Therapy Side Effects
Therapy Side Effects

- **Versions 2004–2015:**
  Albert / Bischoff / Brunnert / Costa / Dall / Friedrich / Friedrichs / Gerber / Göhring / Huober / Jackisch / Lisboa / Lück / Müller / Nitz / Schmidt / Souchon / Stickeler / Untch

- **Version 2016:**
  Lück / Bischoff
# Toxicity Assessment

## Acute Toxicity
According to WHO\(^1\) or NCI-CTC\(^2\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Information required</th>
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<tbody>
<tr>
<td>0 none</td>
<td>organs involved</td>
</tr>
<tr>
<td>1 mild</td>
<td>type of toxicity</td>
</tr>
<tr>
<td>2 moderate</td>
<td>time interval after treatment</td>
</tr>
<tr>
<td>3 severe</td>
<td>effect on general health status</td>
</tr>
<tr>
<td>4 life threatening</td>
<td>treatment required</td>
</tr>
<tr>
<td></td>
<td>recovery achieved</td>
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</table>

## Long-Term Toxicity
No general assessment scale

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\(^1\) WHO Handbook for reporting results of cancer treatment, No 48 (1979) (WHO offset Publications, Geneva)

## Cytotoxic Anti-Cancer Drugs
### Acute Toxicity I

<table>
<thead>
<tr>
<th>Drug</th>
<th>Haematol. Toxicity</th>
<th>Nausea/Vomit</th>
<th>Alopecia</th>
<th>Mucositis/Stomatitis</th>
<th>Cardiac Toxicity</th>
<th>Renal Toxicity</th>
<th>Hepatic Toxicity</th>
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<td>Neurotoxicity</td>
<td>Cutane Tox</td>
<td>Diarrhea</td>
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<tr>
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<td>++</td>
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<td>Myalgia</td>
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</tr>
</tbody>
</table>

Flue-like Synd., Edema: Paravasate, Dexrazoxane

Myalgia, Fluid retention, nails!

Thrombophlebitis, Obstipation
Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Dawn L. Hershman, Christina Lacchetti, Robert H. Dworkin, Ellen M. Lavoie Smith, Jonathan Bleeker, Guido Cavaletti, Cynthia Chauhan, Patrick Gavin, Antoinette Lavino, Maryam B. Lustberg, Judith Paice, Bryan Schneider, Mary Lou Smith, Tom Smith, Shelby Terstrapel, Nina Wagner-Johnston, Kate Bak, and Charles L. Loprinzi

Recommendations:
On the basis of the paucity of high-quality, consistent evidence, there are no agents recommended for the prevention of CIPN. With regard to the treatment of existing CIPN, the best available data support a moderate recommendation for treatment with duloxetine. Although the CIPN trials are inconclusive regarding tricyclic antidepressants (such as nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine, these agents may be offered on the basis of data supporting their utility in other neuropathic pain conditions given the limited other CIPN treatment options. Further research on these agents is warranted.

Long-Term Toxicity
Cardiotoxicity

- Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)
  
- Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity

- Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:
  - Elderly patients
  - Obesity
  - Hypertension
  - Hypercholesterolemia
  - Pre-existing cardiac diseases (incl. borderline LVEF)
  - Diabetes mellitus

- Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)

Oxford / AGO LoE / GR

2b B

1b B

2b B

3b C +
Feasibility of Treatment Combinations Considering Toxicities

Regarding cardiac toxicity
- Trastuzumab simultaneous to radiotherapy  
- Trastuzumab simultaneous to epirubicin  
- Trastuzumab simultaneous to doxorubicin  
- Anthracycline simultaneous to radiotherapy

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b B +</td>
</tr>
<tr>
<td>2b B +/-</td>
</tr>
<tr>
<td>2b B -</td>
</tr>
<tr>
<td>2c C -</td>
</tr>
</tbody>
</table>

Regarding lung and breast fibrosis
- Tamoxifen simultaneous to radiotherapy  
- Chemotherapy simultaneous to radiotherapy

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 C +/-</td>
</tr>
<tr>
<td>1b B -</td>
</tr>
</tbody>
</table>
Side Effects of Trastuzumab/Pertuzumab Algorithm in Case of Cardiac Toxicity

1. LVEF drop from baseline
   - LVEF ≥50%
     - LVEF drop ≤20% points
       - CONTINUE treatment
     - LVEF drop >20% points
       - CONTINUE treatment and repeat LVEF in 3 weeks
   - LVEF <50%
     - LVEF drop <10% points
       - CONTINUE treatment and repeat LVEF in 3 weeks
     - LVEF drop ≥10% points
       - HOLD treatment and repeat LVEF in 3 weeks

   - Not confirmed (LVEF drop ≤20% points or LVEF ≥50%)
     - CONTINUE treatment
   - LVEF drop CONFIRMED (LVEF drop >20% points and LVEF ≥50%)
     - CONTINUE treatment and repeat LVEF in 3 weeks
   - LVEF drop CONFIRMED (LVEF drop <10% points and LVEF <50%)
     - STOP treatment

   - Not confirmed (LVEF drop <10% points or LVEF ≥50%)
     - RESUME treatment
Secondary Malignancies I

- With regard to solid tumors, chemotherapy induced secondary malignancies are rare events 2a
- Alkylating agents increase the risk of leukaemia dose-dependently to a total of 0.2–0.4% within 10 - 15 years 2a
- Anthracycline-containing regimens increase the risk of MDS and leukaemia to 0.2–1.7% within 8 to 10 years 2a
- PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5-1% 2b
- Radiotherapy increases the risk of leukaemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy 2b
- Tamoxifen approximately doubles the risk for developing endometrial cancer 2b

