腫瘍学勉強会　⑤

2005年5月24日　(火曜日)

乳がん治療最近の話題
- ASCO2005 -

渡辺　亨

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http://www.oncoloplan.com

ASCO

American Society of Clinical Oncology(米国臨床腫瘍学会)の第41回年次総会が2005年5月13日から17日にフロリダ州オーランドで開催されました。がん治療に関する最新の情報が集まる最大の学会です。今年も約3万5000人が参加、日本からもたくさんの方が参加しました。観光旅行の口実に学会に参加する、というような間違った姿勢で臨む人はひとりもいません。みんな真剣です。

がん薬物療法研究のトレンド

大目標　治療を必要とする患者に最適な治療を副作用なく提供する。

治療を必要とする患者をどのように選ぶか？
→　治療が要らない患者に治療をしない。
→　明らかに病気のある人、病気が悪化する可能性のある人を選別する。

最適な治療は何か？
→　効果の出る可能性のある治療を選ぶ。

がん薬物療法のトレンド
非特異的治療から特異的治療へ

細胞毒性抗がん剤（アドリアシン、タキソテールなど）
は正常細胞でもがん細胞でも細胞分裂の盛んな細胞を軒並み攻撃する。

非特異的治療

分子標的薬剤（ゲフィチニブ、トラスツズマブなど）
は特定の分子に対して作用するがその分子に依存しない細胞には何の影響もない。

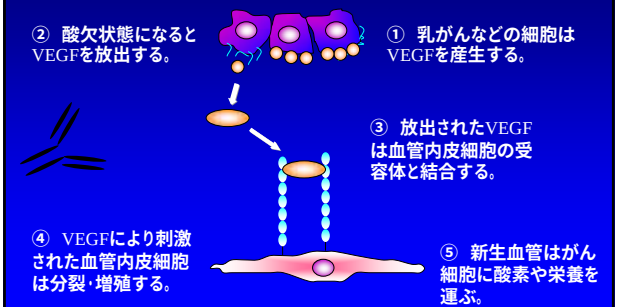
特異的治療

ASCO 2005
乳がん治療の話題

- bevacizumab / 転移性乳がん
- trastuzumab / 原発性乳がん

・・・mab ：**m**onoclonal **a**nti**b**ody

VEGF(Vascular Endothelial Growth Factor)と血管新生(angiogenesis)



E2100
A Randomized Phase III Trial of Paclitaxel versus Paclitaxel plus Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Kathy D Miller et al.
Indiana University Cancer Center

E2100 Rationale

- Tumor growth is dependent on angiogenesis
- Bevacizumab is a humanized monoclonal antibody directed against VEGF
  - recognizes all VEGF-A isoforms
  - Active in patients with refractory MBC
    - 9% response rate as monotherapy
    - Increases ORR but not PFS in combination with capecitabine
- Greater activity expected in less heavily pre-treated patients

E2100 Study Design

Stratify:
- DFS ≤ 24 mos. vs. > 24 mos.
- < 3 vs. ≥ 3 metastatic sites
- Adjuvant chemotherapy yes vs. no
- ER + vs. ER- vs. ER unknown

R → Paclitaxel + Bevacizumab
R → Paclitaxel

28-day cycle:
Paclitaxel 90 mg/m^2 D1,8 and 15
Bevacizumab 10 mg/kg D1 and 15

E2100 Key Eligibility Criteria

- Locally recurrent or metastatic breast cancer
  - HER2+ only if prior treatment with trastuzumab or contraindication
- No prior chemo regimens for MBC
  - Adjuvant taxane allowed if DFI > 12 months
- ECOG PS 0 or 1
- No anti-tumor therapy within 21 days
- No significant proteinuria (> 500 mg/24 hr)
- No therapeutic anticoagulation

E2100 Statistical Design - Efficacy

- Primary endpoint: Progression-Free Survival
  - 85% power for a 33% improvement
    - 6 vs. 8 months
  - One-sided type I error ≈ 2.5%
  - Required 650 eligible patients
- Final analysis after 546 PFS events
  - Interim analyses after 270 and 425 events
  - Asymmetric boundaries to stop early either for demonstrated benefit or for lack of benefit
  - O-Brien-Fleming boundaries and repeated confidence interval analyses at each interim

