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Position Paper

Evidence-based treatment of metastatic breast cancer – 2006 recommendations by the AGO Breast Commission

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ABSTRACT

The Breast Commission of the German Gynecological Oncology Working Group AGO revises in annual intervals their evidence-based recommendations on therapy of primary and advanced breast cancer. A purely scientific assessment of the most recent published literature according to standardized level of evidence and grade of recommendation is supplemented by a newly developed AGO recommendation system which constitutes an expert consensus considering also clinical relevance, feasibility, and compliance. It is an approach of providing readers with an additional assessment trying to help them to select the most appropriate treatment for the individual patient situation. In the following, an overview is given on the most important aspects in diagnosis and therapy of metastatic breast cancer. For detailed aspects, a comprehensive set of slides including a more complete bibliography may be accessed under www.ago-online.org.

1. Objective

The Breast Commission of the German Gynaecological Oncology Working Group AGO revises in annual intervals their evidence-based recommendations on therapy of primary and advanced breast cancer. A purely scientific assessment of the most recent published literature according to standardised level of evidence and grade of recommendation[1] is supplemented by a newly developed AGO recommendation system (Table 1) which constitutes an expert consensus considering also clinical relevance, feasibility, and compliance. It is an approach of providing readers with an additional assessment trying to help them to select the most appropriate treatment for the individual patient situation. In the following, an overview is given on the most important aspects in diagnosis and therapy of metastatic breast cancer. For detailed aspects,

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Table 1 – Definition of the grade of recommendation by the Breast Commission

++	This examination or therapeutic intervention is highly beneficial for the patient, can be recommended without any restrictions and should be carried out.
+	This examination or therapeutic intervention is of restricted benefit for the patient and can be carried out.
+/–	This examination or therapeutic intervention has not shown any benefit so far and may be carried out in single cases. Due to the data basis, no explicit recommendation can be given.
–	This examination or therapeutic intervention may be detrimental to the patient and should therefore not be carried out.
– –	This examination or therapeutic intervention is detrimental and should by no means be carried out/i.e. should be refrained from.

a comprehensive set of slides, including a more complete bibliography, may be accessed under www.ago-online.org.

2. Procedure

Alternating every year, AGO commission members prepare presentations on the most important aspects of metastatic (and early) breast cancer management. For this purpose, a literature search of the Medline database as well as the abstract books of the last 5 years on the ASCO, ECCO, San Antonio Breast Cancer Symposium, and the European Breast Cancer Conference is performed. Subsequently, the experts suggest amendments to the guidelines slides of previous versions or preparation of new slides. At the beginning of every year, the suggestions for changes and amendments are presented and discussed in detail in the presence of all AGO Breast Commission members at a 3-day workshop. The final AGO recommendation grade for each statement is determined by simple majority each time, and it thus represents an expert consensus. Editorial corrections are subsequently made by the spokesman of the commission and the final guideline slide set is subsequently released by all members. The most recent version of the guideline slide set was issued in May 2006.

2.1. *Treatment strategy and objectives*

Metastatic breast cancer still has to be regarded as an incurable disease by treatment modalities available today. However, due to improved therapy options, patients show more often a chronic undulating course, which should be taken into account for the individual therapeutic management. Frequently the motto 'as little as necessary' might thus be more appropriate than 'as much as possible'.

Traditional objectives of palliative therapy are on the short term relief of tumour-induced pain and on the long-term preservation of physical activity resulting in a reasonable quality of life. More than ten recent phase-III studies demonstrated a significant prolongation of survival with patient numbers and study design suggesting high validity (LOE 1b). In addition, retrospective longitudinal observations observed a continuous prolongation of survival over several decades (LOE 2a). Therefore, treatment of patients with metastatic breast cancer today also aims at long-term prolongation of life and not just at palliation of symptoms. Two reasons with possible synergistic effects are currently under discussion for this improvement in prognosis: More effective drugs and combinations, especially when they are used as first-line therapy, and the increasing overall number of drugs that can be used sequentially throughout the course of disease.

Systemic therapy is of prime importance for treatment of metastatic breast cancer. Endocrine therapy appears to be the therapy of choice in patients with a hormone receptor positive tumour due a favourable risk (for toxicity)-benefit ratio (referred to therapeutic index) (LOE 1a, GR A, AGO++).[2,3] Chemotherapy has to be considered in patients with an immediate need for remission. Mono-chemotherapy appears to be in many cases more favourable in terms of treatment efficacy, toxicity profile, and quality of life. It is therefore indicated when the disease shows a slow, not life-threatening progression or if endocrine treatment is predicted ineffective due to low or absent steroid receptor status or exhausted after various treatment lines. Polychemotherapy usually provides higher efficacy at short term with a more unfavourable toxicity profile and impairment of quality of life. The therapeutic index therefore appears more advantageous in the case of foudroyant tumour progression with an imminent danger of organ failure or presence of severe tumour symptoms significantly impairing quality of life. Loco-regional intervention such as radiotherapy and operations is indicated for specific situations dependent on symptoms, metastasis pattern, and general condition of the patient.

2.2. *Prediction and monitoring of treatment effect*

The probability of treatment success in the metastatic situation can be assessed by means of the following predictors[4]:

- positive hormone receptor test in the primary tumour or metastasis for endocrine therapy (LOE 1a, GR A, AGO ++),
- response to 1st line endocrine therapy for a 2nd line endocrine therapy (LOE 1b, GR A, AGO ++),
- response to previous chemotherapy for next chemotherapy (AGO 1b, GR A, ++),
- presence of bone metastasis for the use of bisphosphonates (LOE 1a, GR A, AGO ++),
- amplification/over-expression of HER2 in the primary tumour or even better in metastasis tissue for trastuzumab (LOE 1a, GR A, AGO ++),
- premenopausal status for suppression of ovarian function and postmenopausal status for treatment with aromatase inhibitors (LOE 1c, GR A, AGO ++).

