Chemotherapy and Cognitive Function in Breast Cancer Patients: The so-called Chemobrain
I forget important events like birthdays and appointments.

Sometimes it’s very hard for me to focus during a meeting or a conversation.

I’m not as quick as I used to be.

In mid-sentence, I’m not able to come up with the right word.

I have trouble with directions now when I’m driving, getting lost very easily.

Von Ah et al., Eur J Oncol Nurs 2013
I’m just not the person I used to be and it gets very frustrating.

I mentioned it and my oncologist was like, oh, your’re just under a lot of stress...

Von Ah et al., Eur J Oncol Nurs 2013
Starting in the mid 1990s:

Neuropsychological assessment of cognitive function after chemotherapy
Consistently found across all studies:

Compromised performance on cognitive tests after chemotherapy for breast cancer

Falleti et al., Brain Cogn 2005 (meta-analysis)

- Deficits were mild to moderate
- Only subgroups were affected (15% – 75%)
"...indeed the phenomenon of chemo-fog is now almost universally accepted" - Shilling et al., Breast 2005.
Chemobrain
Cognitive deficits in cancer patients Caused by chemotherapy
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Cognitive deficits in cancer patients Caused by chemotherapy

Open questions:
• How many patients affected?
• Vulnerability?
• Course – Reversibility? Dementia?
• Mechanisms?
• Differential effects of different cytostatics?
Prospective, longitudinal studies
2nd generation studies:

1.) Pretreatment cognitive impairment

- Prior to adjuvant chemotherapy
  Vardy et al., Ann Oncol 2005

- Prior to neoadjuvant chemotherapy
  i.e., prior to any therapy
  Wefel et al., Cancer 2004: 21%, Hermelink et al., Cancer 2007: 30%

Misattributed to chemotherapy effects in cross-sectional studies
Cancer– or cancer-therapy–associated cognitive change

Cognitive deficits in cancer patients Caused by chemotherapy?

Open questions:

• How many patients affected?
• Vulnerability?
• Course – Reversibility? Dementia?
• Mechanisms?
• Differential effects of different cytostatics?
Prospective, longitudinal studies
2nd generation studies:

2.) Several large-scale studies:

No evidence of cognitive deficits before or after chemotherapy

Jenkins et al., Br J Cancer 2006
Debess et al., Acta Oncol. 2009, Breast Cancer Res Treat 2010
Cancer– or cancer–therapy–associated cognitive change

Cognitive deficits in cancer patients?
Caused by chemotherapy?

Open questions:

• How many patients affected?
• Vulnerability?
• Course – Reversibility? Dementia?
• Mechanisms?
• Differential effects of different cytostatics?
Meta-analysis
Jim et al., JCO 2012
17 studies with 803 breast cancer patients

≥ 6 mo. after standard chemotherapy, deficits are
• Small
• Limited to verbal ability and visuospatial ability
Hardly any associations – Why?

- Neuropsychological tests may lack sensitivity
- Deficits may not arise in structured test situations
- “perceived impairment may be an indicator of psychological distress rather than cognitive impairment”

Hutchinson et al., Cancer Treat Rev 2012 (systematic review)
After ~ 20 years of research –

A proportion of patients complains about chemobrain.

• Do substantial cognitive deficits exist at all?
• Are they primarily caused by chemotherapy?
• Do subjective complaints reflect objective deficits?
Neuroimaging Studies
– Mostly MRI and fMRI –

Brain structure

Cross-sectional studies – after chemotherapy relative to controls:
Ahles et al., JCO 2012 (review)

• Decreased white matter integrity
• Reduced regional grey matter volumes

Prospective studies – after chemotherapy:

• Decline in white matter integrity linked with decline of memory and attention Deprez et al, JCO 2012
• Reduction of frontal grey matter density linked with increased subjective complaints McDonald et al, Brain Behav Immun 2013
Neuroimaging Studies
  – Mostly MRI and fMRI –

Brain function

Activity patterns during cognitive tasks after chemotherapy:

• **Regional hypoactivation** Kesler et al., Arch Neurol 2011
• **More widespread activation** McDonald et al., JCO 2012

**Interpretation** Reuter-Lorenz at al., Breast Cancer Res Treat 2013

Dysfunction compensated by activation of additional brain areas?
Thus normal performance but more (compensatory) effort?

– Explanation for the discrepancy of obj. and subj. cognitive deficits –
Neuroimaging Studies
– Mostly MRI and fMRI –

Conclusions

• Brain correlates of objective and subjective cognitive deficits
• Cognitive deficits caused by chemotherapy

Altered activity patterns pretreatment
McDonald et al., JCO 2012, Scherling et al., J Clin Exp Neuropsychol 2012

Altered activity patterns linked with emotional state
Lopez Zunini et al., Brain imaging Behav 2012
Methodological problems

Confounders

- Surgery/Radiation
- Anti-estrogen therapy
- Chemotherapy
- Other medications
- Treatment side effects
- Prognosis
- Life disruption
- Psychological burden
- Sleep problems
- Cancer itself

Cognitive Function

Brain
Cancer– or cancer–therapy–associated cognitive change – the so-called chemobrain –

Tentative knowledge:

- **Causation:** Multifactorial, chemotherapy increases risk
- **How many patients affected?** 0–61%, most studies: 15–25%
- **Vulnerability?** Discussed: genetic disposition, age, cognitive reserve
- **Course – Reversibility?** Dementia? Divergent findings
- Prospective neuropsychological studies:
  
  **Return to baseline within 1 year**  
  Collins et al, Psycho-Oncology 2012; Ahles et al., JCO 2010; Jansen et al., Support Cancer Care 2011

- Cross-sectional neuropsychological and imaging studies:
  
  (Subtle) alterations of performance and brain functioning 20 years after chemotherapy  
  Koppelmans et al., Crit Rev Oncol Hematol 2013 (meta-analysis)

- Population-based studies:
  
  No evidence of increased risk of dementia  
  Koppelmans et al., Crit Rev Oncol Hematol 2013 (meta-analysis)

  Cognitive function in later life (≥65) not associated with cancer survivorship or chemotherapy  
  Porter et al., J Aging Health 2013
A patient complains of cognitive deficits –

**Take it seriously!**

(Subclinical) depression, anxiety, distress

**Emotional State – Depression**

**Objective cognitive deficits**
- Mild
- Limited

**Subjective cognitive complaints**
- Dramatic
- Extensive

Mostly

n.s.

Patients may
- interpret normal lapses pessimistically
- idealize pre-therapy cognitive abilities
- expect pre-therapy performance level soon after therapy
Interventions

Cognitive Rehabilitation Programs
Gehring et al., Expert Review of Anticancer Therapy 2012 (review)

- Trained abilities improve
- Transfer effects are rare
- Patients are highly satisfied

Psychooncological counseling
Psychotherapy
Patients at the start of chemo – should we inform them about „chemobrain“?

Dilemma:
- Relevant problem for a substantial subgroup
- Expectation bias (Nocebo effect)

Patients randomized to receive „chemobrain“ information
- Reported more cognitive problems
- Performed worse on a learning task

Schagen et al., Psycho-Oncology 2012
What should we tell our patients?

- Very mild cognitive deficits are found in a subgroup of patients.
- Most affected patients do not notice these deficits, but they may become a big problem mainly in the context of distress.
- The causation is largely unclear. Chemotherapy is a risk factor, but patients not treated with chemotherapy are also affected.
- Cancer survivors do not have an elevated risk of dementia in old age.

Cancer–related cognitive deficits do not determine time to return to work

Hedayati et al., Scand J of Caring Sci 2013