E2100 Statistical Design - Safety

- Type I event: Grade 4 hemorrhage or HTN
  - Acceptable rate: 1%
- Type II event: Grade 3/4 thrombosis or embolism
  - Acceptable rate: 5%

E2100 Current Analysis

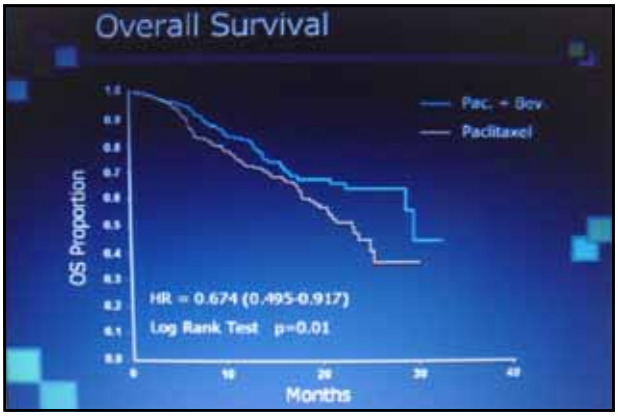
- Study activated Dec 21, 2001
- Closed March 24, 2004
  - 715 eligible patients
- First planned interim analysis
- Data cut-off February 9, 2005
- 355 events
  - progression - 291
  - Death without documented progression - 64

E2100 Patient Characteristics

	Paclitaxel (n=350)	Pac.+Bev. (n=365)
Treated	346	365
Median age	55 (27-85)	56 (29-84)
DFI ≤ 24 months	41%	41%
≥ 3 sites	29%	28%
Adjuvant chemo.	64%	65%
ER +	63%	64%

E2100 Response

	Paclitaxel	Pac.+Bev.
All patients (n)	316	330
Response rate	**14.2**	**28.2**
χ^2	p<0.0001	
Mesurable dis.(n)	250	236
Response rate	**16.4**	**34.3**
χ^2	p<0.0001	



E2100 Toxicity (1)
NCI-CTC Grade 3 and 4

	Paclitaxel (n=330)		Pac.+Bev. (n=342)	
	Grade 3	Grade 4	Grade 3	Grade 4
HTN*	0	0	13	0.3
Thromboembolic	0.3	0.9	1.2	0
Bleeding	0	0	0.6	0.3
Proteinuria**	0	0	0.9	1.5

NCI-CTC v3.0, worst per patient *p<0.0001; **p=0.004

E2100 Toxicity (2)
NCI-CTC Grade 3 and 4

	Paclitaxel (n=330)		Pac.+Bev. (n=342)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neuropathy*	13.6	0.6	19.9	0.6
Fatigue	2.7	0	4.7	0.3
Neutropenia	0	3	0.9	4.4
decreased LVEF	0	0	0.3	0

NCI-CTC v3.0, worst per patient *p=0.01

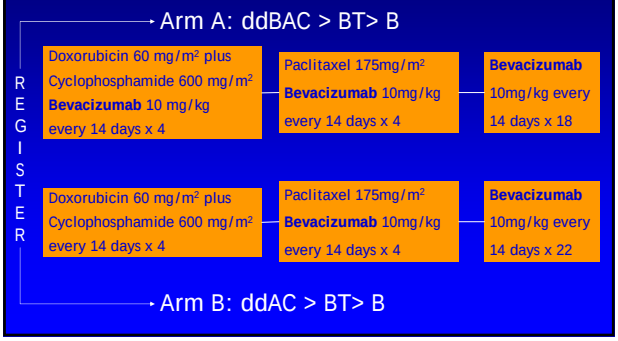
E2100 Ongoing Correlative Studies

- Quality of Life (FACT-B)
- Circulating markers
  - Serum VCAM-1
  - Urine VEGF
- Analysis of primary tumor samples
  - VEGF expression

E2100 Conclusions and Future Directions

- Addition of bevacizumab to paclitaxel
  - Significantly prolongs progression free survival
  - Increases objective response rate
  - Longer follow-up required to assess impact on OS
- Futher studies should
  - Explore the role of bevacizumab in the adjuvant setting
  - Develop methods to identify patients who are most likely to benefit from VEGF-targeted therapies