HER2 status should not be routinely used for selection of specific conventional therapies (anthracyclines, taxanes, tamoxifen, aromatase inhibitors) (LOE 2b-5, GR C-D, AGO +/–). This also holds true for measuring HER2 shed antigen (LOE 2b, GR C, AGO +/–)[5] and for detection of circulating tumour cells in blood (LOE 1b, GR B, AGO +/–).[6]

Table 2 – Comparison of 3rd generation aromatase inhibitors and SERMs with tamoxifen as first endocrine step in metastatic breast cancer

n (%HR+)	Arm A	Arm B	ORR (%)	CBR (%)	TTP(F) (mo)	OS (mo)	Side effects	Reference
Aromatase inhibitors v tamoxifen								
668 (45)	Ana	Tam	ns	ns	ns (P/F)	ns	TE(%) 4.7 v 7.3 VB(%) 1.2 v 2.4	Bonne-terre 2000 Nabholtz 2003
353 (89)	Ana	Tam	ns	59 v 46	11 v 6 (P) ns (F)		TE(%) 4.1 v 8.2 VB(%) 1.2 v 3.8	Nabholtz 2000
238 (100)	Ana	Tam	ns	83 v 56	ND	ns	TE(%) 0 v 8 VB(%) 4 v 16	Milla Santos 2003
916 (66)	Let	Tam	32 v 21	49 v 38	9 v 6 (P/F)	ns	ns	Mouridsen 2001/2003
120 (93)	Exe	Tam	41 v 17*	57 v 42*	ND	ND	Ns	Paridaens 2003
371 (85)			46 v 31	ND	9.9 v 5.8	ns	ns	Paridaens 2004 (a)
SERM v tamoxifen								
587 (78)	Ful	Tam	ns	ns	ns (P)	ND	ns	Robertson 2002 (a)
590 (78)			ns	ns	ns (P,F)	ns	HF 17.7 v 24.7	Howell 2004
1421	Tor 40/60/200/240	Tam 20/40	ns	?	ns (P)	ns	Ns	Pyrhonen 1999 (Meta-5)

SERM, selective oestrogen receptor modulator; CBR, clinical benefit rate; Exe, exemestane; Ful, fulvestrant; G, gosereline; HF: hot flushes; HR, hormone receptor; Let, letrozole; Meta-*x*, metaanalysis (*x* = number of studies); Mo, months; *n*, number of evaluable patients; ND, not mentioned; ns, not significant; SE, side effects; ORR, overall response rate; OS, overall survival; Tam, tamoxifen; QoL, quality of life; TE, thromboembolism; Tor, toremifene; TTP(F), time to progression(treatment failure); v, versus; VB, vaginal bleeding.
* *p*-value not given.

Table 3 – Randomised controlled trials with 3rd generation aromatase inhibitors after tamoxifen as 1st or 2nd line endocrine therapy in postmenopausal patients with metastatic breast cancer

n(%HR+)	Line (pret.)	Arm A	Arm B	ORR (%)	CBR (%)	TTP(F) (mo)	OS (mo)	Side effects (%)	Reference
Aromatase inhibitor v Megestrol acetate (MA)									
764 (75)	1st–2nd(Tam)	Ana 1/10	MA	ns	ns	ns (P)	26 v 23	SW 12 v 8 GW 3 v 13 VB 3 v 6	Buzdar 1998
551	(Tam)	Let 0.5/2.5	MA	24 v 16 (Let 2.5)	?	ns (P) ↑ (F) (Let 2.5)	ns	CV ↑ GW 9 v 12	Dombernowsky 1998
602 (82)	1st–2nd(Tam)	Let 0.5/2.5	MA	ns	ns	6 v 3 (P) 5 v 3 (F) (0.5 Let)	ns	GW 9 v 12 VB 3 v 8	Buzdar 2001
547 (42)	1st– 2nd(Tam)	For	MA	ns	ND	ns (P/F)	ns	CV 6 v 13 GW 0.4 v 4.4 VB 0.4 v 4.8	Freue 2000
769 (68)	1st– 2nd(Tam)	Exe	MA	ns	ns	5 v 4 (P) 4 v 3 (F)	↑	SW 5 v 13 GW 8 v 17 N/V 6 v 12	Kaufmann 2000
Aromatase inhibitor v aromatase inhibitor									
555	(Tam)	Let 0.5/2.5	AG	ns	?	3.4 v 3.2 ($P_{2.5Let}$)	28 v 20 (Let 2.5)	ET 2 v 11	Gerschanovich 1998
713 (48)	1st–2nd(Tam)	Ana	Let	12 v 19	ns	ns (P/F)	ns	Ns	Rose 2003
154 (66)	(82% Tam)	Let	Fad	31 v 13	51 v 35	ns (P)	ND	Ns	Tominaga 2003
130 (98)	1st–2nd	Exe	Ana	Ns	Ns	ns	Nd	Ns	Cameron 2004
antiestrogene v aromatase inhibitor									
400 (87)	1st–2nd(Tam)	Ful	Ana	ns	ns	ns (P/F)	ND	AT 5 v 11	Osborne 2002, Robertson 2003,
451 (77)	1st–2nd(Tam)	Ful	Ana	ns	ns	ns (P/F)	ns		Howell 2002/2003(a)

AG, aminoglutethimide; AH, aromatse inhibitor; AT, arthralgia; CBR, clinical benefit rate; ET, exanthema; Exe, exemestane; Fad, fadrozole; For, formestane; Ful, fulvestrant; GW, gain of weight; HR, hormone receptor; SW, sweating; CV, cardiovascular; Let, letrozole; MA, megestrolacetat; Mo, months; *n*, number of evaluable patients; ND, not mentioned; ns, not significant; N/V, nausea/vomitus; SE, side effects; ORR, overall response rate; OS, overall survival; QoL, quality of life; Tam, Tamoxifen; TTP(F), time to progression(treatment failure);v, versus; VB, vaginal bleeding.

For monitoring of the therapy effect, in addition to changes in symptoms, imaging of a pre-specified target lesion (AGO +), tumour markers Ca 15-3 (and CEA) (if initially elevated above normal) (AGO +)[7] or HER2 shed antigen (ECD) (if initially elevated) (AGO +) are recommended. Only in selected cases, circulating tumour cells or positron emission tomography (PET) seem to be indicated for guiding treatment decisions (AGO +/−).

