Taxanes and anthracyclines in early BC: which first?

多地点ウェブカンファレンス　2010年8月26日

啓明会　相原病院
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背景

- 現在浸潤性乳管癌に対して、Sequentialにアンスラサイクリン系(A)及びタキサン系薬剤(T)を用いた術前/術後補助化学療法が確立されている。
- 術後補助化学療法においてはA→Tの順序で用いる一方、術前化学療法ではA→T / T→A両者のレジメンが存在する。
- 今回、術前/術後化学療法において、AとTどちらを先に投与するべきなのかについて論じた文献を紹介する。

Randomised clinical studies addressing the sequence of anthracyclines and taxanes in early BC

	Setting	Number of patients	Chemotherapy regimens	Results
Puhalla et al (2008)[2]	Adjuvant	28 28	AC→Doc (DD) Doc→AC* (DD)	RDI of AC 0·98, Doc 0·82 RDI of AC 0·95, Doc 0·96
Wildiers et al (2009)[3]	Adjuvant	58 59	FEC→Doc (±DD) Doc→FEC (±DD)	Doses reduced: FEC 5%, Doc 17% Doses reduced: FEC 5%, Doc 3%†
Piedbois et al (2007)[4]	Adjuvant	31 34	EC→Doc (DD) Doc→EC* (DD)	RDI of E 0·97, Doc 0·81 RDI of E 0·96, Doc 0·96‡
Cardoso et al (2001)[5]	Adjuvant	20 14	A→Doc (→CMF) Doc→A (→CMF)	RDI 100% for both drugs and for both groups
Earl et al (2009)[6]	Neoadjuvant	813 (total)	EC→Pac (±G) (DD) Pac (±G)→EC (DD)	pCR 15% pCR 20%†
Miller et al (2005)[7]	Neoadjuvant	35 34	A→Doc (DD) Doc→A* (DD)	pCR 8·6%; RDI of A 0·95, Doc 0·89 pCR 17·1%; RDI of A 0·94, Doc 0·97

A=doxorubicin. C=cyclophosphamide. Doc=docetaxel. DD=dose dense. RDI=relative dose intensity. F=fluorouracil. E=epirubicin. M=methotrexate. Pac=paclitaxel. G=gemcitabine. pCR=pathological complete response rate. *Leucocyte growth factors were administered in both groups of the study. †Statistically significant. ‡Grade 4 toxicity occurred in 18% of patients in the Doc→EC group versus 40% in the EC→Doc group.

Wildiers et al. Lancet oncology(2010) 11:219-220

Randomized Phase II Adjuvant Trial of Dose-Dense Docetaxel Before or After Doxorubicin Plus Cyclophosphamide in Axillary Node-Positive Breast Cancer

Shannon Puhalla, Ewa Mrozek, Donn Young, Susan Ottman, Anne McVey, Kari Kendra, Nancy J. Merriman, Mark Knapp, Taral Patel, Mark E. Thompson, James F. Maher, Timothy D. Moore, and Charles L. Shapiro

JCO(2008) 26:1691

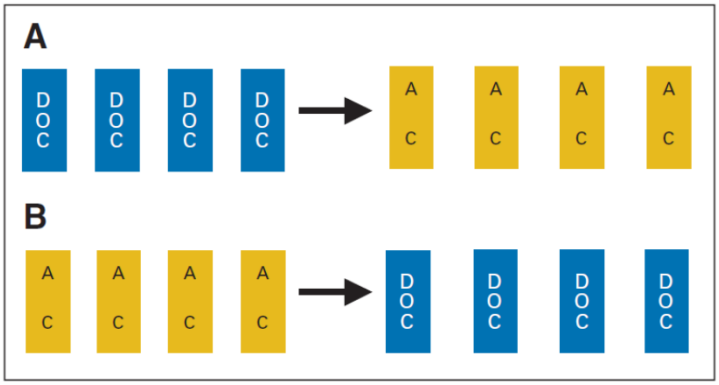


Fig 2. Treatment schema. Fifty-six patients with axillary node-positive, non-metastatic breast cancer were randomly assigned either to group A (n = 28; docetaxel [DOC] 75 mg/m^2 intravenously [IV] every 14 days for four cycles followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 [AC] IV every 14 days for four cycles); or to group B (n = 28; AC followed by DOC] at the identical doses and schedule). Pegfilgrastim 6 mg subcutaneous injection was administered in all treatment cycles.