Oxford / LoE
Secondary Malignancies II
(after Radiotherapy)

- The risk of developing secondary cancers is low if modern radiation techniques are applied and should not deter the use of radiotherapy when indicated 2b
- Radiotherapy 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
Chemotherapy Related Amenorrhea (CRA)

- 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 amenorrhea, but delays conception to a less fertile period
- Risk of CRA increases with age / treatment duration
  
  2b

- Ovarian reserve of women who remain premenopausal after CTX is reduced
  
  2b

- CRA is associated with improved outcome (DFS/OS)
  
  1b

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)
(Therapy Related)

Fatigue

- Fatigue frequently present in breast cancer patients (30–60%)  
  2a B

- Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue  
  1a A ++

- Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue  
  1a A ++

- Physical exercise with ambiguous effects regarding fatigue  
  1b D +

- Methylphenidate might improve fatigue  
  1a D +
Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%).

Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life.
Depression is an often reported adverse event in breast cancer patients (20–30%) 2a B

Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients 1b A

Antidepressents have shown to improve depression in breast cancer patients 1b A

Regular exercise participation can prevent depression among breast cancer survivors 2b B +
(Therapy Associated) Cognitive Impairment

- Therapy-related cognitive deficits (chemobrain frequently described (16–75%))  
  2a  B

- Cognitive-behavioral therapy is beneficial for cognitive function  
  2b  B

- Methylphenidate might improve cognitive function in patients with cancer  
  3a  C
## Side-effects and Toxicity of Endocrine Agents

### Visual Disturbances

<table>
<thead>
<tr>
<th></th>
<th>Visual Disturbances</th>
<th>Osteoporosis</th>
<th>Cerebro-Vascular Events *</th>
<th>Fracture</th>
<th>Cardiac risk</th>
<th>Cognitive functions</th>
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<tr>
<td>AI 3rd Gen*</td>
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### Arthralgia, Myalgia, Flush, Dysfunctional Bleeding*, Endometrial Changes, Deep Venous Thrombosis, Lipid Profile Impaired

<table>
<thead>
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<th>Arthralgia, Myalgia</th>
<th>Flush</th>
<th>Dysfunctional Bleeding*</th>
<th>Endometrial Changes</th>
<th>Deep Venous Thrombosis</th>
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Side-Effects and Toxicity of Bone Modifying Agents (BMA) Bisphosphonates (BP) and Denosumab (DB)

- Renal function deterioration due to IV-amino-BP 1b
- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and DB therapy (appr. 2%) 1b
- Acute phase reaction (IV Amino-BPs, DB) 10–30% 1b
- Gastrointestinal side effects (oral BPs) 2–10% 2b
Recommendations for Precautions to Prevent Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 4        GR: C        AGO: +

- During bisphosphonate treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)

- Optimize dental status before start of bisphosphonate treatment, if feasible (LoE 2b)

- Inform patients about ONJ risk and educate about early symptom reporting

- In case of high risk for ONJ, use oral bisphosphonate

In adjuvant bisphosphonate therapy, ONJ was rare
# Frequent Side Effects of Bone Modifying Agents (BMA)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Phase React.</th>
<th>Renal Tox.</th>
<th>Upper GI-SE</th>
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<th>ONJ</th>
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# Key-Toxicities – Antibodies/Antibody-drug-conjugates

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<th>LoE</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Trastuzumab</td>
<td>Cardiotoxicity in the adjuvant setting (0.8–4.0%)</td>
<td>1b</td>
<td>A</td>
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<tr>
<td></td>
<td>Troponin I might identify patients who are at risk for cardiotoxicity</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Hypertonus, proteinuria, bleeding, left ventricular dysfunction,</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Skin rash, diarrhea, mucositis</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>T-DM1</td>
<td>Thrombocytopenia, hepatotoxicity, pyrexia, headache, pneumonitis</td>
<td>2b</td>
<td>B</td>
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</table>
## Small Molecules

### Lapatinib
- Diarrhea, skin rash, fatigue

### Everolimus
- Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, thrombocytopenia

### PARP-inhibitors (olaparib)
- Fatigue, myelosuppression

### CDK4/6 inhibitors (palbociclib, LEE011)
- Myelosuppression, neutropenia

<table>
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<th>Small Molecules</th>
<th>Oxford / AGO LoE / GR</th>
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<td>Lapatinib</td>
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<tr>
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<td>2b B</td>
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<tr>
<td>PARP-inhibitors</td>
<td>3 C</td>
</tr>
<tr>
<td>CDK4/6 inhibitors</td>
<td>3 C</td>
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</table>
Immun-Checkpoint Inhibitors

- **Therapeutic options (Antibodies)**
  - **PD1 /PD-L1**
    - Nivolumab
    - Pembrolizumab
    - Atezolizumab
  - **CTLA-4**
    - Ipilimumab
Immun-Checkpoint Inhibitoren

- Side effects ≥ Grad 3
  - Diarrhoe
  - Fatigue
  - Colitis
  - Hypophysitis
  - Hepatitis
  - Skin changes
  - Thyreoiditis
Therapy Side Effects (2/24)

Further information:


Screened guidelines:

No references
Toxicity Assessment (3/24)

Further information:

Acute toxicity and in most cases 100 day mortality rates are well documented in the majority of phase III trials. Toxicities are graded according to WHO or NCI standards. This implies that toxicities concerning liver, kidney heart or skin are well documented and graded. Other toxicities like fatigue, depression, menopausal symptoms or impairment of cognitive function are systematically underreported by these tools. Most trials end five or ten years after the last patient in, such that late and very late effects are rarely documented.