2.3. *Endocrine therapy*

Endocrine therapy combines the advantages of good efficiency, low toxicity, and low impact on quality of life. Efficacy of an endocrine therapy largely depends on the expression of both steroid hormone receptors (ER and PgR positive: remission rate (RR) 50–75%; only ER or PR positive: RR 20–50%; ER and PR negative: RR < 10%).[8] Treatment should be continued until disease progression or occurrence of relevant side effects.

For postmenopausal patients after adjuvant tamoxifen treatment, 3rd generation aromatase inhibitors are recommended as first-line therapy of metastatic disease (LOE 1a, GR A, AGO ++). The advantage in comparison to tamoxifen is based on an improvement in time to progression and clinical benefit, but not on prolongation of survival. Clinically relevant differences between anastrozole, exemestane and letrozole have not been demonstrated so far (Table 2).[9,10]

After failure of first-line aromatase inhibitor treatment, fulvestrant (LOE 3b, GR C, AGO+), switch to another aromatase inhibitor (steroidal to non-steroidal or vice versa) (LOE 3b, GR C, AGO +) or tamoxifen again (LOE 3b, GR C, AGO+/−) represent valid treatment options. Progestogens (LOE 4, GR D, AGO+) or repletion of previous drugs (LOE 5, GR D, AGO +) as further endocrine treatment lines have not been investigated widely, but fit well into the general treatment strategy of a chronic disease (Table 3).

As the number of patients with adjuvant use of an aromatase inhibitor will increase in the future, more data are needed on how these patients might be treated in the case of relapse. Tamoxifen (LOE 2b, GR B, AGO ++) or exemestane (LOE 2b, GR B, AGO+) can be recommended as first-line metastatic treatment after adjuvant use of a non-steroidal aromatase inhibitor. Later line options are fulvestrant (LOOE 3b, GR C, AGO+) or progestogens (LOE 4, GR C, AGO +).

If patients received an adjuvant sequence with tamoxifen and an aromatase inhibitor, it may be appropriate to use fulvestrant (LOE 4, GR D, AGO +) or an aromatase inhibitor of the other pharmacological group (steroidal versus non-steroidal) (LOE 4, GR D, AGO +) after a short treatment-free interval. If the treatment.free interval lasted more than 1 year, tamoxifen may also represent a valid option (LOE 4, GR D, AGO +) (Table 4).

For premenopausal women, combination therapy of GnRH analogues (or ovarectomy) with tamoxifen is recommended

Table 4 – Uncontrolled trials (> 50 patients enrolled) exploring endocrine agents in endocrine pretreated postmenopausal patients with metastatic breast cancer

n (%HR+)	Line (pretreatment)	Therapy	ORR (%)	CBR (%)	TTP(F) (mo)	OS (mo)	Reference
Postmenopausal							
91 (92)	3rd(tam, ma)	exe	13	30	2 (P)	26	Jones 1999
241 (70)	2nd (nsAI)	exe	7	24	n.a.	n.a.	Loenning 2000
119 (72)	2nd (ana)	tam	10	49	n.a.	n.a.	Thürlimann 2003
95 (74)	2nd(tam)	ana	7	57	n.a.	n.a.	(retrospective)
54	(tam, ful → CB)	AI (46/54)	7	39	n.a.	n.a.	Vergote 2003
51	(tam, ful → noCB)	AI (48/51)	2	33	n.a.	n.a.	(retrospective)
88	1st–4th(tam, ana, exe)	ful	7	57	n.a.	n.a.	Steger 2003 (a) (retrospective)
76 (100)	1st–3rd	AI 3rd gen.	39.1	n.a.	8.2	n.a.	Kai 2004 (a)
n.a.	2nd (anastrozole failure)	exemestane	11.1	n.a.	n.a.	n.a.	Retrospective
n.a.	2nd (failure to 2nd gen AI or MPA)	AI 3rd gen.	55.6 or 26.7	n.a.	n.a.	n.a.	
n.a.	3rd (failure to 3rd gen AI)	MPA	23.1	n.a.	n.a.	n.a.	
60 (90/97)	1st–2nd (tam, ana)	ana -> tam tam -> ana	79 (a) 44 (t) 50 (ana->tam) 44 (tam->ana)	n.a.	P: 28.2 (a -> t) versus 19.5 (t -> a) ns	69.7 (a->t) versus 59.3 (t -> a) ns	Thürlimann 2004 (a) retrospective
100	1st line anastrozole	exemestane after progression under anastrozole	8%	50%	5 Mo	ND	Laffaioli RV: Br J Cancer 92;2005:1621
54	1st–3rd	exemestane letrozole anastrozole	n.a.	47 (exemestane) 40 (exemestane >anast/letro) 25 (anast/letro >exemestane)	n.a.	n.a.	Bertelli 2002 (a)

Ana, anastrozole; AI, aromatse inhibitor; CBR, clinical benefit rate; Exe, exemestane; Ful, fulvestrant; HR, hormone receptor; MA, megestrolacetat; Mo, months; MPA: megestrol progesteron acetat; *n*, number of evaluable pat.; ND, not mentioned; nsAI, non-steroidal AI; ORR, overall response rate; OS, overall survival; Tam, tamoxifen; TTP(F), time to progression(treatment failure).

