

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Guidelines Breast
Version 2009.1.0

Therapy Side Effects



Therapy Side Effects

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- **Version 2004:**
Jackisch / Göhring / Souchon
- **Version 2005–2008:**
Friedrichs / Lisboa / Stickeler
- **Version 2009:**
Nitz / Costa

Further
Information

References

Toxicity Assessment

Acute Toxicity According to WHO¹ or NCI-CTC²

Grade	Necessary information
0 non	organs involved
1 mild	kind of toxicity
2 moderate	time delay after treatment
3 severe	effect on general health status
4 life threatening	requiring treatment recovery achieved

Long-Term Toxicity No general assessment scale

Further
Information

References

¹ WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)

² National Cancer Institute, NCI, Bethesda, USA, Common Toxicity Criteria, <http://ctep.info.nih.gov>

Chemotherapy – Acute Toxicity I

	Haematol. Toxicity	Nausea/ Vomit.	Alopecia	Mucositis/ Stomatits	Cardiac Toxicity	Renal Toxicity	Hepatic Toxicity
Cyclophosphamide	++	++	+++	+	++ ¹	++ ¹	
Methotrexate	++	+	+	++	+ ²	++ ¹	+
5-Fluorouracil	++	++		++	+ ²		
Carboplatin	++	++	+			++	
Capecitabine	+	+		+			
Gemcitabine	++	+		+			+
Epi-/Doxorubicin	++	++	+++	++	+		
Pegliposomal Doxorubicin	++	++	+	+++			
Liposomal Doxorubicin	++	++	+	++			
Mitoxantrone	++	++	+++	++	+		
Paclitaxel	++	+	+++	+			
Docetaxel	++	+	+++	++			
Etoposid	++	++	++	++			
Vinorelbine	++		(+)	+			

¹ if high dose; ² Angina pectoris (Myocardial infarction is a rare event)

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Chemotherapy – Acute Toxicity II

	Allergic Reaction	Bladder Toxicity	Neuro-pathy	Skin Toxicity	Diarrhea	Hand-Foot-S.	Other
Cyclophosphamide	+	+ ⁴	+ ⁵	+			SIADH
Methotrexate	+		+	++			
5-Fluorouracil				+	++	++ ⁶	
Carboplatin							
Capecitabine					++	++	
Gemcitabine							Flue-like Synd., Oedema
Epi-/Doxorubicin	+						Paravasates
Liposomal Doxo.	+			+			
Pegliposomal Doxo.	+			+++			
Mitoxantrone				++			140 mg/m ²
Paclitaxel	+++ ⁷		++ ⁸				Myalgia
Docetaxel	++		+	++ ⁹			Myalgia, Fluid retention
Etoposid	++				+		
Vinorelbine			++				Thrombophle.

⁴ haemorrhage of the bladder; ⁵ acute encephalitis; ⁶ prolonged infusion; ⁷ anaphylaxis (rare event);

⁸ peripheral polyneuropathy in up to 60–88%; ⁹ depending on total dose administered (> 400mg/m²)

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Long-Term Toxicity Cardiotoxicity I

Oxford / AGO
LoE / GR

- **Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)** 2b B
- **Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity** 1b B
- **Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:** 2b B
 - **Age > 65 yrs**
 - **Obesity (> 27 kg/m²)**
 - **Hypertension**
 - **Hypercholesterolemia**
 - **Pre-existing cardiac diseases (incl. borderline LVEF)**
 - **Diabetes mellitus**
- **Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)** 3b C +

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Feasibility of Treatment Combinations considering Toxicities

Oxford / AGO
 LoE / GR

Regarding Cardiac Toxicity

➤ Trastuzumab simultaneous to radiotherapy	2b	B	+
➤ Trastuzumab simultaneous to epirubicin	2b	B	+/-
➤ Trastuzumab simultaneous to doxorubicin	2b	B	-
➤ Anthracycline simultaneous to radiotherapy	2c	C	-

Regarding Breast fibrosis

➤ Tamoxifen simultaneous to radiotherapy	3	C	+
➤ Chemotherapy simultaneous to radiotherapy	1b	B	-

Side Effects of Trastuzumab

Algorithm in Case of Cardiac Toxicity

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Symptoms	LVEF	Trastuzumab	LVEF Monitoring	Therapy
asymptomatic	Slightly decreased	Continue	Check within 4 weeks	Consider b-blocker
	Decreased below 45%	Reconsider Continue if M1 Stop if M0	Check within 2–4 weeks ➤ Improved: further monitoring ➤ Not improved: stop Trastuzumab	Consult cardiologist
	Decreased below 30%	Interrupt	Check within 2 weeks ➤ Improved to > 45%: cont. Trastuzumab ➤ Not improved: stop Trastuzumab	Consult cardiologist
symptomatic	Slightly decreased	Continue	Check within 4 weeks	Exclude anemia
	Decreased below 45%	Reconsider Continue if M1 Stop if M0	Check within 2–4 weeks ➤ Improved: further monitoring ➤ Not improved: stop Trastuzumab	Consult cardiologist
	Decreased below 30%	Stop		Consult cardiologist

