validation yet. They are not recommended as standard procedure. This also applies to monitoring by determination of circulating tumor cells outside clinical trials.

Adverse effects are monitored during each therapy cycle by anamnesis, clinical examination, laboratory analysis and, if necessary, diagnostic imaging. The response to the systemic therapy is controlled every 2 – 3 months using clinical examination and targeted, diagnostic imaging. Closer monitoring may be indicated in patients with extensive and / or rapidly progressive disease, or in patients with severe local symptoms.

5.4.2.1 Monotherapy or Combination Therapy

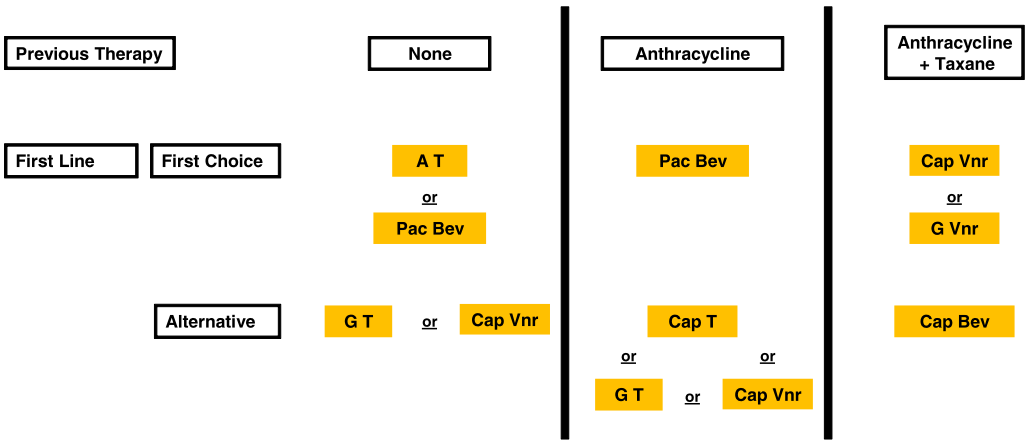
Combination therapy, either with cytostatic substances or with bevacizumab, results in higher remission rates and longer progression-free survival. In some studies, prolongation of overall survival was achieved. Combination chemotherapy is hampered with more severe side effects. In patients with oligosymptomatic disease and slow tumor growth, monochemotherapy is recommended [26, 27, 28]. In patients with severe symptoms, advanced visceral metastases or rapid tumor growth, combination chemotherapy is preferable. An alternative to combination chemotherapy is sequential application of single cytostatics. An algorithm for palliative chemotherapy is shown in Figure 6 and 7, broken down by monotherapy and combination therapy.

Figure 6: Palliative chemotherapy – Monotherapy



Legend:
A – anthracycline; Cap – capecitabine; Eri- eribulin, G – gemcitabine; lip A – liposomal doxorubicin; nab P – albumin-bound paclitaxel; T – taxane; Vrb – vinorelbine;

Figure 7: Palliative chemotherapy – Combination therapy



Legend:
A – anthracycline; Bev – bevacizumab; Cap – capecitabine; G – gemcitabine; Pac – paclitaxel; T – taxane; Vnr – vinorelbine;

5.4.2.2 Substances (in alphabetical order)

Anthracyclines / Anthracenes

This group includes doxorubicin, epirubicin, liposomal doxorubicin and mitoxantrone. They are the most active cytostatics in metastatic breast cancer. Median remission rates of the monotherapy of non-pretreated patients are between 35 and 40%. Anthracyclines are indicated in patients without anthracycline pre-treatment or after an interval of at least 12 months. Liposomal doxorubicin is an alternative for patients with indication for anthracyclines but who have cardiac comorbidity, or who have reached the cumulative maximum anthracycline dose. Serious adverse effects (grade 3/4) are alopecia, mucositis and hematological toxicity (neutropenia, thrombocytopenia, anemia). Less common, severe complications are left ventricular failure due to cardiomyopathy or dysrhythmias. The risk of cardial complications is lower with epirubicin or liposomal doxorubicin. Nausea and vomiting can be prevented using adequate supportive therapy.

Bendamustine

The effect of this alkylating substance has been demonstrated in a randomized phase III study by comparison of B(endamustine)MF to CMF. Common serious adverse effects are mucositis and leukocytopenia.

