The DBCG – Programmes: Rationales and results. International collaboration

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Hypotheses about breast cancer biology relevant to therapeutic intervention

- Halsted 1880
- Fisher 1950
- Hellman 1990

Hypotheses about breast cancer biology relevant to therapeutic intervention

Halsted 1880:

- **Breast cancer remains localized to the breast during the early course, later progressing by direct extension through the lymphatics to the lymphnodes and then to distant metastatic sites**

I.E. effective local control determines the prognosis

Hypotheses about breast cancer biology relevant to therapeutic intervention

Fisher 1950:

- **Breast cancer is a systematic disease early on**

  I.E. prognosis is mainly determined by effective systemic antineoplastic therapy

Hypotheses about breast cancer biology relevant to therapeutic intervention

Hellman 1980:

- Breast cancer is to be considered a heterogeneous disease extending from a disease that remains local throughout its course to one that is systemic when first diagnosed.
- Residual local disease can serve as a source of distant metastases.

I.E. prognosis is determined by as well effective local as well as systemic approaches

Scientific background for the establishment of DBCG

According to the Fisher theory early data of adjuvant chemotherapy demonstrated a significant reduction of recurrence rate (1,2)

These results should be tested in Denmark – in a selected risk group of patients

- High risk patients: Systemic therapy
- Low risk patients: No systemic therapy

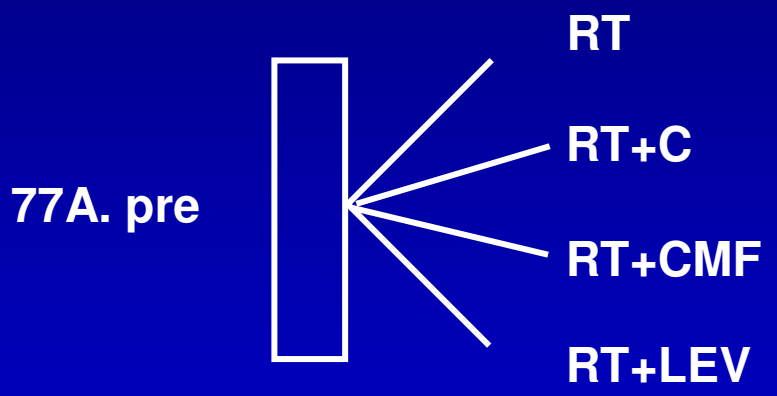
1. Bonadonna et al. 1975;294:405
2. Fisher et al. 1975;292:117

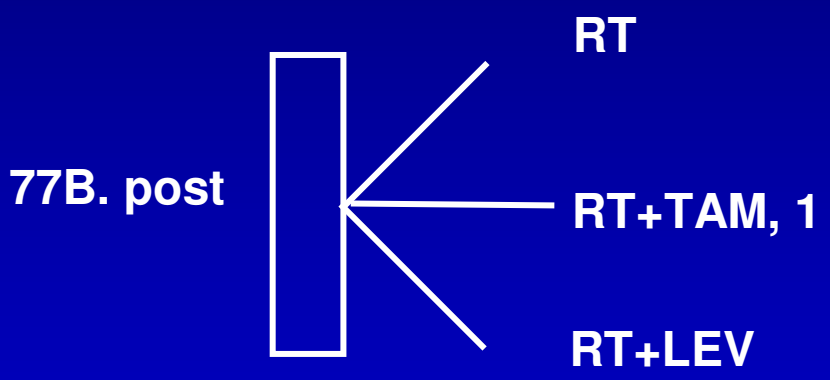
Definition and proportion of low risk patients according to time

Variable	77	82	89	99	01	04	07
Nodal status	NEG	NEG	NEG	NEG	NEG	NEG	NEG
Size (cm)	≤ 5	≤ 5	≤ 5	≤ 2	≤ 2	≤ 2	≤ 2
Grade			I, pre	I	I	I	I
Rec. status				Pos/?	Pos/?	Pos/?	Pos/?
Age					> 35	≥ 35	≥ 35
HER2 status						Neg/?	Neg/?
TOP2A status							Normal/?
Proportion (%)	50	53	50	23	21	21	