Acute Toxicity according to WHO1 or NCI-CTC2:

References:

2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v4.0 (CTCAE; published 2010); http://evs.nci.nih.gov/ftp1/CTCAE/About.html
Cytotoxic Anti-Cancer Drugs – Acute Toxicity I (4/24)

No further information

References:

No further information

References:
see slide 4
No further information

No references
**Long-Term Toxicity Cardiotoxicity I (7/24)**

*Further information:*

Anthracycline (A) based standard chemotherapy regimens as used in the adjuvant therapy of breast cancer are associated with a relatively low acute toxicity and treatment related mortality rates < 1 %. In terms of long-term toxicity cardiotoxicity and secondary acute leukemia/MDS are clinically relevant.

**Cardiotoxicity:**

Early cardiotoxicity of anthracyclines has been well established in clinical trials. Limited data are available on long-term cardiac safety of A based regimens. As patients with breast cancer are getting older and as survival rates improve long term cardiotoxicity is of growing interest.

**AC:** Among patients treated with four cycles of AC on NSABP B31 17 % of patients developed asymptomatic cardiac disease defined as the decline in left ventricular ejection fraction of more than 10 % to an ejection fraction of less than 55 %. Similar data were presented recently by Perez et al. in N9831 trial. In 2992 patients completed AC 5% had LVEF decrease disallowing trastuzumab (decrease below normal: 2.4%, decrease > 15%: 2.6%).

**FAC:** The Southwest Oncology Group evaluated long term cardiotoxicity from patients randomized to protocol S8897. In this trial patients were randomized to CAF or to CMF. A was given on day 1 and 8. 180 patients from an potential sample of 1176 patients entered. There was no significant difference in the proportion of women with an LVEF less than 50 % at 5 to 8 years (CAF vs. CMF: 8% vs. 5%, p=0.68) or at 10 to 13 years (CAF vs. CMF: 3% vs. 0%, p=0.16). However in an exploratory analysis the mean LVEF in the doxorubicin group was statistically significantly lower in the 5 to 8 year sample (p=0.01), but not in the 10 to 13 year sample.

**French FEC:** The FASG reports ten year follow-up data in patients receiving either FE50C or FE100C from FASG 05. Delayed (> 1 month after the end of chemotherapy) symptomatic cardiotoxicity was reported in 1.5 % of patients from the FE50C arm and in 1.1 % of patients from the FE100C arm. In summary early and delayed cardiotoxicity was reported in 4.3 % and in 4.8 % of patients.
The second analysis from the FASG trials compared E+ and E- (antihormontherapy or nil) regimens in 3577 breast cancer patients. E+ therapy was associated with 1.36% decrease in LVEf after 7 years vs. only 0.21% in controls (p=0.004). In these analysis age > 65 years old and body mass index > 27 were significant predictors of cardiac toxicity.

A containing regimens outside clinical trials in the elderly

There are 2 important studies from the SEER database in older women. The first one by Doyler et al. analyzed data from 31478 patients, 5575 of them received A-based chemotherapy (18%). This study highlights bias of all studies, investigating cardiac affects of A-chemotherapy, because these patients are per se younger, with less comorbidities and a higher risk of recurrence. The hazard ratios for cardiomyopathy, cardiac failure, and heart disease for patients > 65 years treated with doxorubicin compared with patients who received no chemotherapy were 2.48 (95% CI, 2.10 to 2.93), 1.38 (95% CI, 1.25 to 1.52), and 1.35 (95% CI, 1.26 to 1.44), respectively. The relative risk remained elevated 5 years after diagnosis. Preexisting heart disease was beside of afro-american race the most important risk factor for cardiac failure after A-exposure.

Pinder et al reported data from a total of 43,338 women from the SEER’S database. Similarly as in the previous study anthracycline–treated women were younger, with less comorbidity and had more advanced diseases than women who received non anthracycline based regimens. The adjusted hazard ratio was 1.26 for women aged 66 to 70 treated with a compared other chemotherapy. In this age group at five years of follow-up the observed absolute differences were of 1% and 4.6% respectively in rates of chronic heart failure between anthracycline based chemotherapy and other adjuvant chemotherapy or no chemotherapy. After ten years the increased risk of chronic heart failure was amplified rather than attenuated, with absolute differences of 5.9% and 9.7% when comparing anthracycline treated patients to the other or no adjuvant chemotherapy groups. For women aged 71 to 80 adjuvant chemotherapy was not associated with chronic heart failure.

Taxanes and cardiac safety

Data on cardiac safety in anthracycline-taxane sequential trials are in favour of taxane-based combinations, in which lower doses af anthracyclines are used. E.g. the PACS 01 trial reported significantly lower incidence of cardiac toxicity in the 3xFEC-3xDoc arm than in the 6xFEC arm (0.4% vs. 1.3%, p=0.027). These data have been confirmed in the Cochrane analysis, where trials in which total doses of anthracycline was reduced by substitution of taxane, had subsequently less
cardiac events, than standard A-based regimens (OR=0.37 (95%CI: 0.14-0.95)). There are only limited data on cardiac safety of A-free regimens in adjuvant setting in breast cancer. Jones et al. reported 5 cardiac events in 510 patients treated by 4 cycles of AC and only 1 in 506 patients in the 4xTC arm in the US Oncology study. In the BCIRG 006 study there were also significantly less patients with >10% decrease of LVEF value in the Taxotere/Carboplatin/Herceptin (TCH) arm than in AC-TH arm (8% vs. 17.3%), although the negative synergistic cardiac effect of Herceptin should be considered separately of anthracycline cardiac side effects.