Bevacizumab

Bevacizumab is a monoclonal antibody with anti-angiogenetic effects. In combination with taxanes or other cytostatics (anthracyclines, capecitabine), it leads to an increase of remission rates and to a moderate but statistically significant prolongation of progression-free survival compared to monochemotherapy. Overall survival is not prolonged, see Breast Cancer Study Results. Serious adverse effects (grade 3/4), which occurred in more than 5% of patients in the pivotal trials, were hypertension and proteinuria. Less common, severe complications are thromboembolic events and perforations in the gastrointestinal tract.

Capecitabine

This oral compound is metabolised in the liver to form fluorouracil. Capecitabine is effective in monotherapy, with remission rates of 20 – 30%. Better results are achieved in combination with bevacizumab or docetaxel. Capecitabine ist active in the treatment of metastatic HER2 positive breast cancer after failure of taxanes or anthracyclines, and also active in combination with lapatinib. Serious adverse effects (grade 3/4), which occurred in more than 5% of patients in the pivotal trials, were stomatitis, diarrhea and hand-foot-syndrome.

Eribulin

Eribulin is the synthetic of halichondrin B, an antineoplastic substance isolated from marine sponges. In the third line therapy of patients with advanced breast cancer after anthracyclines and taxanes, eribulin lead to a significant prolongation of overall survival compared to a therapy of physician’s choice, see Breast Cancer Study Results. Remission rates were 12%. Serious adverse effects (grade 3/4), which occurred in more than 5% of patients in the pivotal trial, were neutropenia (45%), asthenia/fatigure (9%) and neuropathia (8%).

5-Fluorouracil

5-Fluorouracil (5-FU) is active as a monotherapy agent and in combinations. 5-FU can be administered either as a short infusion or as a continuous infusion during 24 hours. A synergistic effect of leucovorin in breast cancer has not been proven. Serious adverse effects are diarrhea and mucositis. Patients with functionally relevant polymorphisms in genes of 5-FU degradation have an increased risk for severe adverse effects including neutropenia and neutropenic fever.

Gemcitabine

In monotherapy, remission rates are between <10 % and 20%; in combination therapy with taxanes, up to 60% are achieved. After pretreatment with anthracyclines and taxanes, in combination with vinorelbine, remission rates of more than 30% were achieved. Serious adverse effect (grade 3/4), which occurred in more than 5% of patients in large randomized trials, was neutropenia.

PARP Inhibitors

Poly([ADP]-Ribose)polymerases (PARPs) are DNA repair enzymes and the targets of a new class of drugs. Preliminary data on efficacy were obtained in patients with triple-negative breast cancer and in patients with BRCA mutations.

Platinum

Platinum derivatives are among the active drugs. Current phase II trials and one phase III trial show remission rates of more than 50% in combination therapies with carboplatin and paclitaxel in patients with HER-positive or triple-negative carcinomas. Serious adverse effects (grade 3/4) of carboplatin, which occur in more than 5% of patients, are hematological (neutropenia, thrombocytopenia, anemia).

Taxanes

These include paclitaxel, docetaxel and albumin-bound paclitaxel (nab paclitaxel). Average remission rates in the monotherapy of non-pretreated patients are between 30 and 35%. In combination with anthracyclines, higher remission rates of 55 – 60% and extension of progression-free survival were achieved. The study results are not uniform in terms of prolongation of overall survival achieved by taxane-comprising combinations. Retreatment after adjuvant pretreatment is feasible. In paclitaxel, weekly application is more effective than three-weekly application. Serious adverse effects (grade 3/4) are alopecia, infections, onychodystrophy, stomatitis and diarrhea. Nausea / vomiting and allergic reactions can be prevented using adequate supportive therapy.

Vinorelbine

This vinca alkaloid can be administered intravenously or orally. In monotherapy, remission rates of up to 25% have been achieved. It is suitable both for monotherapy and combination therapy, also with trastuzumab for HER-2 positive carcinoma. Serious adverse effects (grade 3/4), which occur in more than 5% of patients, are neutropenia and anemia).

5.4.3 Palliative Anti-HER2 Therapy

The monoclonal antibody trastuzumab is an active substance in HER2-positive patients, with remission rates of 20%. In combination with anthracyclines, taxanes, capecitabine, vinorelbine and platinum derivatives, remission rates of > 50% with a significant prolongation of progression-free survival times compared to chemotherapy alone are achieved, see Breast Cancer Study Results. Due to an increased risk of cardiomyopathy, trastuzumab should not be used simultaneously with anthracyclines.