DBCG 77 programme

Question: • Do patients with high risk breast cancer benefit from adjuvant systemic therapy





Results: • Significant superiority with adjuvant chemotherapy and endocrine therapy over control, in agreement with the Fisher hypothesis

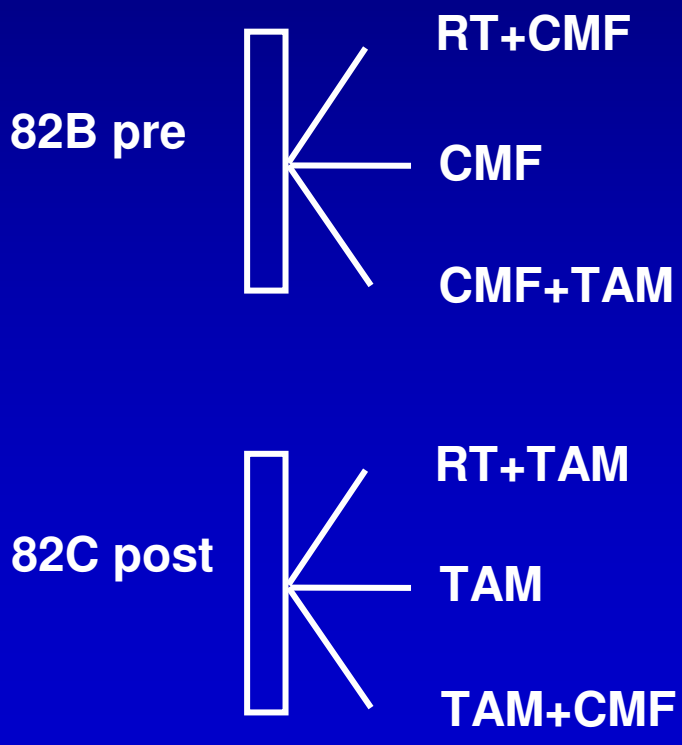
- **Following the data from the first generation trials demonstrating significant improvement of the prognosis in primary breast cancer a world-wide enthusiasm – finally we knew how to cure breast cancer**
  - **Systemic adjuvant therapy is the treatment option**
  - **No needs for local approaches, except for diagnostic procedures**

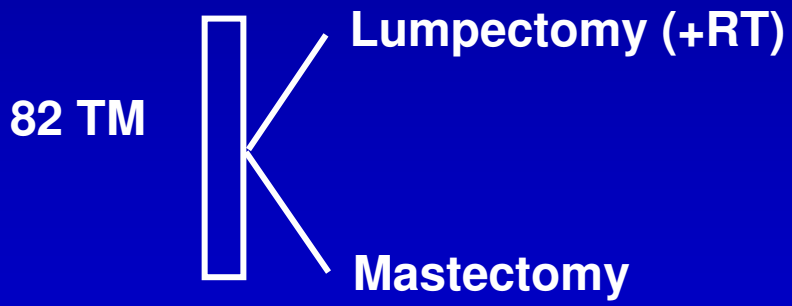
- Following the data from the first generation trials demonstrating significant improvement of the prognosis in primary breast cancer a world-wide enthusiasm – finally we knew how to cure breast cancer
  - Systemic adjuvant therapy is the treatment option
  - No needs for local approaches, except for diagnostic procedures
- But we got wiser

DBCG 82 programme

Questions

- Can radiotherapy be avoided
- Should chemo- and endocrine therapy be combined
- Is breast conserving therapy safe





DBCG 82 programme. Results

- Benefit with the addition of radiotherapy in terms of local and distant control (Hellman)
- No significant benefit of adding TAM to CMF
- Similar outcome with breast conserving therapy and mastectomy in patients otherwise eligible for lumpectomy

Clinical consequences of the DBCG 82 results

- Since then radiotherapy has remained part of the primary local therapy
- Chemo- and endocrine therapy is given sequentially
- Lumpectomy to be offered to eligible patients (20% in 1990 to 52% in 2006)

DBCG 89 programme. Question

- Chemotherapy or endocrine therapy in premenopausal women with hormone responsive tumors
- Duration of tamoxifen and sequenced endocrine therapy in postmenopausal women with hormone responsive tumors is superior to CMF
- Is CEF superior to CMF
- Does the addition of pamidronate reduce the risk of bone metastases

DBCG 89 programme. Design

89B pre, rec. pos

CMF

Ovarian ablat.