Table 5 – First line endocrine therapy in premenopausal patients with metastatic breast cancer

n (%HR+)	Arm A	Arm B	ORR (%)	CBR (%)	TTP (Mo)	OS (Mo)	Side effects	Reference
220	Tam	OA	ns	→	ns	ns	ND	Crump 1997 (Meta-4)
136 (100)	G	OA	ND	ND	ns	ns	ND	Taylor 1998
161 (71)	B + Tam	Tam	48 v 28	75 v 44	10 v 6	3.7 v 2.9	ND	Klijn 2000
	B + Tam	B	48 v 34	75 v 62	10 v 6	3.7 v 2.5	ND	
	B	Tam	ns	ns	ns	ns	ND	
506 (62)	GnRH-A + Tam	GnRH-A	39 v 30	ND	↑ (HZ 0.7)	↑ (HZ 0.78)	ND	Klijn 2001 (Meta-4)
119 (100)	G + Tam	G + Ana	53 v 80	↓	ND	14 v 19	ns	Milla Santos 2002 (a)

Ana, anastrozole; B, busereline; CBR, clinical benefit rate; G, gosereline; GnRH-A, gonadotropine-releasing-hormone-agonists; HR, hormone receptor; HZ, hazard ratio; Meta-*x*, metaanalysis (*x* = number of studies); Mo, months; *n*, number of evaluable pat.; ND, not mentioned; ns, not significant; OA, ovarian ablation; ORR, overall response rate; OS, overall survival; Tam, Tamoxifen; TTP, time to progression; v, versus.

(LOE 1a (2b), GR A (B), AGO ++) since this combination seems to be superior to either ovarian suppression or tamoxifen therapy alone. Primary administration of an aromatase inhibitor with GnRH analogues may be regarded as a 2nd option only due to lack of sufficient data (LOE 2b, GR B, AGO +) (Table 5).[11]

If disease progression is detected but prognosis still remains favourable, changing from tamoxifen to an aromatase

Table 6 – Impact of cross-over to investigational regimen in randomised controlled trials of patients with metastatic breast cancer

Regimen		Crossover		Survival Benefit	Reference
Standard	Investigational	Agent	Frequency		
Single A or P	AP combined	Single agent	57%	NO	Sledge 2003
A	D	D	47%	NO	Paridaens 2000
MV	D	D	24%	YES	Nabholtz 1999
D	XD	X	17%	YES	O'Shaughnessy 2002
P	GP	G	14%	Strong trend	Albain 2004
CMFPd	P	P	6%	YES	Bishop 1999

A, doxorubicin; C, cyclophosphamide; D, docetaxel; F, 5-fluorouracil; G, gemcitabine; M, methotrexate; P, paclitaxel; Pd, prednisolone, X, capecitabine.

Table 7 – Overview on studies for comparison mono- versus polychemotherapy in metastatic breast cancer

n	Line	Anthracycline	Control	ORR (%)	TTP(F) (Mo)	OS (Mo)	QoL Mon	Reference
2242	⩾1st	Mon	Pol	34 v 48	n.d.	HR: 0,82	ND	Fossati 1998 (meta-15)
40	1st	E	CM	29 v 58	2 v 5(F)	n.s.	→	Fraser 1993
91	2nd	D	V	54 v 44	7 v 5	n.s.	n.s.	Bonneterre 1997 (a)
735	1st	P → A	A P	33 v 46	6 v 8 (F)	n.s.	→	Sledge 2003
		A → P	A P	34 v 46	6 v 8 (F)	n.s.	→	
294	1st–2nd	E(→Mc)	CEF(→McVb)	n.s.	n.s.	n.s.	↑	Joensuu 1998
209	1st	P	CMFP	n.s.	n.s.	17 v 14	→	Bishop 1999
287	1st–2nd	D	McV	30 v 12	4 v 2	11 v 9	→	Nabholtz 1999
267	1st–2nd	D	MF	42 v 21	6 v 3	n.s.	→	Sjostrom 1999, Hakamies-Blomqvist 2000
300	1st–2nd	A	AV	n.s.	n.s. (P/F)	n.s.	→	Norris 2000
65	⩾2nd	V	Mx	n.s.	2 v 5 (F)	n.s.	→	Venturino 2000
65	⩾2nd	F	Mx	n.s.	3 v 5 (F)	n.s.	→	
511	1st–4th	D	DC	30 v 42	4 v 6	12 v 15	→	O'Shaughnessy 2002
260	1st	Mx	FEC	n.s.	n.s.	n.s.	↑	Heidemann 2002
182	1st	E → P	EP	n.s.	ND	ND	ND	Baldini 2002 (a)
48	1st	A → D	AD	n.s.	ND	ND	ND	Ramos 2002 (a)

M, methotrexate; Mc, mitomycin C; Mo, months; Mon, monochemotherapy; Mx, mitoxantrone; *n*, number evaluable patients.; ND, no data; n.s., not significant; ORR, overall response rate; OS, overall survival; P, paclitaxel; Pd, prednisolon; Pol, polychemotherapy; QoL, quality of life; TTP(F), time to progression(treatment failure); v, versus; V, vinorelbin; Vb, vinblastin.

Table 8 – Randomised controlled trials evaluating anthracycline monotherapy as 1st line therapy of metastatic breast cancer

n	Line	Anthracycline	Control	ORR (%)	TTP(F) (Mo)	OS (Mo)	QoL An	Reference
Doxorubicin, liposomal doxorubicin								
739	1st	P(→A)	AP	33 vs 46	6 vs 8 (F)	ns	→	Sledge 2003
		A(→P)	AP	34 vs 46	6 vs 8 (F)	ns	→	
509	1st	A	PLD	ns	ns	ns	ND	O'Brien 2004
331	1st	A	P	41 vs 25	8 vs 4	ns	→	Paridaens, Kramer 2000
154	1st	A	nPLD	ns	ND	ND	ND	Harris 1998 (a)
141	1st	A	E	ns	ns	ns	ND	Perez 1991
300 (225†)	1st–2nd	A	AV	ns	ns (F)	ns	→	Norris 2000
322 (152†)	1st–2nd	A	D	33 vs 48	ns	ns	→	Chan 1999
71 (37†)	1st–2nd	A	I	46 vs21	ns	ns	ND	Lopez 1989
Epirubicin								
294	1st	E (→Mc)	CEF (→McVb)	Ns	ns	ns	↑	Joensuu 1998
40	1st	E	CMF	29 vs 58	2 vs 5 (F)	ns	→	Fraser 1993
410	1st	E	G	40 vs16	6.1 vs 3.4	19.1 vs 11.8	?	Feher 2005
Mitoxantrone								
260	1st	Mx	FEC	ns	ns	ns	↑	Heidemann 2002

A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, 5-fluorouracil; G, gemcitabine; I, idarubicin; M, methotrexate; Mo, month; Mc, mitomycin C; Mx, mitoxantrone; *n*, number evaluable patients.; ND, no data; ns, not significant; nPLD, non-pegylated liposomal doxorubicin; ORR, overall response rate; OS, overall survival; P, paclitaxel; PLD, pegylated liposomal doxorubicin; QoL, quality of life; TTP(F), time to progression(treatment failure); V, vinorelbin; Vb, vinblastin; vs, versus.† = 1st line.

inhibitor while continuing ovarian suppression may be considered (LOE 4, GR C, AGO +).

