Overtreatment with systemic treatment - Long term sequelae

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- Why study long term sequelae?
- Long term sequelae induced by hormonotherapy and chemotherapy (some might be due to cancer)
- Risk benefit ratio

Why study long term sequelae ?

Survival of patients treated for breast cancer

- One woman out of 8 is affected with breast cancer during her life.
- Breast cancer is often diagnosed at an early stage.
- The number of different medical treatments is increasing.
- The results of treatments are overall good and overall survival increases
- Several millions women in the world are breast cancer survivors (Rowland 2000) and their number increases dramatically (12 millions of cancer survivors in the USA in 2008 overall)
- Long term complications, even rare, are becoming a public health issue

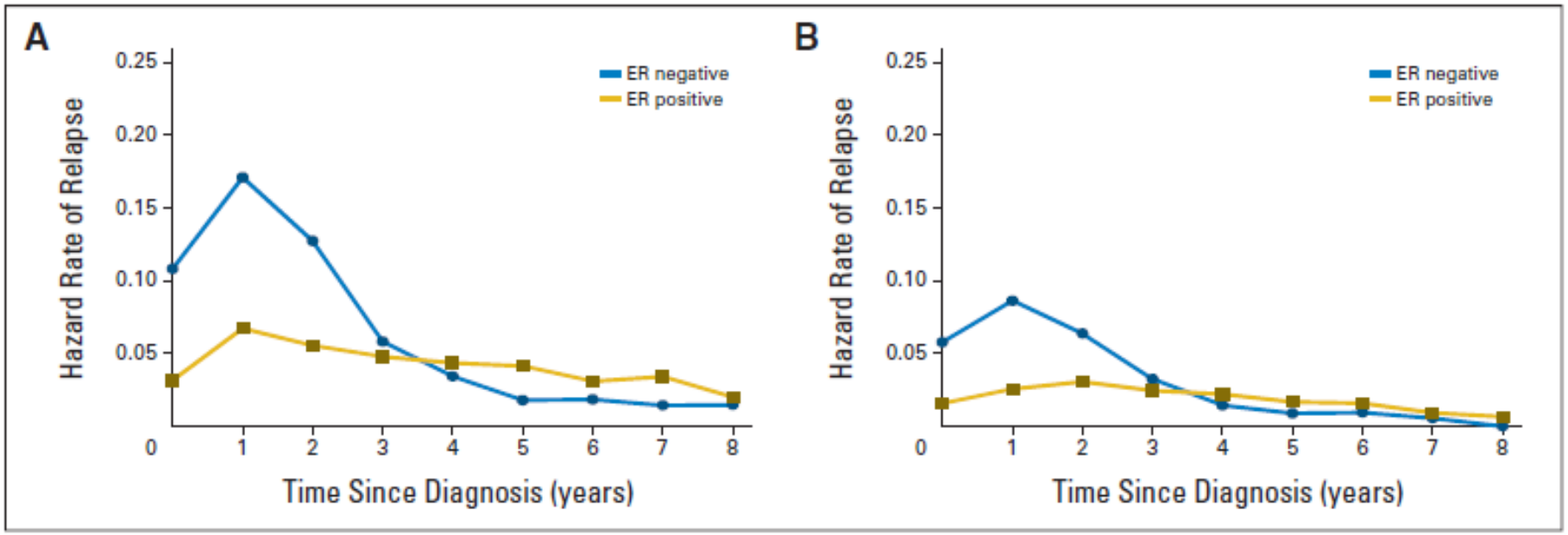


Fig 2. Hazard rate of relapse according to estrogen receptor (ER) status in (A) cohort 1 and (B) cohort 2.

Comparison of Breast Cancer Recurrence and Outcome Patterns Between Patients Treated From 1986 to 1992 and From 2004 to 2008
Cossetti R.J.D. et al
J Cllin Oncol 2015:33(1):65-73

Survival of patients treated with breast cancer

- The increased knowledge of the biology of breast cancer as well as the increased number of new treatments explain why more and more drugs are used simultaneously or sequentially and for longer duration, especially in the adjuvant setting, increasing the risk of side effects
- The medical oncologist is well aware of short term side effects but not of long term sequelae. Long term complications are not studied in clinical trials.
- There is a lack of definition and standardization of methods to study late complications

Long term sequelae of Hormonotherapy and Chemotherapy

HORMONOTHERAPY

Tamoxifen vs no Tamoxifen (2011)

- Endometrial cancer

  - Relative risk: 2.40 ($p<0.00002$)

- Thrombo-embolic disease

  - Relative risk: 2.50 (p: 0.07)

- Overall, the absolute risk of death for both complications is 0.2% in ten years (ECCTCG 2005)

TAM 5 years vs TAM 10 years (2013)