Further Information

References

Secondary Malignancies I

Oxford
LoE

- **With regard to solid tumours, chemotherapy induced secondary malignancies are rare events**
- **Alkylating agents increase the risk of secondary leukaemia dose-dependently to a total of 0,2–0,4 % within 10 to 15 years**
- **Anthracycline-containing regimens increase the risk of MDS and secondary leukaemia to 0,2–1,7 % within 8 to 10 years**
- **Radiotherapy increases the risk of leukaemia by 0,2–0,4% in patients treated with anthracycline-containing chemotherapy**
- **Tamoxifen doubles the risk for developing endometrial cancer**

2a

2a

2

2b

2b

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Secondary Malignancies II (after Radiotherapy)

Oxford
LoE

- **The risk of developing secondary cancers is low if modern radiation techniques are applied and should not avoid the use of radiotherapy when indicated.** **2b**

- **Postmastectomy radiotherapy (PMRT) may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma appearing 5–10 years after treatment** **1a**
 - **Enhanced risk especially among ever smokers** **2b**

- **PMRT may moderately enhance the risk of oesophageal cancer appearing after treatment with probable relationship to smoking, alcohol use and chronic inflammatory disease (not applicable to patients treated with current techniques)** **2b^a**

(Chemotherapy Related) Amenorrhoea

Oxford
LoE

- **CRA may be permanent or temporary**
- **Depends on CTX regimen used**
- **CRA is an (imperfect) surrogate for menopause and fertility**
- **Adjuvant endocrine therapy induces reversible amenorrhoea, but delays conception to less fertile period**
- **Risk of CRA increases with age/treatment duration** **2b**
- **Ovarian reserve of women who remain premenopausal after CTX is reduced** **2b**

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Synonyma: Chemotherapy / Treatment induced Amenorrhoea (TIA, CIA)

(Chemotherapy Related) Fatigue

Oxford
LoE

- **Wide variation in the measures of fatigue and the duration of follow-up**
- **No data beyond year 10**
- **Fatigue and/or differences of fatigue levels remain an relevant clinical issue at year 5**

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Side-effects and Toxicity of Endocrine Agents I

	Visual Disturbances	Osteoporosis	Cerebro-Vascular Events *	Fracture	Cardiac risk	Cognitive functions
SERMs	(+)		+			
AI 3rd Gen*		+		+	+	(+)
SERD		+		+		
GnRHa		+		+		

	Arthralgia Myalgia	Flush	Dysfunctional Bleeding*	Endometrial Changes	Deep Venous Thrombosis	Lipid Profile Impaired
SERMs	(+)	+	+	+	(+)	
	(+)	+	+	+		
Als	+	(+)				(+) Letrozole Anastrozole
SERD						
Goserelin	(+)	+				

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Side-Effects and Toxicity – Bisphosphonates

Oxford
LoE

- **Renal function deterioration due to i.v. bisphosphonates mostly mild and reversible** **2b**
- **Osteonecrosis of the jaw (ONJ) in up to 2,5% during long-term i.v.-bisphosphonate therapy (caution: length of exposure)** **3b**
- **Acute phase reaction** **3b**
- **Gastrointestinal side effects** **3b**

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Recommendations for Precautions to Prevent ONJ

Oxford LoE: 4

GR: C

AGO: +

- **During bisphosphonate treatment, avoid any elective dental procedures, which involve jaw bone manipulations**
- **Optimize dental status before start of bisphosphonate treatment, if feasible**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**

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Frequent Side Effects of Bisphosphonate Treatment

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Drug	Acute Phase	Renal Tox.	Upper GI-SE	Diar-rhea	ONJ	
Clodronate 1500 i.v.	0	+	0	0	0	
Clodronate 1600 p.o.	0	0	+	+	0	Non-A
Ibandronate 50mg p.o.	0	0	+	0	0	Amino
Ibandronate 6mg i.v.	+	0	0	0	+	
Zoledronate 4mg i.v.	+	+	0	0	+	
Pamidronate 90mg i.v.	+	+	0	0	+	
Zoledronate 4mg i.v. q6m		0	0	0	0	0

Further Information

References

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Side-Effects and Toxicity – Small Molecules / Antibodies

Oxford

LoE

- **Trastuzumab: flue like syndrom at first appliction
Cardiotoxicity (°3/4 ca. 4 %) , CHF**
- **Lapatinib: diarrhea, rash, fatigue**
- **Bevacizumab: hypertension , fatigue, bleeding (<2 %)**

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References