Concurrent endocrine treatment with chemotherapy is not recommended (LOE 1b, GR A, AGO − −) since marginally higher remission rates have not manifested themselves in a prolongation of progression-free or overall survival, but higher toxicity was observed.

2.4. *Chemotherapy*

Before start of palliative chemotherapy, patient compliance needs to be assessed (LOE 1c, GR A, AGO ++). Only if chemotherapy can be administered over a sufficient period of time in the planned dosage, the treatment objective will be achievable. Particularly in elderly patients, with reduced general condition or pre-existing co-morbities this assessment requires appropriate therapeutic experience. During therapy, both objective and subjective side effects should be inquired regularly and taken into account for further treatment decisions. Dosages should be administered according to published therapy regimens. At least one indicator parameter (metrics of a metastasis, tumour markers or symptoms) should be recorded before therapy and thereafter in at least 2-month intervals in order to be able to promptly assess treatment efficiency.

Chemotherapy should be administered as long as the therapeutic index remains positive (i.e. benefit is greater than side effects). In case of disease progression or objectively or subjectively intolerable side effects, treatment should be discontinued immediately (LOE 1c, GR A, AGO ++). Maintenance therapy with cytotoxics is not recommended (LOE 2b, GR B, AGO −); yet, it may be considered in case of monotherapy (LOE 2b, GR B, AGO +/−). In principle, intermittent use of chemotherapy at onset of progression is rated to be most advantageous (LOE 2b, GR B, AGO ++).

For choice between different mono- or combination therapies, patients' wishes, their general condition, patient age, disease aggressiveness, metastasis location as well as prior therapies need to be considered.

Monotherapy is associated with a somewhat more favorable therapeutic index than polychemotherapy (LOE 1b, GR A, AGO ++). This recommendation is particularly supported by a phase III trial comparing sequential monotherapy and polychemotherapy with doxorubicin and paclitaxel which did not demonstrate any difference in overall survival between the different approaches.[12]

In two recent studies, however, a survival benefit for polychemotherapy (docetaxel and capecitabine, paclitaxel and gemcitabine) versus taxane-monotherapy was shown.[13,14] In one of these studies, non-hematological toxicity was comparable in both arms, and quality of life did improve over time in the polychemotherapy arm. However, only a minority of patients in the monotherapy arm received the antimetabolite in sequence to the taxane. Thus, these studies have not yet confuted the general preference towards monochemotherapy stated above (Tables 6, 7).

The most effective mono-chemotherapies in metastatic breast cancer are anthracyclines (including its liposomal preparation) (LOE 1b, GR A, AGO ++), taxanes (LOE 1b, GR A, AGO ++), and vinorelbine (LOE 3b GR B, AGO +). They should therefore be used as 1st line treatment (Tables 8, 9).

(PEG-)liposomal encapsulated doxorubicin shows the same effectiveness as doxorubicin; it is, however, less cardiotoxic and therefore is an alternative in case of pre-existing cardiac disease or if the cumulative cardiotoxic threshold dose has already been reached.[15]

Polychemotherapy may consist of a combination of taxanes with anthracyclines (LOE 1b, GR A, AGO ++), with capecitabine (LOE 1b, GR A, AGO ++) or with gemcitabine (LOE 2b, GR B, AGO ++) after anthracycline pre-treatment. Further

Table 9 – Randomised controlled trials evaluating taxane monochemotherapy as 1st line therapy of metastatic breast cancer

n	line	T	Control arm	ORR (%)	TTP(F) (Mo)	OS (Mo)	QoL T	Reference
3663	1st–4th	T	kein T	↑	↑	↑	→	Gershi 2003 (Cochrane Meta)
Paclitaxel								
739	1st	P(→A)	AP	33 vs 46	6 vs 8 (F)	ns	→	Sledge 2003
		A(→P)	AP	34 vs 46	6 vs 8 (F)	ns	→	
331	1st	P	A	25 vs 41	4 vs 8	ns	→	Paridaens, Kramer 2000
209	1st	P	CMFPd	ns	ns (P)	17 vs 14	→	Bishop 1999
41(?†)	1st–3rdApt	P	Ca	ns	ns	ns	ND	Talbot 2002
Docetaxel								
511(171†)	1st–4thApt	D	DCa	30 vs 42	4 vs 6	12 vs 15	→	O'Shaughnessy 2002
322(152†)	1st–2nd	D	A	48 vs 33	ns	ns	→	Chan 1999
267(132†)	1st–2ndApt	D	MF	42 vs 21	6 vs 3	ns	→	Sjostrom 1999, Hakamies-Blomqvist 2000
387(74†)	1st–2ndApt	D	McVb	30 vs 12	4 vs 2	11 vs 9	→	Nabholtz 1999
Docetaxel vs paclitaxel								
449	1st	D	P	32 vs 25 (ns)	5,7 vs 3,6 (s)	15,4 vs 12,7 (s)	ns	Jones 2005
ABI 007 vs paclitaxel								
457	1st–3rd	ABI 007	P	33 vs 19 (s)	23 vs 17 weeks (s)	65 vs 55,7 weeks (n.s.)	→	Gradishar 2005

A, doxorubicin; Apt, anthrazyklin-pretreated; C, cyclophosphamide; Ca, capecitabine; D, docetaxel; F, 5-fluorouracil; M, methotrexate; Mc, mitomycin C; Mo, month; *n*, number evaluable patients; ND, no data; ns, not significant; ORR, overall response rate; OS, overall survival; P, paclitaxel; Pd, prednisone; QoL, quality of life; T, taxane; TTP(F), time to progression(treatment failure); Vb, vinblastin; vs, versus. † = 1st-line.

options are [5-flurorouracil]/(epi-)doxorubicin/cyclophosphamide, liposomal doxorubicin + cyclophosphamide (LOE 1b, GR B, AGO ++), as well as CMF (LOE 2b, GR B, AGO +/−) or bendamustin/methotrexate/5-fluorouracil (BMF) (LOE 1b, GR B, AGO +/−) in selected cases.