- Thrombo-embolic disease RR: 1.87 (p:0.01)
- Endometrial cancer RR: 1.74 (p: 0.0002)

When compared to no TAM, the RR of 10 year TAM is between 4 and 5

Tamoxifen vs aromatase inhibitors (Amir 2011)

Differences	OR (IAvsTAM)	Absolute risk ( ) difference	NNH
Cardio vasc disease Hyper cholesterol	1.26 (1.10-1.43) 2.36 (2.15-2.60)	4,2 vs 3,4% (0.8%)	132
Thrombosis	0.55(0.46-0.64)	1,6 vs 2,8% (1.2%)	79
Bone fractures	1.47(1.34-1.61)	7,5 vs 5,2% (2.3%)	46
Endometrial cancer	0.34(0.22-0.53)	0,1 vs 0,5% (0.4%)	258

NNH: number needed to harm

Risk for each individual patient

- According to age, comorbidities
- Very difficult to evaluate

- 2 exemples

  - absolute risk of endometrial carcinoma in a patient of 55 years after 5 years TAM 3.8% (vs 1.1% without TAM)(EBCTCG 2011)

  - ATAC trial: if preexisting cardiac disease, the absolute risk of cardiovascular complications is 17% vs 10%(FDA files)(Amir 2011)

Long term sequelae of Hormonotherapy and Chemotherapy

CHEMOTHERAPY

Long term sequelae – chemotherapy (Mrozek 2005)

- Chronic fatigue
- Ovarian failure
  - Vasomotor symptoms
  - Bone loss
  - Sexual problems
- Cardiovascular disease
- Cognitive function
- Secondary malignancies

Chronic fatigue

- 0 - 60% Broeckel (1998), Bower(2000), Servaes(2002), Cella(2001)
- Predictors: depression, pain,poor sleep, menopausal symptoms (Lawrence 2004)
- More studies are needed to evaluate the burden of this side effect

Ovarian failure

- Depends on drugs, total cumulative dose and age of the patient.
- Younger women (less than 40 years) are likely to have transient amenorrhea
- Chemotherapy induced ovarian failure leads to a rapid decrease in estradiol levels.
- Many patients will be prematurely postmenopausal with vasomotor symptoms, osteoporosis, increase in cholesterol levels and cardiovascular disease, genito urinary symptoms
- Patients who resume menstruations will experience a decreased fertility
- Sexual problems

Cardiovascular disease (Mrozek 2005)

Congestive heart failure in the first year

Dose dependent

less than 1% up to 300 mg/m² DXR

26% over 500mg/m² (Swain 2003)

Decrease of LVEF >15% in 3% of pts receiving less than 240 mg/m² DXR (Perez 2004)

Cardiovascular disease (Mrozek 2005)

Late onset cardiovascular disease (years or decades)

- congestive heart failure, ventricular dysfunction, arrhytmia
- dose dependent
- Reduction in left ventricular mass, diastolic dysfunction

These cardiovascular conditions have often to be treated on the long term

Cardiovascular disease induced by targeted therapy (Mrozek 2005)

- Hypertension : angiogenesis inhibitors, especially bevacizumab
- Cardiac insufficiency , reversible, induced by Trastuzumab

Cognitive function (Ahles 2012)

- Post chemo but also post hormonotherapy
- Impairment of verbal, visual ..memory, of attention, vigilance and processing speed
- A lot of studies are ongoing

Neurological sequelae (Pachman 2012)

- Peripheral neuropathy can remain for years , only partially reversible (Taxanes, Oxaliplatin)
- Chronic pain syndrom in 33% of the patients after chemotherapy but also hormonotherapy
- Symptomatic treatment

Secondary leukemias

- Praga (2005):
  - 8 year absolute risk: 0.55%(0.33-0.78%)
    * « standard » regimen : 0.37%
    * High doses: 4.97% (2.06-7.87%)
- Le Deley (2006)
  *RR Mitoxantrone vs anthracyclines: 15.6 (7.1-34.2)
  *RR 3.9 (1.4-10.8) if RT, 6.3 (1.9-21) if G CSF
- Wolff (2015) : Risk of marrow neoplasms
  * HR surgery and chemo: 6.8 (1.3-36.1)
    surgery,chemo and RT: 7.6 (1.6-35.8)
  * Risk at 10 years twice the risk at 5 years
  * Risk per 1000 person.year: 0.5