E2104 Adjuvant Pilot Trial

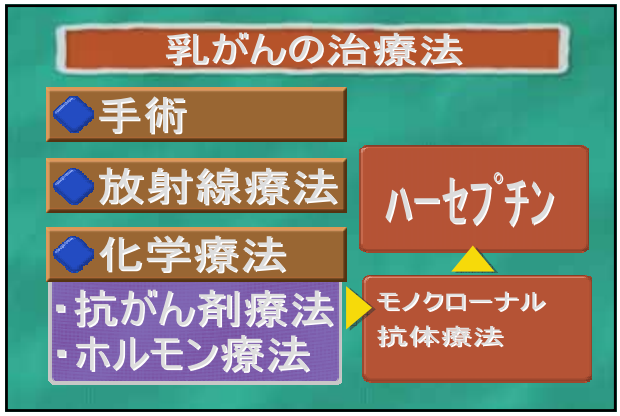


ASCO 2005
乳がん治療の話題

- bevacizumab / 転移性乳がん
- trastuzumab / 原発性乳がん

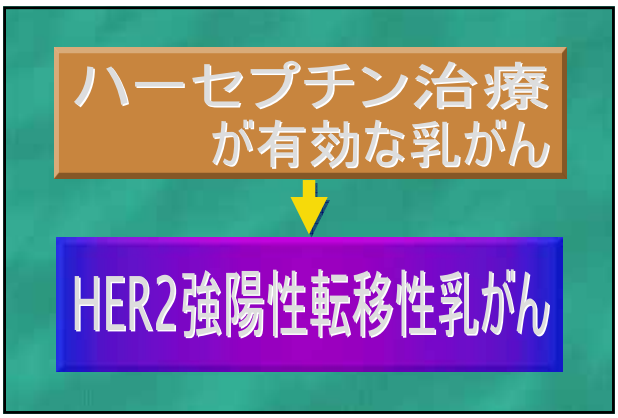
・・・mab ：**m**onoclonal **a**nti**b**ody

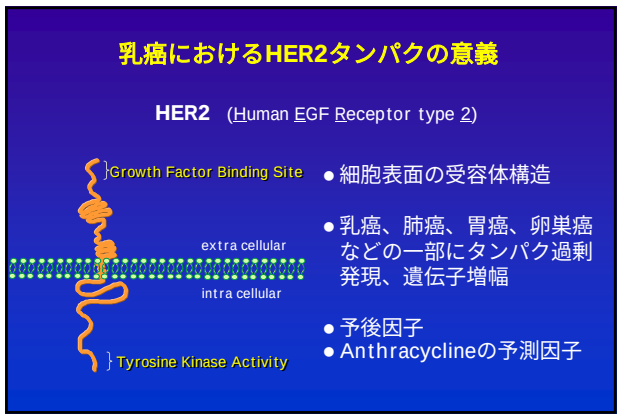

知っておきたい最新治療
乳がん


乳がんの治療法
手術
放射線療法
化学療法
・抗がん剤療法
・ホルモン療法
ハーセプチン
モノクローナル
抗体療法


乳がんの新しい治療法
従来の抗がん剤
モノクローナル
抗体療法


乳がんの新しい治療法
従来の抗がん剤
モノクローナル
抗体療法


ハーセプチン治療
が有効な乳がん
HER2強陽性転移性乳がん

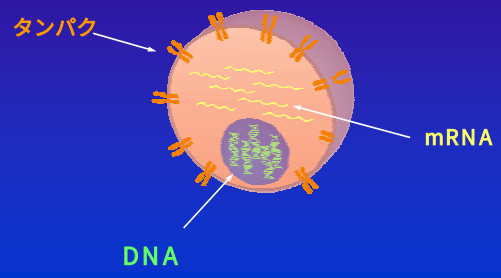

乳癌におけるHER2タンパクの意義
HER2 (Human EGF Receptor type 2)
Growth Factor Binding Site
extra cellular
intra cellular
Tyrosine Kinase Activity
● 細胞表面の受容体構造
● 乳癌、肺癌、胃癌、卵巣癌などの一部にタンパク過剰発現、遺伝子増幅
● 予後因子
● Anthracyclineの予測因子