89C post, rec. pos/?

TAM 1

TAM 2

TAM½ → megace ½

89D

Pre, ER neg/?

Post, ER neg

Pre, grade II-III

CMF +/- pamidronate

CEF +/- pamidronate

DBCG 89 programme. Results

- Similar outcome with ovarian ablation and CMF
- Similar outcome with TAM 1, TAM 2 and TAM ½ ⟶ megace ½
- No benefit with adjuvant pamidronate
- CEF significantly superior to CMF. Translational studies done 10 years later demonstrated the benefit to be limited to patients with TOP2A abnormal tumors

DBCG 99, 01, 04 and 07 programmes

General guidelines. Evidence based according to data from previous national and international trials

Treatment according to menopausal status and hormone receptor status

Programme	Pre, rec. pos.	Pre, rec. neg.	Post, rec. pos.	Post, rec. neg.
99	CMF/ov. ablat	CMF	TAM 5	CMF
01	CMF/CEF → TAM 5	CEF	TAM 5	CMF
04	CEF → TAM 5	CEF	TAM+AIs	CEF
07	EC+DOC → TAM 5	EC+DOC	≤ 60 EC+DOC → TAM + AIs > 60 TAM + AIs	EC+DOC

From Jan. 06 CT followed by trastuzumab if HER 2 pos. status

International collaboration. EBCTCG

Data from the DBCG 77, 82 and 89 protocols have all been part of the meta-analysis of benefits of theraputic intervention conducted by the EBCTCG

DBCG International collaboration

Study	N		DBCG%	Topic	Inclusion
	Total	DBCG			
BIG 1-98	8010	1396	17	AIS	98-03
IES	4704	136	3	AIS	98-03
BIG 2-98	2890	156	5	Taxane	98-01
SBG 2000-1 (DK, SV)	1534	564	37	HD-epirubicin	01-03
HERA	5081	133	3	Trastuzumab	01-05
NICE (DK,SW)	188	126	67	Gefitinib	04-07
FACE	4115	269	7	AIS	05-08
TEACH	2370	71	3	Lapatinib	06-08
ALTTO	-	-	-	Trast./lap.	07-

In the multinational trials (SBG 2000-1 and Nice excluded) an average of 8% of patients are recruited by DBCG.

Relative reduction of mortality with adjuvant systemic therapy

Generation	Chemotherapy	Endocrine therapy	Biological therapy
I, 1990	CMF, 15% (<50 yrs 30%, >50 yrs 10%)	TAM 1-2 yrs, 15% Ovarian ablation, 24%	
II, 1998	Anthracyclines, +15%	TAM 5 yrs, +15%	
III, 2005	Taxanes, +15%	Aromatase inhibitors, +15 % ?	Trastuzumab (35% if HER 2 pos)

Conclusions

DBCG has managed to

- run large nationwide trials
- participate actively to international trials

- and thus to contribute to provide data to national and international evidence – based treatment guidelines

Future

- Continue the development of the new effective agents
- Develop markers to better select patients eligible for specific therapies (individualized therapies)

DBCG. Future

Two large nation-wide trials to be launched

- **READ**
- **REAL**

REAL. Randomized trial of endocrine against loco-regional therapy first

QUESTIONS (in patiens ≥ 60 years with HR positive tumors > 20mm)