Trastuzumab and cardiac safety

Most studies have excluded elderly patients (> 60 or 65 years) or patients with other risk factors (cardiovascular diseases, obesity, hypertension) from studies including trastuzumab. In clinical practice, 32% of HER2+ EBC patients treated with trastuzumab are 'over-60'. These patients have an increased cardiovascular risk profile and develop trastuzumab related cardiotoxicity commonly. Also with regard to other risk factors there is an increased risk of trastuzumab related cardiotoxicity during treatment, which is reversible after cessation of trastuzumab.

References:

Statements

“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)”

“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”


“Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently…”


“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”


“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”


**Further references:**


Feasibility of Treatment Combinations Considering Toxicities (8/24)

Further information:

The frequency of adverse events for patients with HER-2 positive early breast cancer was examined in a randomized study with a median follow-up time of 3.7 years. 1503 patients were irradiated. Radiotherapy (RT) was administered either without or with concurrent trastuzumab (H). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with H did not increase relative frequency of cardiac events (CEs) regardless of treatment site. The cumulative incidence of CEs with AC-T-H was 2.7% with or without RT. With AC-TH-H, the cumulative incidence was 1.7% v 5.9% with or without RT, respectively. Thus, concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs (Halyard al, 2009). Reported data regarding the influence of tamoxifen given simultaneously to radiotherapy are diverging. Simultaneously given tamoxifen to radiotherapy might increase the risk of Grade 1 lung fibrosis (p = 0.01) and might increase the risk of late lung sequelae (OR = 2.442, 95% CI 1.120-5.326, p = 0.025). However other reports did not confirm such an connection. Therefore the results of the ongoing CONSeT-trials has to be awaited.

References:

Statements
“Trastuzumab simultaneous to radiotherapy”

“Trastuzumab simultaneous to epirubicin”


“Trastuzumab simultaneous to doxorubicin”


“Anthracycline simultaneous to radiotherapy”

“Tamoxifen simultaneous to radiotherapy”


Further references:


Side Effects of Trastuzumab and Pertuzumab: Algorithm in Case of Cardiac Toxicity (9/24)

Further information:

Cardiotoxicity has been reported to occur with trastuzumab when administered alone and in combination with antineoplastic agents, particularly anthracyclines. The risk of cardiotoxicity with trastuzumab has been reported to be 4% with monotherapy and 27% when administered in combination with an anthracycline and cyclophosphamide. However, severe and life-threatening damages are rare and the majority of reported cardiac effects are mild to moderate, nonspecific, and medically manageable. Signs and symptoms are similar to those observed in patients who develop anthracycline-induced cardiomyopathy and include tachycardia, palpitations, and exertional dyspnea, which may ultimately progress to congestive heart failure (Keefe, 2002). Trastuzumab-associated toxicity usually responds to standard treatment or the discontinuation of trastuzumab, and there is no evidence that the toxicity is dose related. Left ventricular ejection fraction (LVEF) should be measured at baseline and at regular intervals. An algorithm based on LVEF changes is presented to aid in the question whether continuation of trastuzumab is safe and feasible or whether discontinuation is warranted.

There are also data for trastuzumab and pertuzumab from phase 2 trials and randomized phase 3 trials, in neither trial cardiotoxicity was increased through the addition of pertuzumab to trastuzumab both in the absence or presence of taxane containing chemotherapy. In the Cleopatra trial 808 pts with metastatic breast cancer were randomized to docetaxel and trastuzumab and placebo or to docetaxel and trastuzumab and pertuzumab. LVEF dysfunction (any grade) was more frequently seen in the placebo group than in the pertuzumab group (8,3% vs 4,4%). LVEF dysfunction of grade 3 or higher was reported in 2,8% and 1,2% of the patients in the placebo and pertuzumab arms respectively.

References:


Secondary Malignancies I (10/24)

Further information:

Approximately one in every 20 breast cancer patients developed a second non-breast primary tumour within 10 years following a breast cancer diagnosis (10 years cumulative incidence rate 5.4%; 95%CI 5.1 to 5.7). Compared with the general female Dutch population, these breast cancer patients had a 22% increased relative risk in second non-breast primary cancers and an absolute excess risk of 13 cases per 10,000 women-years (13.6 (95%CI 9.7 to 17.6). The occurrence of a second non-breast cancer was associated with a decrease in overall survival (HR 3.98, 95%CI 3.77 to 4.20). Standard incidence ratios were elevated for cancers of esophagus, stomach, colon, rectum, lung, uterus, ovary, kidney, bladder, soft tissue sarcomas, melanoma, non Hodgkin’s lymphoma, acute myeloid leukemia.

Patients younger than 50 years, radiotherapy was associated with increased lung cancer risk (HR 2.31; 95%CI 1.15 to 4.60) and chemotherapy with decreased risk for all secondary non-breast cancers. Patients 50 years and older, radiotherapy was associated with increased risk of soft tissue sarcoma (HR 3.43, 95%CI 1.46 to 8.04), chemotherapy with increased risk of melanoma, uterine cancer, acute myeloid leukemia and homonal therapy with uterine cancer (HR 1.78, 95%CI 1.40 to 2.27).