乳癌におけるHER2

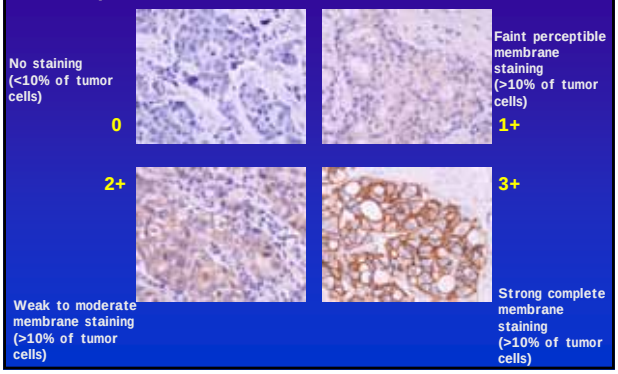
(Human EGF (Epidermal Growth Factor) Receptor type 2)

- HER2/*neu* 癌遺伝子
  - 17番目の染色体に存在、正常では２コピーあり
- HER2 タンパク
  - 細胞膜表面の受容体構造をもつ糖タンパク
- 20-30%の乳癌でDNA増幅またはタンパク過剰発現
- 乳癌の発育・増殖に深く関与

「HER2過剰発現」と「HER2/*neu*増幅」



HercepTest（ハーセプテスト）による免疫組織化学染色

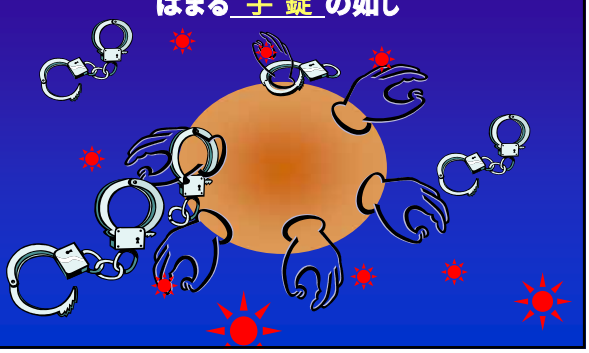


ハーセプチン® (トラスツズマブ)
ヒト化マウス抗HER2 モノクローナル抗体

- IgG (分子量 145 kd)
- 95%ヒト 5%マウス アミノ酸
- 第I相試験（1996-1997）
  British J Cancer **81**:1419, 1999
- 第II相試験（2000-2001）