Lapatinib is administered orally. In trastuzumab-pretreated patients it is active in combination with capecitabine. Trastuzumab and lapatinib are also active in combination with aromatase inhibitors in patients with endocrine sensitive breast cancer. In patients with progressive disease under treatment with trastuzumab, the combination of lapatinib plus trastuzumab is more active than lapatinib monotherapy.

A new substance is pertuzumab, a humanized anti-HER2 antibody. It binds to a different epitope than trastuzumab. The addition of pertuzumab to a combination of trastuzumab plus docetaxel lead to remission rates of 80% with a significant prolongation of progression-free and overall survival, see Breast Cancer Study Results.

A further development of the trastuzumab concept involves the chemical linkage to cytostatic drugs. A recently presented, randomized phase III study used Trastuzumab-Emtansine (T-DM1). In pretreated patients T-DM1 was superior to the combination of lapatinib plus capecitabine, see Breast Cancer Study Results.

5.4.3.1 Substances (in alphabetical order)

Lapatinib

Lapatinib is an oral tyrosine-kinase inhibitor on HER2 and EGFR. It is active in the palliative and in the neoadjuvant setting. Remission rates in the monotherapy of advanced stages are between 15-20%, significantly higher in combination with chemotherapy, AI or trastuzumab. In the neoadjuvant therapy pCR rates or lapatinib are potentially lower than those of trastuzumab. Characteristic side effect of lapatinib is rash. Serious adverse effects (grade 3/4) are uncommon. Diarrhea grade 3/4 has been reported in various combination regimens.

Pertuzumab

Trastuzumab is a humanized anti-HER2 antibody. It binds to the subdomain II of the extracellular portion of HER2 and inhibits the dimerization with other HER2 receptors. Its clinically activity was recently demonstrated in a phase III study in the first-line therapy of patients with HER2 positive, metastastic breast cancer. The triple combination of pertuzumab, trastuzumab and docetaxel lead to higher remission rate, prolongation of progression-free survival and decreased mortality as compared to the combination of trastuzumab / docetaxel, see Breast Cancer Study Results. The incidence of grade 3/4 diarrhea and febrile neutropenia were higher in the pertuzumab-containing arm.

Trastuzumab

Trastuzumab was the first monoclonal antibody which interferes specifically with the HER2 receptor and which was authorized for the treatment of patients with HER2 over-expressing or gene-amplified breast cancer. It is active in the neoadjuvant, the adjuvant and the palliative situation. Remission rates of monotherapy in patients with metastatic disease range between 19-25%, significantly higher in combination with chemotherapy. Serious adverse effects (grade 3/4) are uncommon. A critical complication is the decrease of left ventricular function up to symptomatic heart failure. This complication occurs more often in patients with previous cardiac disease and in conjunction with the application of anthracyclines.

5.4.4 Maintenance Therapy

The realistic goal in the treatment of patients with metastatic breast cancer is remission with alleviation of symptoms and extension of the progression-free survival. The side effects and burden of the treatment must be balanced against the benefit. It is recommended to continue the palliative endocrine therapy until progression. In chemotherapy, generally 4 – 6 cycles will be applied to achieve maximum response. For maintenance chemotherapy, so far no benefits have been demonstrated. Therapy with trastuzumab and lapatinib or bevacizumab may be continued until progression; there are no randomised phase III studies to compare this approach to interval therapy yet.

5.4.5 Palliative Therapy – Symptom-Oriented

Palliative therapy addresses physical and mental ailments. It is administered in multidisciplinary teams. The need for and options in palliative therapy should be discussed early and comprehensively with all persons concerned. The following specific symptoms are particularly common in patients with advanced breast cancer.

5.4.5.1 Bone Metastases

For the treatment of patients with bone metastases, local and systemic measures are available [7, 8]. In case of pain symptoms or danger of fracture, radiotherapy is the treatment of choice. An additional option is surgery for pathological fractures, for unstable vertebral fractures or for

spinal decompression. Myelon- or nerval compression are emergencies which need immediate multidisciplinary therapy.