JCO(2008) 26:1691

Table 1. Patient Characteristics

Characteristic	Group A No.	Group A %	Group B No.	Group B %	Total No.	Total %
Regimen	DOC→AC		AC→DOC			
No. of patients	28		28		56	
Median age, years	47		52		51	
Range	33-67		33-77		33-77	
ECOG PS	0		0		0	
Premenopausal	12	43	13	46	25	45
Histologic grade III	15	54	10	36	25	45
ER positive	18	64	23	82	41	73
Median No. positive axillary nodes	2		2		2	
Range	1-35		1-20		1-35	
Stage						
II	17	61	24	86	41	73
III	11	39	4	11	15	27
Mastectomy	19	68	19	68	38	68

Abbreviations: DOC, docetaxel; AC, doxorubicin and cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ER,

JCO(2008) 26:1691

Table 4. Dose Reductions, Delays, and RDI

Parameter	Group A No.	Group A %	Group B No.	Group B %
Regimen	DOC→AC		AC→DOC	
Cycles completed	219/224	98	210/224	94
DOC dose reduction	4/28	14	11/28	39
DOC dose delay	4/28	14	3/28	11
DOC reduction and delay	1/28	4	2/28	7
RDI				
DOC	0.96		0.82	
AC	0.95		0.98	

Abbreviations: RDI, relative dose intensity; DOC, docetaxel; AC, doxorubicin and cyclophosphamide.

JCO(2008) 26:1691

まとめ 1

- 術後補助化学療法に関して、タキサン系先行レジメンはアンスラサイクリン系先行レジメンと比較し、忍容性が高いことが示唆された。

Neo-tAnGo

A neoadjuvant study of sequential epirubicin + cyclophosphamide and paclitaxel ± gemcitabine in the treatment of high-risk early breast cancer

H. M. Earl[1,2,7], A. Vallier[3], L. Hiller[4], N. Fenwick[5], M. Iddawela[6], L. Hughes-Davies[7], E. Provenzano[2,7], K. McAdam[8], T. Hickish[9] and C. Caldas[6] for the Neo-tAnGo Investigators

1/University of Cambridge, Cambridge, UK; 2/National Institute of Health Research Cambridge Biomedical Research Centre, UK; 3/Cambridge Cancer Trials Centre, Cambridge, UK; 4/Warwick Medical School Clinical Trials Unit, University of Warwick, UK; 5/Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, UK; 6/Cancer Research UK, Cambridge Research Institute, Cambridge, UK; 7/Addenbrookes Hospital, Cambridge, UK; 8/Peterborough Hospital NHS Foundation Trust, Peterborough, UK; 9/Royal Bournemouth Hospital, Bournemouth, Hampshire, UK

Neo-tAnGo

Neoadjuvant Paclitaxel, Anthracycline, Gemcitabine & Cyclophosphamide

2009 ASCO

Neo-tAnGo Trial Design

Histologically confirmed invasive breast cancer
T2 tumour and above
Diameter ≥20mm
Suitable for neo-adjuvant chemotherapy

Stratification variables
Age: ≤ 50yrs; > 50yrs
ER status: negative; positive
Tumour size: ≤50mm; >50mm
Clinical involvement of axillary nodes: no; yes
Inflammatory / Locally advanced disease: no; yes

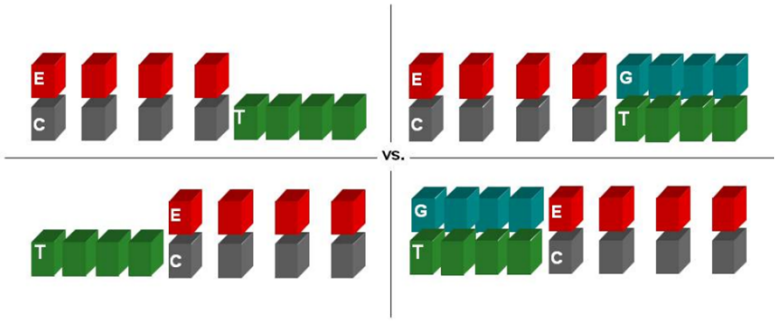
Randomisation (<4 wks from diagnostic biopsy)