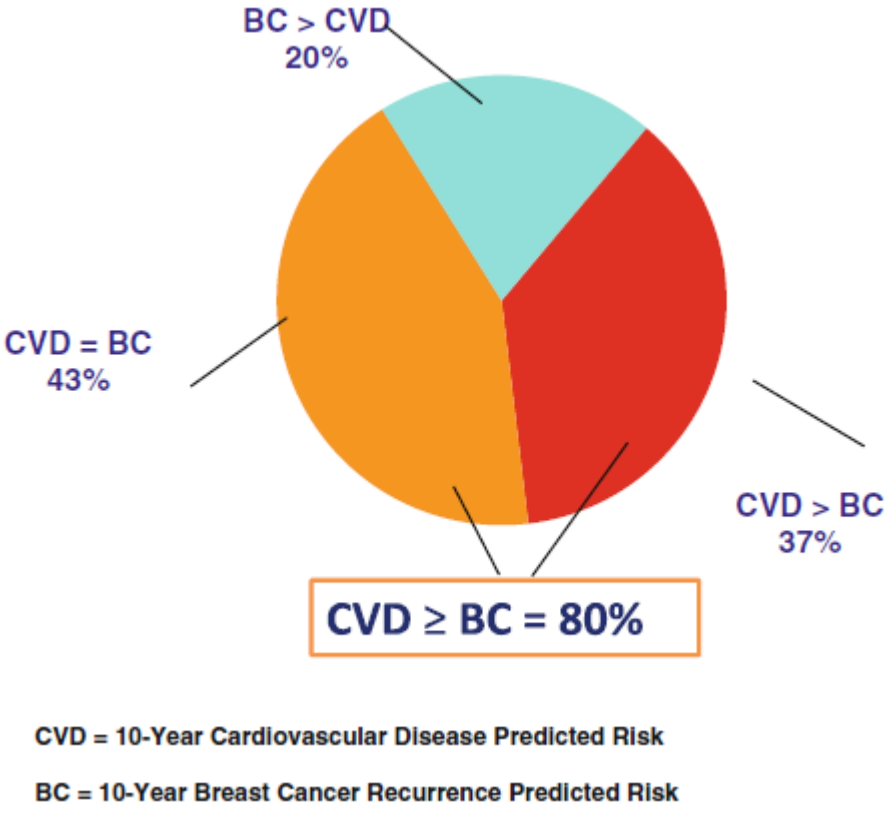
Risk-benefit ratio

Primum non nocere

Example of cardiovascular disease
(Bardia 2011)

- Comparison of the 10 year breast cancer recurrence rate according to Adjuvant!on line and the 10 year cardiovascular disease risk according to the Framingham risk score
- 415 pts receiving AI as an adjuvant treatment

Fig. 3 Relative distribution of the predicted breast cancer recurrence risk (*BC*) and cardiovascular disease (*CVD*) risk among the study participants. CVD = 10-year CVD predicted risk. BC = 10-year breast cancer recurrence predicted risk



Comparison of breast cancer recurrence risk and cardiovascular disease incidence risk among postmenopausal women with breast cancer
A Bardia
BRCT 2011

The poorest benefit/risk ratio
(Bardia 2011)

- CVD risk was higher than breast recurrence risk in grade 1 tumors OR: 6.1(3.4-11.2) and in patients over 65 years OR:12.4 (7.0-22.6)

Clinical case 1

- Postmenopausal 60 y of age patient , average health condition, with a tumor of 1cm, SBR1, ER positive, no axillary node
- Risk of cancer death at 10 years : 1%
- Absolute benefit with hormonotherapy: 0,3%

But

- TAM 5y: Thrombo-embolic disease: RR: 2.5

  Endometrial carcinoma: RR: 2.5
- IA : Absolute increase of CV disease: 0.8%

  Absolute increase of bone fractures: 2.3%

  Risk of arthromyalgia , vasomotor symptoms, weight gain..

Clinical Case 2

- Premenopausal 35 y of age patient, average clinical condition, with a tumor of 1.5 cm, SBR 1, ER positive, no axillary node
- Risk of cancer death at 10 years: 3%
- Benefit with hormonotherapy:1%, with chemo:1%, with both 1.2%

  But
- If TAM: RR of thromboembolic disease : 2.5

  Small increase of endometrial carcinoma

  Effects on « quality of life », weight control, sexual problems..
- If chemotherapy: risk of bone marrow neoplasms of 0.3 to 0.5 % (much more if high dose chemotherapy), low risk of CV complications, chronic fatigue syndrom, ovarian suppression

Social and financial consequences of overtreatment

- Overtreatment have psychological and social consequences: no or late return to work, less efficiency …
- Overtreatment sequelae have to be treated.
- Overtreatment costs a lot to the patient and to society

Conclusion or.... what next ?

- The oncologist is more influenced by the prognostic factors of the tumor and the « statistical results » of clinical trials than by the potential benefit/risk (short and long term) ratio for the individual patient . Who cares if the p is highly significant ?

- The clinician must balance efficacy of the drug and long term sequelae ,to evaluate the risk/benefit ratio on the long term

- The clinician must be aware of the late sequelae and be able to deliver post treatment survivorship care