Systemic measures include causal therapy and the administration of supportive therapy with bisphosphonates (clodronate, ibandronate, pamidronate, zoledronate) or the RANKL antibody denosumab. Bisphosphonates or denosumab reduce the risk of skeletal-related events. In a recently published, randomized trial denosumab lead to a significant delay of skeletal-related events compared to zoledronate. Denosumab had no effect on progression-free and overall survival.

Bisphosphonates are also indicated in hypercalcaemia.

5.4.5.2 CNS Metastases

The first measure in cases of symptomatic metastasis is administration of steroids for the reduction of perifocal edema. In case of an isolated cerebral metastasis, local therapy by surgery or stereotactic treatment is expedient. For multiple metastases, palliative radiotherapy of the entire brain is recommended.

5.4.5.3 Malignant Pleural Effusion

A Cochrane Review of 36 randomized studies involving 1499 patients identified thoracoscopic pleurodesis with talc as the most treatment in patients with malignant pleural effusion. A more detailed recommendation is summarized in the Onkopedia Guideline Lung Cancer, Non Small Cell (NSCLC).

6 Rehabilitation

The need for rehabilitation is very high in patients in breast cancer. This involves somatic as well as psychosocial aspects. The need for rehabilitation is less guided by the tumor stage or subsequent therapy than by the functional and psychological impairments. In 2009, 29% of all inpatient rehabilitations in Germany were performed in patients with breast cancer.

The patients should be informed about the options for inpatient and outpatient rehabilitation, as well as further claims on the basis of social legislature. The information should be provided early, i. e. prior to the termination of radiation or chemotherapy. Concerning the rehab clinic, the wishes of the patient should be taken into account (legal basis in Germany: §9 SGB IX). Nevertheless a hospital with oncological focus should be recommended in order to ensure optimally successful rehabilitation.

7 Follow-up

Goals of posttherapeutic follow-up are the early diagnosis of loco-regional relapse or of secondary breast cancer with the chance of curative therapy. Further objectives are detection and treatment of therapy-related side effects and the continuation of psychosocial support and consultation.

Breast cancer follow-up begins with the completion of the primary therapy. It consists of anamnesis, physical examination, consultation and support. If necessary, follow-up must be designed in symptom-oriented fashion. For follow-up, the patient needs intensive multidisciplinary consultation. In women who are asymptomatic after completion of breast-conserving therapy, imaging diagnostics (e.g. mammography, sonography) of the ipsilateral breast are recommended. For all patients, mammography controls of the contralateral breast are to be carried

out annually. In patients with BRCA1 or BRCA2 mutations, magnetic resonance imaging is the method of choice. MRI is also indicated in patients after reconstructive surgery and for the differential diagnosis of scar tissue versus secondary neoplasia.

Laboratory and imaging diagnostics are to be used in case of anamnestic or clinical suspicion of relapses or metastases. Routine search for distant metastases in asymptomatic patients is not indicated due to the unreliability of the methods used. Targeted diagnostics are recommended in symptomatic patients.

Follow-up examinations should be performed quarterly during the first 3 years after local primary therapy, semiannually in the 4^{th} and 5^{th} year and annually from the 6^{th} year on. Screening tests for early detection are to be included.

All patients with axillary lymphadenectomy must be informed postoperatively about the option of detection, prevention and treatment of lymphedema of the arm. Initiation of prophylactic lymph drainage is not indicated.

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9 Active Studies

- Neoadjuvant
- Geparsixto / Geparsepto (www.germanbreastgroup.de)
- WSG ADAPT (www.wsg-online.com)
- Late adjuvant

Neratinib after Trastuzumab in HER2 positive patients

- Metastastic 1st line

CARIN - Phase IIb Study for the establishment of a non-anthracycline, non-taxane containing regimen with Capecitabine / Bevacizumab ± Vinorelbin; www.aio-portal.de

- Metastastic 2nd+3rd line

PASO - Phase II Study for the efficacy of Sorafenib / Paclitaxel;

www.aio-portal.de

11 Study Results

- Breast Cancer in Women - Study Results (RCT, Metaanalysis)

12 Links

www.frauenselbsthilfe.de

www.dgho.de/gesellschaft/verein/arbeitskreise/onkologische-rehabilitation

www.mamazone.de

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14 Disclosure of Potential Conflicts of Interest

according to the rules of the German Association of Hematology and Medical Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.

The authors declare that they have no conflicts of interest.