EC → T | T → EC | EC → TG | TG → EC

2009 ASCO

Neo-tAnGo Treatment Schema

2 x 2 factorial design



Epirubicin 90mg/m² Cyclophosphamide 600mg/m² Q 21 days	Paclitaxel 175mg/m² Gemcitabine 2000mg/m² Q 14 days

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Stratification Variables: Component qn

%		EC & T (n=413)	EC & TG (n=415)
Age	≤50 years	63	63
	>50 years	37	37
ER Status	Negative	33	33
	Positive	67	67
Tumour size	≤50mm	80	79
	>50mm	20	21
Clinical involv. of ax nodes	No	50	50
	Yes	50	50
Inflammatory/locally adv	No	75	75
	Yes	25	25

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Treatment Toxicity

Severe toxicity incidences were as expected, with no differences of note between randomised treatments groups. However, for the individual regimens, higher incidences were noted for:

-neutropenia, sup thrombophleb, infection, nausea & fever on EC

-neurosensory toxicity, rash & acute hypersensitivity on T+-G

- transaminitis on TG

%pts with severe toxicity	EC→T		T→EC		EC→TG		TG→EC	
	EC	T	T	EC	EC	TG	TG	EC
Alopecia	95	94	88	96	93	98	93	96
Neutropenia	19	11	8	22	20	14	8	24
Sup thrombophleb	6	4	3	11	10	7	3	10
Infection	7	2	2	5	5	4	4	7
Fatigue	3	2	3	2	1	4	5	5
Muscle/joint pain	0	5	4	0	0	8	3	2
Vomiting	5	1	0	4	5	0	1	5
Nausea	2	1	0	5	6	1	0	4
Neurosensory	1	4	4	1	0	5	3	1
Transaminitis	0	0	1	1	1	5	5	1
Rash	0	2	2	0	0	1	6	0
Acute hypersens	0	1	1	0	0	2	5	0
Fever	2	1	0	1	1	0	1	3
Diarrhoea	0	0	0	1	1	1	1	2
Dyspnoea	1	1	0	1	0	0	1	1
Constipation	0	0	1	0	1	1	1	0
Anaemia	1	1	0	0	0	0	0	0
DVT	0	0	0	0	1	0	1	0
Cough	0	0	0	0	0	0	0	1
Stomatitis	0	0	1	0	0	0	0	0
Thrombocytopenia	0	0	0	1	0	0	0	0

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Primary endpoint: pCR rates

- A 2-reader review of pathology reports, blinded to treatment, was undertaken (812 pts)
- pCR defined as
  - pCR in all breast tumours AND
  - absence of disease in AxLNs in all breast tumours

Component qn	EC & T (n=404)	EC & TG (n=408)	p
pCR rate (95% CI)	17% (14-21)	17% (14-21)	0.98

Sequencing qn	EC→T±G (n=406)	T±G→EC (n=406)	p
pCR rate (95% CI)	15% (11-18)	20% (16-24)	0.03

Adjustment for stratification variables does not alter results
(Age, ER status, Tumour size, Nodal status, Inflammatory / Locally advanced disease)

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Conclusions

- The Neo-tAnGo results confirm those of the adjuvant tAnGo trial in terms of gemcitabine effect (ASCO 2008)
- The sequence of Taxol ± Gemcitabine - first has demonstrated a significant advantage in pCR compared with anthracycline-first sequencing

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まとめ 2

- 術前化学療法において、タキサン系先行レジメンはアンスラサイクリン系先行レジメンと比較し、より効果が高いことが示唆された。

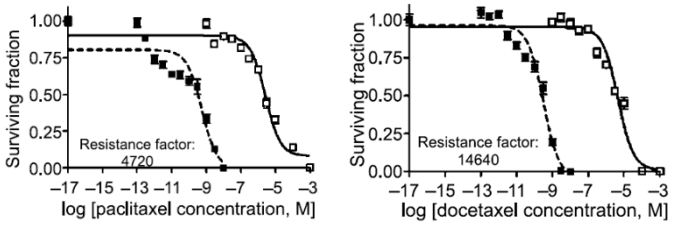
Cross-resistance studies of isogenic drug-resistant breast tumor cell lines support recent clinical evidence suggesting that sensitivity to paclitaxel may be strongly compromised by prior doxorubicin exposure