After anthracycline failure, docetaxel or paclitaxel (LOE 1a, GR A, AGO ++) as well as capecitabine (LOE 2b, GR B, AGO ++) are recommended. Further options are PEG-liposomal doxorubicin, vinorelbine (LOE 2b, GR B, AGO +) or gemcitabine (LOE 3b, GR B, AGO +/−) in selected cases.

As a monochemotherapy, so far only docetaxel was able to improve survival compared to standard therapy in anthracycline-pretreated metastatic breast cancer in a randomised study.[16] According to a Cochrane meta-analysis on the value of taxanes in metastatic breast cancer, use of taxanes leads to a significant survival benefit as compared to non-taxane

Table 10 – Salvage therapies in patients with tumour progression after pretreatment with anthracyclines and taxanes

n	Phase	Compound/combination	ORR (%)	TTP (Mo)	OS (Mo)	Reference
301 (253†)	III	PLD vs (V or McVb)	ND	5.8 vs 2.1	11 vs 9 (ns)	Keller 2004
Monotherapy						
162	II	Capecitabine	20	3	13	Blum 1999
36	II	Capecitabine	26	4.6	18.1	Lee 2004
31	II	Pemetrexed	26	ND	13	Spielmann 2001
23	II	G	0	2	8	Smorenburg 2001
20	II	Irinotecan	5	1	4	Shigeoka 2001
19	II	Vinorelbine	35	3	ND	Udom 2000
Polychemotherapy						
84	II	FEn	10	2	9	Rivera 2002
60	II	OxF	27	5	12	Zelek 2002
44	II	FEn	16	ND	ND	Skovsgaard 2001
41	II	CF	27	10	13	Kalbakis 2001
33	II	CGF	42	ND	ND	Frasci 2002
29	II	GV	48	ND	ND	Valenza 2000
38	II	CisG	40	6	13.5	Heinemann 2005
39	II	Cis/capecitabine	35.9	5.2	10.9	Donadio 2005
39	II	G/capecitabine	48.7	5	10	Andres 2005

C, cyclophospamide; En, eniluracil; F, 5-fluorouracil; G, gemcitabine; Mc, Mitomycin C; Mo, months; *n*, number of evaluable patients; ND, no data; ORR, overall response rate; OS, overall survival; Ox, oxaliplatin; PLD, pegylated liposomale doxorubicin; TTP, time to progression; V, vinorelbine; Vb, vinblastin; vs, versus; C, cisplatin. † anthracycline- and taxane-pretreated.

therapies.[17] Moreover, no significant difference was found regarding quality of life or therapy-associated cases of death. Final assessment of further endpoints of this meta-analysis is severely hampered by the significant heterogeneity of the underlying studies. Based on an indirect and a direct comparison of docetaxel versus paclitaxel, an increased efficacy of docetaxel is suggested. Yet, due to the different side effect profiles of the two taxanes, adequate indication, timing and dosage (every 3 weeks, weekly) need to be considered for each taxane in the individual patient.

After anthracycline and taxanes failure, response rates of 3rd line therapies with established cytostatics are rather low. Thus, treatment in therapy trials with experimental substances is highly recommended in this indication (AGO ++). Capecitabine (LOE 2b, GR B, AGO ++), PEG-liposomal doxorubicin (LOE 1b, GR B, AGO +), and vinorelbine (LOE 1b, GR B, AGO +) do have a proven efficiency in this therapy setting with response rates between 9 and 20% and median survival times of 9–13 months (Table 10).[18,19]

High-dose chemotherapy beyond established clinical protocols is currently not recommended (LOE 1b, GR B, AGO − −).

2.5. *Therapy with antibodies and small molecules*

Proof of HER2 overexpression is a prerequisite for use of trastuzumab (LOE 1b, GR A, AGO ++). For HER2 status assessment, immunohistochemistry in tumour tissue using a validated detection method and scoring system are recommended as well as fluorescence *in situ* hybridisation (FISH) in case of an immunohistochemical 2+ or unclear result (AGO ++). Detection of HER2 shed antigen in serum does correlate with immunohistochemical or FISH HER2 detection in tumour tissue; however, measurements are not sufficiently validated (AGO +/−). This method as well as others techniques (PCR, Elisa, CISH etc.) should only be used within scientific studies (AGO +/−).

Trastuzumab should be administered as 1st line therapy in combination with docetaxel or paclitaxel or as monotherapy after prior chemotherapy (LOE 1b, GR A, AGO ++).[20–22] Weekly intravenous trastuzumab application of 2 mg/kg body weight with a single loading dose of 4 mg/kg is best established so far (LOE 1b, GR A, AGO ++), but a 3-weekly regimen with 6 (8) mg/kg body weight has demonstrated efficacy, especially in the adjuvant setting (LOE 2b, GR C, AGO +).[23] Trastuzumab therapy should be started as early as possible in metastatic disease (LOE 2b, GR B, AGO ++) and should be continued until progression (LOE 1b, GR A, AGO ++). Effectiveness of a continued therapy after progression on trastuzumab is unknown – thus, this approach should preferentially be taken in a prospective clinical trial (LOE 3b, GR C, AGO +/−).