HER2タンパクは個を取り込む手の如し

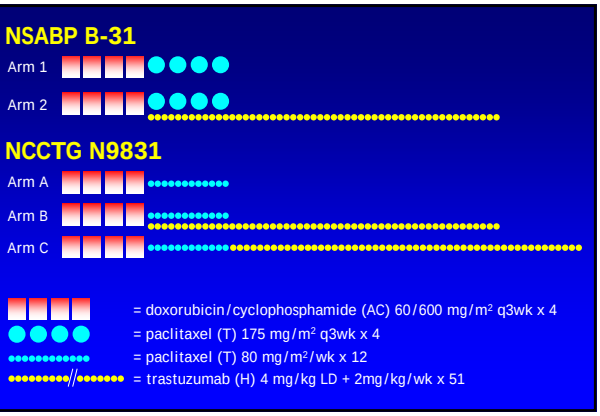
ハーセプチンはHER2タンパクに はまる 手 錠 の如し

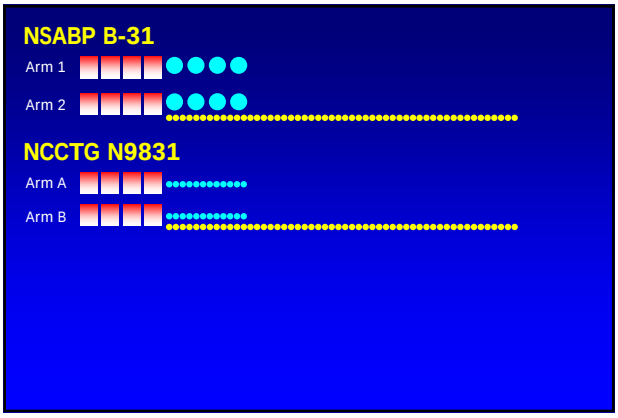


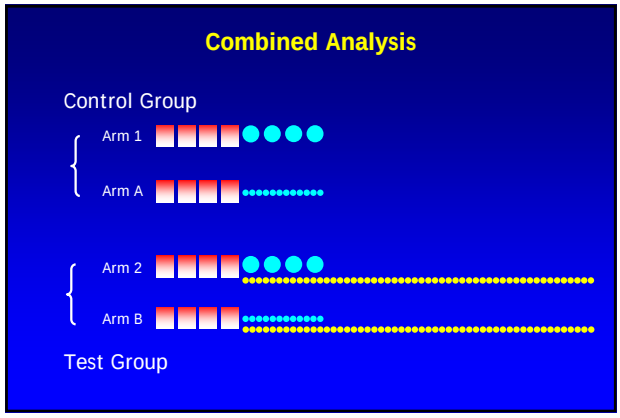
Doxorubicin and Cyclophosphamide
Followed by Paclitaxel
with or without Trastuzumab
as Adjuvant Therapy for Patients with
HER-2 Positive Operable Breast Cancer

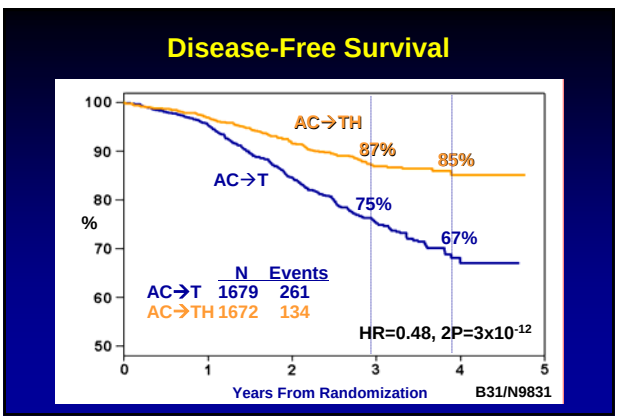
Combined Analysis of
NSABP-B31/NCCTG-N9831

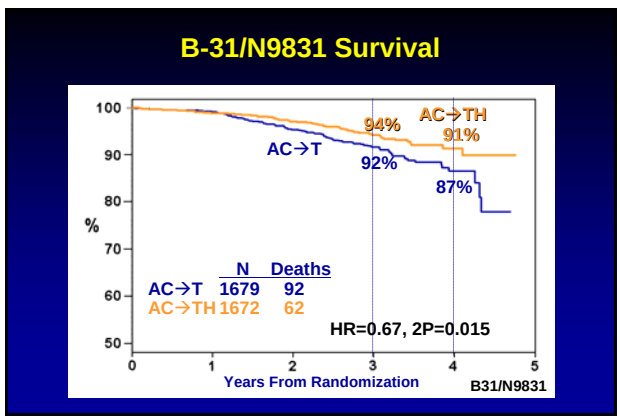
Romand EH et al.