Risk of secondary acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)

Women with a prior breast cancer were ~2.6 times more likely to develop AML than the total female Australian population, with highest age-specific relative risk for AML in the 30- to 49-age group. Mitoxaontrone-based chemotherapy was associated with a higher leukemic risk than with anthracyclines (RR 16.8, 95%CI 7.1 to 34.2 than RR 2.7, 95%CI 1.7 to 4.5). Epirubicin and doxorubicin had a similar risk. For women > 65 years receiving polychemotherapy (CAF, ACP) the risk to develop grade 4 hematologic toxicity, to have discontinued treatment for toxicity or to die of acute myeloid leukemia/MDS was significantly elevated. Granulocyte colony-stimulating factor (G-CSF) increased the risk of developing AML/MDS.
Details to chemotherapy regimes:

French FEC
The French Adjuvant Study Group reviewed their 16-year experience with their FEC regimen of 5-Fluorouracil, epirubicin (50, 75, 100 mg/m2) and cyclophosphamide i.v. q3w. Cumulative epirubicin doses mostly were below 600 mg/m2. As for leukemia, data of 3653 women are available, which were followed for a median of 104 months. About two-third of the patient population received epirubicin-based adjuvant chemotherapy while slightly lower than one-third received CMF-like regimens. The incidence of secondary leukemia was very low: 0.3% for those patients treated with adjuvant epirubicin and <0.1% for those treated with other adjuvant therapies (CMF-like, antihormonal therapy).

Canadian FEC
The National Cancer Institute of Canada Clinical Trials Group analysed the risk of secondary acute leukemia (sAL) following adjuvant therapy with regimens containing epirubicin. The analysis were performed to assess the conditional probability of sAL in 1545 women having received adjuvant (n = 1477) or neoadjuvant (n = 68) chemotherapy in four National Cancer Institute of Canada Clinical Trials Group trials from 1990 to 1999. The leukemia risks associated with epirubicin-containing regimens (CEF or EC) and other regimens as doxorubicin and cyclophosphamide (AC or CMF) were registered. A total of 10 cases of sAL were observed (eight acute myelogeneous leukemia, two acute lymphoblastic leukemia): Seven among women treated with CEF, two who had received AC, and one following CMF. Using competing risk statistics, the conditional probability of sAL was 1.7% (95% confidence interval [CI], 0.5 to 3.6) among 539 women treated with CEF chemotherapy at a follow-up of 8 years, 0.4% (95% CI, 0% to 1.3%) among the 678 who received CMF, and 1.3% (95% CI, 0% to 4.7%) among the 231 treated with AC. Of note, Canadian CEF comprises epirubicin doses of 120 mg/m2. The conditional probability for breast cancer death at 8 years for the whole group treated with epirubicin-containing regimens in all four trials was approximately 34.9%. The group concluded that CEF chemotherapy for breast cancer carries a small increased risk of sAL compared with CMF which has to be taken into account when discussing treatment options with patients who are at a lower risk of breast cancer death, e.g. node negative patients. The rates of acute leukemia had not changed since the original report when updated 10-years results have been reported in 2005.
Purpose: We reviewed data from all adjuvant NSABP breast cancer trials that tested regimens containing both doxorubicin (A) and cyclophosphamide (C) to characterize the incidence of subsequent acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Materials and Methods: Six complete NSABP trials have investigated AC regimens (B-15, B-16, B-18, B-22, B-23, and B-25). Six distinct AC regimens have been tested and are distinguished by differences in cyclophosphamide intensity, cumulative dose and by the presence or absence of mandated prophylactic support with growth factor and ciprofloxacin. In all regimens, A was given at 60 mg/m² q 21 days x 4. C was given as follows: 600 mg/m² q 21 days x 4 ("standard AC"); 1200 mg² q 21 days x 2; 1200 mg/m² q 21 days x 4; 2400 mg/m² q 21 days x 2; and 2400 mg/m² q 21 days x 4.

Occurrence of AML/MDS was summarized by incidence per 1,000 patient-years at risk and by cumulative incidence. Rates were compared across regimens, by age, and by treatment with or without breast radiotherapy.

Results: The incidence of AML/MDS was sharply elevated in the more intense regimens. In patients receiving two or four cycles of C at 2400 mg/m² with granulocyte colony-stimulating factor (G-CSF) support, cumulative incidence of AML/MDS at 5 years was 1.01% (95% confidence interval [CI], 0.63% to 1.62%), compared with 0.21% (95% CI, 0.11% to 0.41%) for patients treated with standard AC. Patients who received breast radiotherapy experienced more secondary AML/MDS than those who did not (RR = 2.38, \( P = .006 \)), and the data indicated that G-CSF may also be independently correlated with increased risk.

AML/MDS in older patients

In summary Conclusion for FEC and AC secondary AML/MDS rates correlate with regimens employing intensified doses of cyclophosphamide requiring, G-CSF support and to a smaller extent which were characterized by increased rates of subsequent AML/MDS, although the incidence of AML/MDS was small relative to that of breast cancer relapse. Breast radiotherapy appeared to be associated with an increased risk of AML/MDS, but data are inconsistent (see slide 10/20).