Additional options for combination of trastuzumab with chemotherapy are combinations with paclitaxel and carboplatin (LOE 1b, GR A, AGO ++),[24] vinorelbine (LOE 2b, GR C, AGO +), and with docetaxel and platinum complexes, epirubicin/cyclophosphamide, PEG-liposomal doxorubicin, capecitabine or gemcitabine (LOE 2b, GR C, AGO +/−). Trastzumab administration together with tamoxifen or an aromatase inhibitor should preferentially be performed in studies (AGO +/−).[25]

The clinically most relevant side effect of trastuzumab is a probably transient myocardial dysfunction resulting in clinical symptoms of congestive heart failure. Confirmed risk factors are simultaneous doxorubicin treatment or patients older than 60 years. Additional risk factors are pretreatment with more than 400 mg/m^2 doxorubicin or an equivalent, previous thoracic wall irradiation, exertional dyspnea, arterial hypertension, coronary heart diseases, and haemodynamically relevant valvular heart disease. The most important contraindication for trastuzumab therapy is a dyspnea at rest since in such cases high-grade respiratory insufficiency was repeatedly observed.[26]

For bevacizumab, an antibody against VEGF, prolongation of progression-free and overall survival was recently demonstrated when used in combination with weekly paclitaxel (versus paclitaxel alone) (LOE 2b, GR B, AGO+/−). These promising results, however, are not completely confirmed by results of a bevacizumab/capecitabine combination in heavily pretreated patients.[27] Other targeted therapies, e. g. against the EGF receptor (e.g. gefitinib, erlotinib, imatinib, celecoxib) have not been successful in breast cancer so far and should therefore only be used within clinical trials (LOE 3–4, GR C, AGO −).

2.6. *Complementary and alternative medicine (CAM)*

The use of CAM shows substantial regional differences. For example, mistletoe preparations do not virtually play any role outside of Europe. Complementary methods are used in addition to conventional medicine, whereas alternative methods are used as sole measures. CAM methods do at least provide a theoretic proof of their assumed efficacy; unproven methods are mostly known very restrictedly or propagated by self-proclaimed 'miracle healers'.[28]

A possible impact of dietary factors on breast cancer risk has been investigated in several studies, whereas such investigations in patients with breast cancer are rare. In many cases, results from the prevention setting are extrapolated to the palliative situation. Since obesity is associated with an increased risk of breast cancer in the postmenopause it should be avoided after diagnosis of breast cancer (LOE 4, GR C, AGO+).[29] There is no evidence for a benefit of dietary measures (low-fat diet, increased consumption of fruit and vegetable or wholegrain) regarding outcome improvement in breast cancer patients (LOE 3a–4, GR B–C, AGO +/−).

Most complementary approaches, in particular administration of certain medications, have insufficient proof of their efficacy. This holds true for orthomolecular substances (selenium, zinc etc.), high-dose vitamins, proteolytic enzymes (papain, trypsin, chymotrypsin), mistletoe therapy, thymus preparations, and splenic peptides as well as oxygen- and ozone therapy (LOE 3b–5, GR C–D, AGO −).[30] With regard to high-dose vitamin preparations, orthomolecular substances, oxygen- and ozone therapy, toxic side effects due to overdosing may occur.[31] Regarding gymnastics and sports, a favourable impact on breast cancer incidence has not been sufficiently substantiated, and their effect after primary disease is also questionable. Since sports are undoubtedly of great value for health in general, they are recommended after the diagnosis of (metastatic) breast cancer (LOE 3a, GR C, AGO +).[32]

2.7. Treatment of specific localisations

2.7.1. Bone metastases

Bone metastases constitute the most frequent metastasis localisations in breast cancer. Since supporting bones are particularly affected, complications occur frequently.[33]

If spinal cord compression with consecutive transverse spinal cord syndrome occurs in spinal metastasis, emergency surgical relief (e.g. laminectomy) should be carried out as quickly as possible (target: < 24 h) followed by postoperative local irradiation (LOE 2b GR C, AGO ++). In case of a longer time interval, the added value of surgery is not clear, and therefore radiation alone should rather be used. The extent of involution of spinal symptoms largely depends on the time interval between onset of symptoms and time of operation/radiotherapy as well as the patient's pre-therapeutic mobility.[34]

Further indications for surgical interventions are spinal column instability or symptomatic metastasis in already irradiated areas (LOE 2b, GR C, AGO ++). Osteosyntheses and/or insertion of polymethylmethacrylate (PMMA, bone cement) are standard procedures for treatment of metastasis-related pathologic fractures (LOE 3b, GR B, AGO ++).[35] Prophylactic surgical fixation of immanent fractures due to bone metastasis may be considered in statically important long tubular bones if such consolidation cannot be achieved by radiotherapy or systemic antitumour and bisphosphonate therapy.

Indications for irradiation of bone metastases are increased fracture risk, functional impairment, bone pain, or neuropathic pain (LOE 1a/b, GR B, AGO ++). Factors to be taken into account before therapy decisions are duration of treatment, estimated life expectancy, necessity for hospitalisation as well as possible side effects and burden for the patient (Table 14). For pain irradiation, single irradiation using 8 Gy (LOE 3b, GR C, AGO ++) or four fractioned irradiations at 4 Gy each (LOE 3b, GR C, AGO+) as well as a radionuclide therapy (e.g. for small foci of disseminated metastases) with ^{153}samarium (sm-EDTMP), ^{89}strontium (sr-chloride), or ^{186}rhenium (re-HEDP) (LOE 2b, GR B, AGO +) may be used.[36]

Bisphosphonates should be administered for treatment of hypercalcaemia, bone pain, and skeletal complications (i.e. pathologic fractures, reduction of irradiation therapies etc.) (LOE 1a–b, GR A, AGO ++). If symptoms occur (acute bone pain, hypocalcaemia), intravenous interval therapy should be started.[37] Bisphosphonates may be administered for prevention and treatment of tumour therapy-induced osteoporosis (LOE 1b, GR B, AGO ++). Due to inconsistent evidence, possible prevention of bone metastases by adjuvant bisphosphonates is not definitively verified (LOE 1b GR B, AGO +); thus participation in ongoing studies is recommended; the same holds true for the metastatic setting (LOE 2b, GR C, AGO +/−). Despite lack of evidence, it is recommended to continue bisphosphonate therapy upon progression of bone metastasis (LOE 5, GR D, AGO ++) (Table 15).[38]