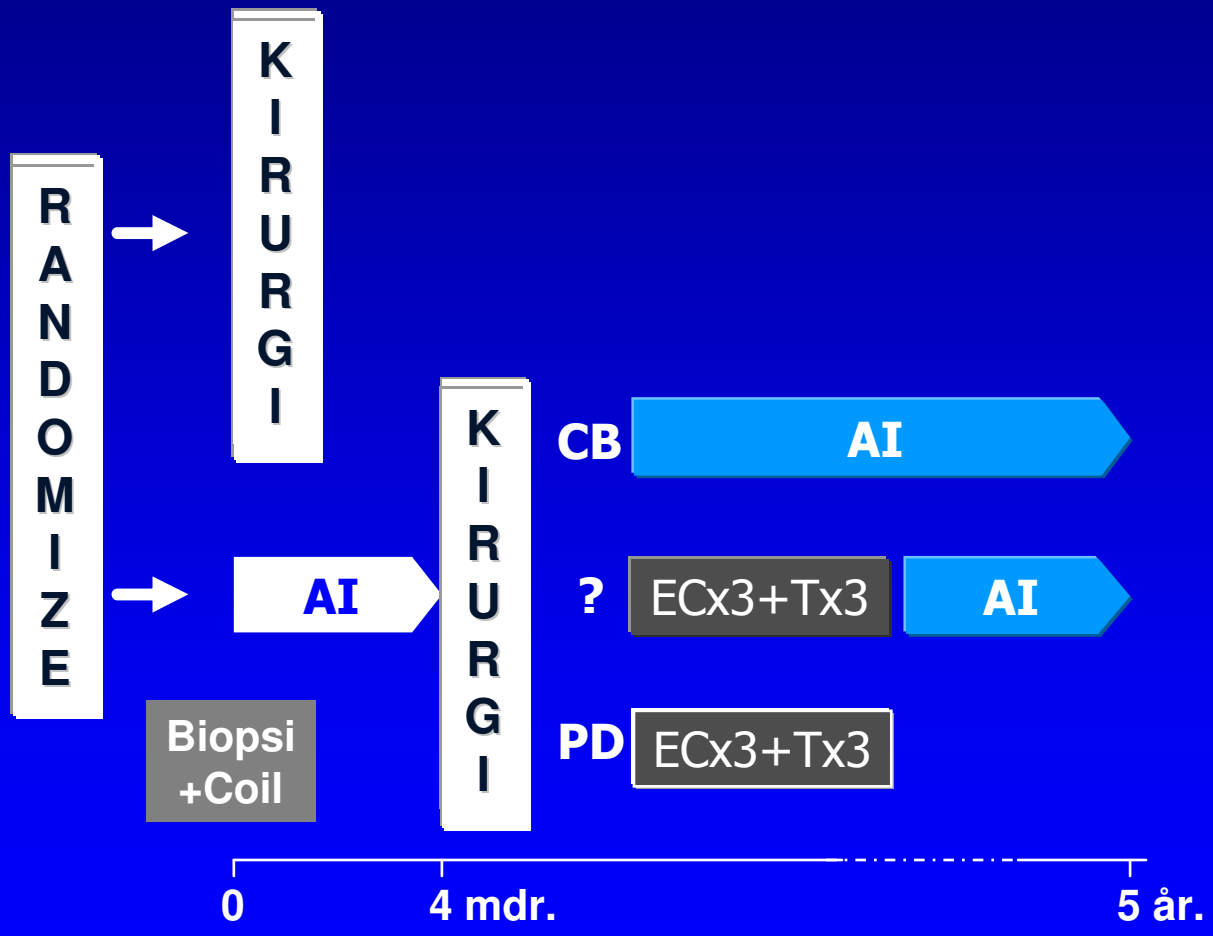
- Can preoperative therapy improve IRFS and OS
- Can we identify the subgroups which needs chemotherapy
- Can the effect of endocrine therapy be predicted according to
  - molecular markers
  - histopatological characheristics
  - imaging technigues (MR/PET)

REAL

Randomised trial of **e**ndocrine **a**gainst **l**ocoregional therapy first

Patienter
- Operabel
- Tumor >20mm
- Alder > 59 år
- HR+

Effekt
- RFS & OS
- Respons
  - UL, MR, PET
- Markører
  - DNA, RNA



DBCG's FU i samarbejde med de videnskabelige udvalg

Tak til alle i DBCG