References for statements 1-4:


Reference for Statement Tamoxifen and endometrial cancer

Further information:

Radiotherapy increased the risk of sarcoma and lung cancer. Results of a Dutch population-based study, patients younger than 50 years, radiotherapy was associated with an increased lung cancer risk (HR 2.31, 95%CI 1.15 to 4.60) and patients older than 50 years were more likely to develop soft tissue sarcoma (HR 3.43, 95%CI 1.46 to 8.04).\(^1\)

According to the cohort data of the SEER registries 1973 to 2000 risk for second cancers was dose dependend. Radiotherapy treatment assuming standard protocol with 50Gy tumour dose and beam energy 6 MV photons. The RR were 1.45 (95%CI 1.33 to 1.58) for high dose second cancer sites (1 +Gy, lung, oesophagus, pleuro, bone and soft tissue sarcoma) with no evidence of elevated risk for sites receiving medium (0.5-0.9 Gy) or low doses (< 0.5 Gy). Overall risks were generally lower for patients treated in recent years (1993 +). But the pattern of risks observed were consistent with the general literature on radiation carcinogenesis, risks were higher for sites that should have received higher doses and also higher for young age at exposure.\(^6-8\)

The risk of lung cancer was elevated for ever-smokers who receive PMRT (HR18.9, 95%CI 7.9-45.4) according the results of the nested breast cancer cohort study population of the Connecticut Tumor Registry.\(^5\)

Data are inconsistent for an elevated risk of AML/MDS after radiation exposure.\(^6-8\)

References:


Chemotherapy Related Amenorrhea (CRA) (12/24)

Further information:

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

Preservation of ovarian function is an important issue in the population of breast cancer patients especially in the patient younger than 40. Up to now neither data for ovarian protection with e.g. GnRH analogues nor cryopreservation of ovarian tissue are convincing. The treatment compromising most oftenly fertility is chemotherapy. After modern taxan-anthracyclin containing chemotherapy the risk of CRA is markedly lower compared to older chemotherapy regimens. Especially in younger patients the restitution of menses after 2 years is greater than 90 %. However one third of the patients probably will be infertile after chemotherapy. The effects are more pronounced the older the patient and the longer the chemotherapy.

Data from the NSABBP B-30 trial (sequential versus concurrent ACT, doxorubicin-docetaxel in women with operable, node-positive, early stage breast cancer) amenorrhoe in premenopausal women was associated with improved disesease-free and overall survival regardless of treatment, in particular when the tumor was ER-positive. The dose of drug delivered was not a key factor explaining the differences.

References:

(Therapy Related) Fatigue (13/24)

Further information:

Fatigue is a common side effect during and after antineoplastic therapy. Especially in breast cancer incidence of moderate to severe fatigue ranges between 30 and as high as 60% (Lawrence 2004, Blaney 2012). This symptom is typically under-reported and under-treated and might adversely affect quality of life (Bower, 2008). Studies of long-term breast cancer survivors suggest that approximately one quarter to one third experience persistent fatigue for up to 10 years after cancer diagnosis (Bower et al, 2006).

Several factors are thought to contribute to cancer-related fatigue, including direct effects of cancer, adverse effects of cancer treatment, psychosocial factors, comorbid physical symptoms, and comorbid medical conditions. Anemia might contribute to a subset of cancer patients presenting with fatigue (Cella et al, 2004). Recent studies suggest an inflammatory basis for persistent fatigue in breast cancer survivors like increased NF-κB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue (Bower et al, 2010).

Behavioral and psychological interventions (Stanton et al, 2005) as well as physical exercise (McNeely et al, 2006, Bower et al, 2011) have demonstrated efficacy in reducing fatigue among breast cancer patients and survivors. It was shown in a meta-analysis by the Cochrane Collaboration that psychosocial interventions specifically addressing fatigue proved efficient (Goedendorp et al, 2009) and the same authors reported a randomized controlled trial showing that cognitive behavioural therapy was effective in reducing cancer-related fatigue. Contrary to what was expected, physical activity did not mediate the effect of cognitive behavioural therapy on fatigue in this study (Goedendorp et al, 2010). Another Cochrane Collaboration meta-analysis for physical exercise and fatigue only found statistically non-significant improvements for participants in the exercise intervention groups compared to control (non-exercising) groups. These authors concluded that improvements in fatigue were ambiguous and that strategies for behaviour change should underpin these interventions (Markes et al, 2006). In terms of pharmacological treatments for fatigue in a palliative setting, a study using methylphenidate (Ritalin™) in 112 cancer patients showed that this medication was not significantly superior to placebo after 1 week of treatment (Bruerat al, 2006). However, a significant effect of methylphenidate against cancer-related fatigue was confirmed in a meta-analysis performed by the Cochrane Collaboration (Peuckmann-Post et al, 2010). However the effectiveness of glucocorticoids, which are used broadly in daily praxis, has not yet been evaluated.
References:

Fatigue is frequently present...


Psycho-social interventions...


Physical exercise.....


Methylphenidate...


Further information:

Sleep disturbances are a common problem of breast cancer patients during and after therapy (20-70%) leading to disruption in women's quality of life and general ability to function (Bower, 2008; Savard et al, 2001; Ancoli-Israel et al, 2006). In a recently published study examining 823 cancer patients treated with chemotherapy, it was shown that 43% of the patients met the criteria for insomnia syndrome. Insomnia was approximately three times higher than the proportions reported in the general population. 60% of the patient sample reported that their insomnia symptoms remained unchanged from cycle 1 to cycle 2. Those with insomnia complaints had significantly more depression and fatigue than good sleepers (Palesh et al, 2010). Comorbidity, evening fatigue, and depressive symptoms predicted baseline levels of subjective sleep disturbance, and depressive symptoms predicted the trajectory of subjective sleep disturbance (Dhruva et al 2012).