2.7.2. Visceral metastases

Surgical resection should be carried out only in selected cases (solitary metastasis, no other affected organs, long disease-free interval, previous histological confirmation, possibility of R0 – resection) (LOE 3b GR C, AGO +/−). The same holds true for regional chemotherapy or thermoablation of liver metastases (LOE 3b, GR C, AGO +/−).[39,40]

2.7.3. Effusions

Local treatment is indicated if symptoms become clinically relevant. Pleurodesis using talcum assisted by video-assisted thoracoscopy reaches success rates of up to 90%, and thus by far the highest success rates (LOE 2b GR C, AGO ++). Pleurodesis using bleomycin, doxycycline or mitoxantrone are distinctly less effective (LOE 2b–4, GR C–D, AGO +/−).[41]

In case of massive ascites, peritoneal puncture is indispensable and should be carried out for symptom relief (LOE 5, GR D, AGO ++). Application of local cytostatics (LOE 5, GR D, AGO +/−) may be considered in addition to systemic therapy (LOE 3b, GR D, AGO +).[42]

A malignant pericardial effusion should be drained and fenestrated either video-assisted or ultrasonically controlled (LOE 3b, GR B, AGO ++) since this constitutes an emergency situation. Efficacy of intrapericardial installation of mitoxantrone 10 mg is not proven (LOE 5, GR D, AGO +/−).[43]

2.7.4. Bone marrow infiltration

In case of bone marrow carcinosis with possible concomitant pancytopenia, which has a rather unfavourable prognosis, systemic therapy may consist of initially low-dose weekly chemotherapy administration of epirubicin or taxanes (LOE 5 GR D, AGO ++).[44]

2.7.5. Soft tissue metastases

Tumour infiltration into spinal cord, nerve plexus, or soft tissue structures may cause severe localised or radiating pain. This requires multimodal analgesia including surgical interventions and/or radiotherapy, as well as analgesics and oncological systemic therapy. Palliative radiotherapy may be used in the above mentioned situations (LOE 2–3b, GR C, AGO ++) as well as in order to achieve haemostasis in an inoperable exulcerated tumour.

2.7.6. CNS metastases

The incidence of brain metastases in breast cancer is increasing and currently reaches 15–40%. It depends on the extent of the extracerebral tumour; brain metastases as first manifestation of metastasis are observed in about 16% of metastatic breast cancer patients. Improved imaging procedures (MRT, CT) allow diagnosis of occult brain metastases; the improved survival attributable to adjuvant and palliative treatments is also responsible for the fact that nowadays more breast cancer patients experience CNS metastases.[45]

Possible risk factors for the occurrence of CNS metastases are young age at primary diagnosis, receptor-negative tumours, and HER2 overexpression.

The occurrence of CNS metastasis is generally associated with an unfavourable prognosis (LOE 2a). Combined intracerebral and extracerebral metastasis, older age, reduced general condition, short disease-free interval after primary therapy, lack of response to prior therapies, and negative hormone receptor status (LOE 2a) are unfavourable prognostic factors. In case of solitary metastasis, histological verification of diagnosis should be considered in order to exclude other central

nervous diseases. For exclusion of multiple metastases, MRI should be performed.

2.7.7. Solitary brain metastases

These should be treated neurosurgically with subsequent whole-brain radiation (LOE 2a GR B, AGO ++).[46] Stereotactic radiosurgical procedures (e. g. Gamma Knife or Linear Accelerator) can be used for solitary lesions with a diameter below 3 cm (LOE 2a GR B, AGO +); they are, however, to be regarded as being equally effective as neurosurgical treatments (LOE 2a GR B, AGO +). Combination of stereotactic irradiation with whole-brain radiation leads to an improved local control and survival time when compared to whole-brain radiation alone (LOE 1b, GR A, AGO ++).[47] In particular, in cases of perifocal edema, steroids are an integral part of brain metastasis therapy. Administration of phenytoin is not indicated unless metastasis-induced epileptic spasms occur.

2.7.8. Multiple brain metastasees

Standard therapy of multiple brain metastases is percutaneous whole-brain radiation; if perifocal edema is present this therapy is supported by steroid medication in order to control progressing neurological symptoms (LOE 1a GR A, AGO ++). Considerable (temporarily complete) improvements of symptoms are achieved for headache in 50–70%, for pareses in 30–40%, and for cerebral dysfunction in 40–50%. Disseminated metastases do not represent an indication for surgery or chemotherapy alone (LOE 3a, GR D, AGO −). In case of anewed progression, stereotactic irradiation may be indicated in single cases.

Among other solid tumours, leptomeningeosis carcinomatosa occurs most frequently (< 5%) in breast cancer. It spreads across the liquor cerebrospinalis throughout the neuroaxis and can be verified by cerebrospinal puncture (note: 10% false negative rate). In imaging procedures, such as MRI, subarachnoid swellings, diffuse contrast medium meningeal enhancement or hydrocephalus may suggest presence of leptomeningeosis carcinomatosa. If untreated, mean survival is 4–6 weeks as a consequence of progressing neurological dysfunctions. Intrathecal chemotherapy of methotrexate (LOE 2b, GR B, AGO ++), liposomal cytarabin (LOE 3b, GR C, AGO++)[48], or thiotepa (LOE 3b, GR C, AGO +) as well as localised radiotherapy of bulky disease or whole brain radiotherapy (LOE 4, GR D, AGO +) may prolong mean survival to 3–6 months depending on performance status, extent of neurological symptoms, and therapy response of extracranial tumour manifestations to systemic antineoplastic therapy.[49]

3. Future perspectives

Treatment of metastatic breast cancer will rapidly change over the next couple of years. Systemic medical treatment will continue to play the most important role with a considerable number of new targeted therapies emerging in the near future. Treatment algorithms have to be adapted within short intervals especially to include proven predictive biological markers for therapy decision making. The AGO Breast Commission will therefore continue to annually evaluate and update scientific basis and clinical relevance of the various treatment options for patients with metastatic breast cancer.

Conflict of interest statement

None declared.

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