Baoqing Guo[1], David J. Villeneuve[1], Stacey L. Hembruff[2], Angie F. Kirwan[1], David E. Blais[3], Michel Bonin[4], and Amadeo M. Parissenti[1,2,3]
[1]*Tumor Biology Research Program, Northeastern Ontario Regional Cancer Centre;* [2]*Department of Biology,* [3]*Department of Chemistry and Biochemistry, Laurentian University;* [4]*Department of Pathology, Sudbury Regional Hospital, Sudbury, Ont., Canada*

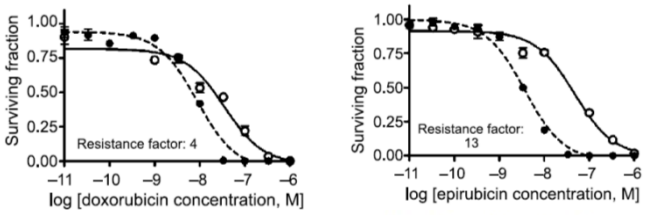
Breast Cancer Research and Treatment **85:** 31–51, 2004.

薬剤耐性

MCF7 Cells selected for resistance to doxorubicin

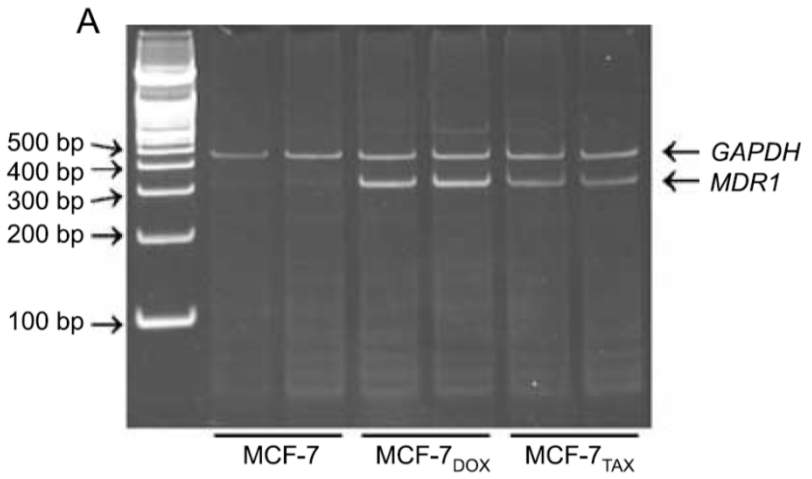


MCF7 Cells selected for resistance to paclitaxel



Breast Cancer Research and Treatment **85:** 31–51, 2004.

Expression of P-gp (MDR1) and GAPDH mRNA expression in MCF-7, MCF-7TAX, MCF-7DOX cells as measured by RT-PCR.



Breast Cancer Research and Treatment **85:** 31–51, 2004.

まとめ 3

- In vitroでドキソルビシン耐性乳癌培養細胞(MCF7)がパクリタキセルに示す耐性は、パクリタキセル耐性乳癌培養細胞がドキソルビシンに対して示す耐性と比較し1000倍以上の高値を認めた。

現在進行中のタキサン系薬剤先行のトライアル

- 術前化学療法: NSABP B-40

  DTX q3w*4cycles → ± Cape or Gem → AC*4cycles

  (±Bevacizmab)

- 術後化学療法: SOLD trial

  Trastuzumab (9 weeks) + DTX q3w*3cycles → FE75C*3cycles

  → ± Trastuzumab q3w(up to 51 weeks)

結語

- 術前/術後化学療法において、タキサン系先行レジメンは、アンスラサイクリン系先行レジメンと比較しより忍容性が高くより有効である可能性がある。