Empirical studies of benzodiazepines and benzodiazepine receptor antagonists indicate that they are effective in improving various aspects of sleep, although no trials have evaluated the efficacy of these medications in cancer populations. Behavioral therapies have demonstrated efficacy in the treatment of insomnia, including insomnia secondary to medical conditions, supporting their use among breast cancer patients (Berger et al, 2009). Comparative studies have shown that behavioral therapies are at least as effective and longer lasting than pharmacotherapy in treating insomnia (McChargue DE et al 2012; Berger et al. 2009). Indeed, a randomized controlled trial of behavioural therapy for women with insomnia caused or exacerbated by breast cancer found significant improvement in subjective sleep complaints, as well as improvements in mood and quality of life (Savard et al, 2005).

References:

Sleep disturbances are a common problem....


Behavioral therapies have demonstrated efficacy.....


Further information:

Depression is an often reported adverse event in breast cancer patients. The majority of studies find that 20-30% of breast cancer patients experience elevated depressive episodes (Bower, 2008), even though the occurrence of a major depressive disorder might be lower. Psychological distress and depressive symptoms are typically highest in the first 6 months after cancer diagnosis and then decline over time. Depression negatively affects quality of life and there is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients (Gallo et al, 2007). The occurrence of depression in breast cancer patients is more strongly influenced by psychosocial and physical factors, rather than severity of the disease or treatment regimen (Bardwell et al, 2006). Depressed mood is correlated with fatigue and sleep disturbance in the context of breast cancer. In terms of treatment psychological interventions seem to be most effective distressed patients even though these interventions do not prolong survival. Regular exercise participation and tea consumption were shown in a population-based cohort study from Shanghai to play an important role in the prevention of depression among breast cancer survivors (Chen et al, 2010). Antidepressents have also shown to improve depression, in particular paroxetine has been shown to be effective in reducing depressive symptoms in breast cancer patients, even among those who were not depressed at study entry.

References:

Statements 1-4


Reports of cognitive deficits, often referred to as chemobrain, among breast cancer patients during and after chemotherapy have been reported in 16 to 75% (Bower et al. 2008; Vardy et al. 2007; Stewart et al. 2006). Neuroimaging findings provide compelling evidence that chemotherapy has a negative effect on cognition in a subset of women and that these effects may persist for years after successful treatment (Silverman et al, 2007). A study on young premenopausal patients was able to clearly correlate chemotherapy-induced changes in cerebral white matter with impaired cognitive functioning (Deprez et al, 2011). Among breast cancer survivors who remain disease-free for more than a decade, the previous cancer treatment may further augment cognitive dysfunction associated with age-related brain changes. In patients after treatment completion there is improvement in cognitive function over time, although a subset of patients continued to show deficits for up to 10 years after treatment (Fan et al, 2005). Interestingly, subjective cognitive complaints are typically not correlated with objective cognitive performance in breast cancer patients but are correlated with subjective reports of fatigue and depressed mood. In a current study examining 120 breast cancer patients treated with CMF, neuropsychological tests did not reveal any differences in cognitive function between breast cancer patients after chemotherapy and healthy controls (Debess et al, 2010). Patients rated their own cognitive functions as improved after 6 months. These results again do not support that adjuvant chemotherapy is associated with cognitive side effects in breast cancer patients. Considering adjuvant endocrine treatment, tamoxifen use was associated with statistically significant lower functioning in verbal memory and executive functioning, whereas exemestane use was not associated with statistically significant lower cognitive functioning in postmenopausal patients with breast cancer (Schilder et al, 2010).

The biologic base for these changes is unclear. However, are there several candidate mechanisms for chemotherapy-induced cognitive changes, including direct neurotoxic effects, DNA damage and telomere length, inflammation and cytokine dysregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms (Ahles et al, 2007). Cognitive behavioral therapy might lead to significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance after treatment and at the 2-month and 6-month follow-ups (Ferguson et al, 2007). Other potential treatment approaches include methylphenidate, which has been used to improve cognitive
References:

**Therapy-related cognitive deficits (chemobrain)...**


**Cognitive-behavioral therapy....**


**Methylphenidate might improve cognitive function....**

Side-effects and Toxicity of Endocrine Agents I (17/24)

Further information:

In a metaanalysis on 19,818 pts. treated with 3rd generation aromatase inhibitors the risk of developing cardiovascular adverse events was slightly higher in comparison to tamoxifen with an RR of 1.34 translating into a minimal risk of 0.5%. (Cuppone F et al 2008)

In an actual systematic review and metaanalysis of 30,023 patients in 7 trials comparing aromatase inhibitors with tamoxifen, the increased risk for developing cardiovascular disease (OR=1.26) for aromatase inhibitors was confirmed, as well as the occurrence of bone fractures (OR=1.47), while the OR for endometrial carcinoma (OR=0.34) and venous thrombosis (OR=0.55) was significantly lower in comparison to tamoxifen (Amir et al, 2011).

References:

Further information:

A recently published randomized study compared denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor κ B (RANK) ligand, with zoledronic acid in delaying or preventing skeletal-related events (SREs) in patients with breast cancer with bone metastases. In terms of toxicity rates of adverse events (AEs) and serious AEs were similar between groups. An excess of renal AEs and acute-phase reactions occurred with zoledronic acid; hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred infrequently (2.0%, denosumab; 1.4%, zoledronic acid; P = .39) (Stopeck et al, 2010). In a pooled analysis of three randomized phase III trials of denosumab versus zoledronic acid in patients treated for metastatic cancer this occurrence rate for denosumab was confirmed with 1.67% (RR= 1.61) (Van den Wyngaert et al, 2011).

Although there amounting data, that bisphosphonates might have anticancer benefits for older postmenopausal women, the routine use of bisphosphonates as adjuvant treatment for patients with early breast cancer is not recommended (Paterson et al 2012; Wong et al 2012).

References:


Acute phase rea
Gastrointestinal side effects...

Recommendations for Precautions to Prevent ONJ (19/24)

Further information:

The reported incidence of osteonecrosis of the jaw (ONJ) ranges from 0.94% to 18.6%. A study with 1,621 patients who received 29,006 intravenous doses of BP, given monthly reported an crude ONJ incidence of 8.5%, 3.1%, and 4.9% in patients with multiple myeloma, breast cancer, and prostate cancer, respectively. Patients with breast cancer demonstrated a reduced risk for ONJ development, which turned out to be non-significant after adjustment for other variables. Multivariate analysis demonstrated that use of dentures (aOR = 2.02; 95% CI, 1.03 to 3.96), history of dental extraction (aOR = 32.97; 95% CI, 18.02 to 60.31), having ever received zoledronate (aOR = 28.09; 95% CI, 5.74 to 137.43), and each zoledronate dose (aOR = 2.02; 95% CI, 1.15 to 3.56) were associated with increased risk for ONJ development. Smoking, periodontitis, and root canal treatment did not increase risk for ONJ in patients receiving BP. In conclusion, validated dental extractions and use of dentures are risk factors for ONJ development. Ibandronate and pamidronate at the dosages and frequency used in this study seem to exhibit a safer drug profile concerning ONJ complication; however, randomized controlled trials are needed to validate these results. Before initiation of a bisphosphonate, patients should have a comprehensive dental examination.

References:

Frequent Side Effects of Bone Modifying Agents (BMA) (20/24)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

Go to slide 18-19/22!
Key-Toxicities Antibodies/Antibody-drug-conjugates – Small Molecules (21/24) and (22/24)

Further information:

In the HERA trial, the incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac end points remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% v 0.0%; confirmed significant LVEF decreases, 3.6% v 0.6%) In the trastuzumab group, 59 of 73 patients with a cardiac end point reached acute recovery; of these 59 patients, 52 were considered by the cardiac advisory board (CAB) to have a favorable outcome from the cardiac end point. The incidence of cardiac end points remains low even after longer-term follow-up and the majority of cardiac events resolved (Procter et al, 2010).

In the NSABP B-31- and NCCTG 9831-trial trastuzumab-treated patients had a 2.0% incidence of symptomatic heart failure events compared with 0.45% in the chemotherapy-alone arm. Complete or partial recovery was observed in 86.1% of trastuzumab-treated patients with symptomatic heart failure events after cessation of trastuzumab. Independent predictors for cardiac events were age older than 50 years, a low ejection fraction at the start of paclitaxel treatment, and trastuzumab treatment. The majority of these patients recover with appropriate treatment (Russell et al, 2010).

The usefulness of troponin I in the identification of patients at risk for trastuzumab induced cardiotoxicity (TIC) and in the prediction of LVEF recovery was investigated in 251 women treated with trastuzumab. TNI was measured before and after each trastuzumab cycle. TIC occurred more frequent in patients with troponin elevation (TNI+; 62% v 5%; P < .001). Thus, Troponin increase identifies trastuzumab-treated patients who are at risk for cardiotoxicity and are unlikely to recover from cardiac dysfunction despite HF therapy.

In the Phase III trial of Capecitabine with or without the oral tysosinkinase-inhibitor lapatinib which led to the approval of lapatinib in advanced HER-2 positive breast cancer, asymptomatic cardiac events were identified in four women in the combination-therapy group and in one woman in the monotherapy group. All of these events in the combination-therapy group were considered to be related to treatment, and all women had an LVEF value that was at or above the lower limit of the normal range on subsequent assessment.
The most common adverse events were diarrhea, the hand–foot syndrome, nausea, vomiting, fatigue, and rash that was distinct from the hand–foot syndrome. Most adverse events were grade 1, 2, or 3. Grade 4 diarrhea occurred in two women in the combination-therapy group (1%). One case each of grade 4 fatigue, headache, and dizziness was reported in the monotherapy group. Diarrhea, dyspepsia, and rash occurred more often in the group of women who received combination therapy.

A systematic review and meta-analysis of five randomized phase III clinical trials that used bavcizumab alone or in combination with chemotherapy in metastatic breast cancer showed a statistically significant bevacizumab associated increased risk for proteinuria (OR=27.68), hypertension (OR=12.76), left ventricular dysfunction (OR=2.25) and hemorrhagic events (OR=4.07), while no increased incidence was found for gastrointestinal perforation, vascular or fatal events and febrile neutropenia, respectively.

References

Cardiotoxicity....


**Troponin I...**


**Bevacizumab ...**


**Lapatinib...**


**Pertuzumab**


**T-DM1**


**Everolimus:**

**Immun-Checkpoint Inhibitors (23-24/24)**

No further information

No references