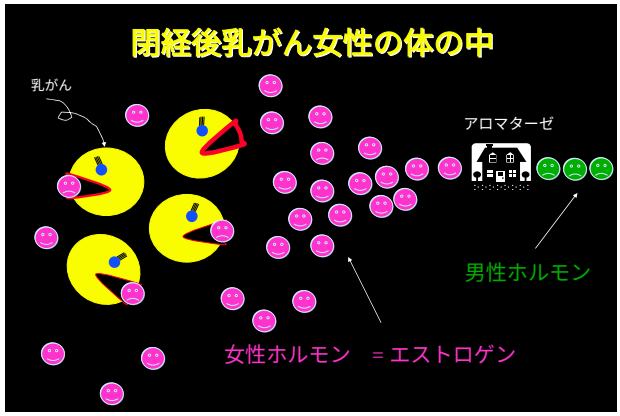




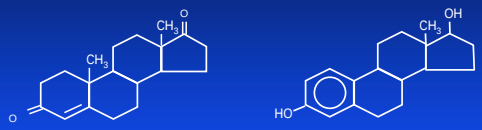
少し前の
乳がん治療の話題
- ホルモン療法のトレンド-

抗エストロゲン（タモキシフェン）　から
アロマターゼ阻害剤　へ

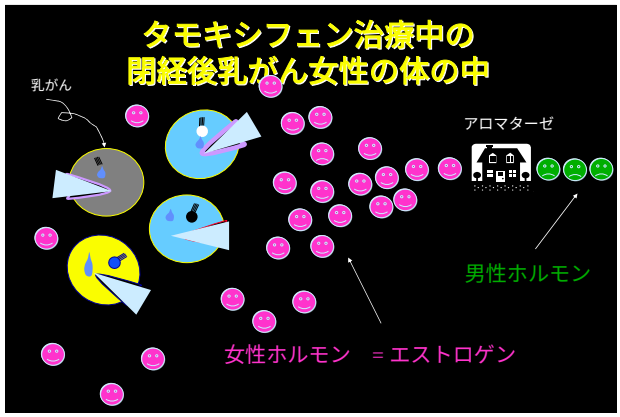
閉経後乳がん女性の体の中



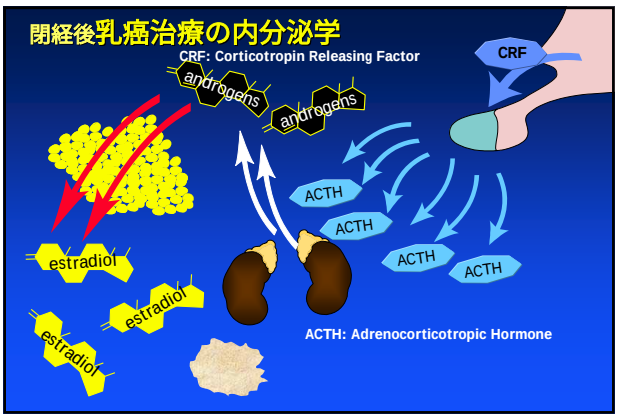
Androgen and Estrogen



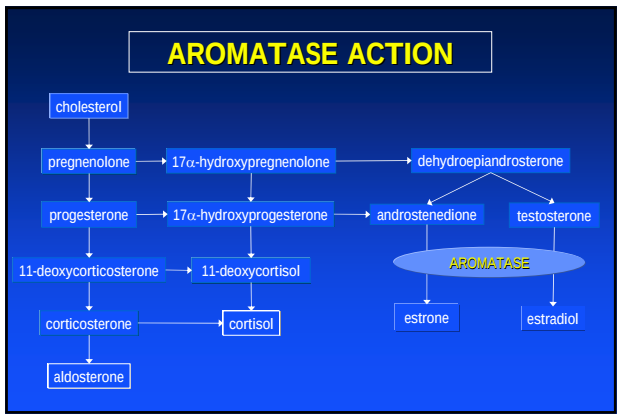
タモキシフェン治療中の
閉経後乳がん女性の体の中

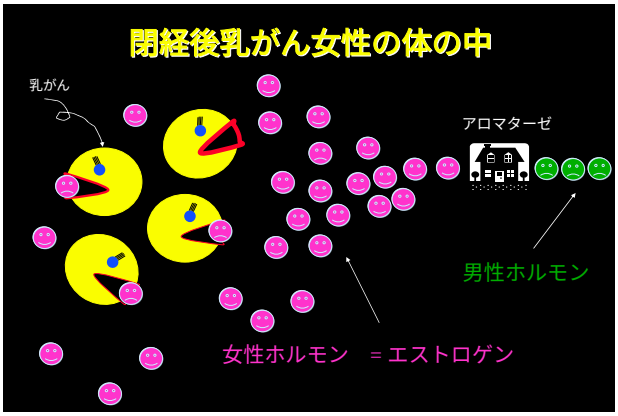


閉経後乳癌治療の内分泌学

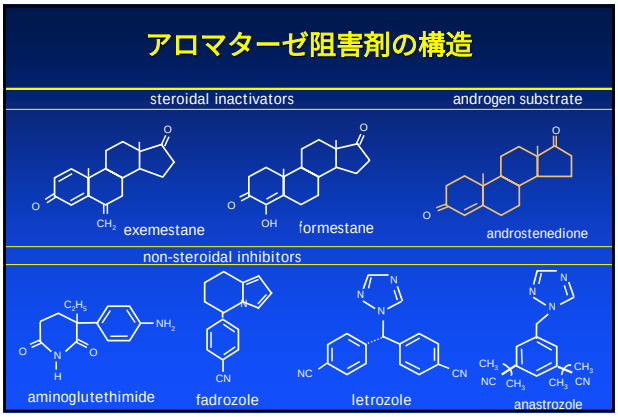


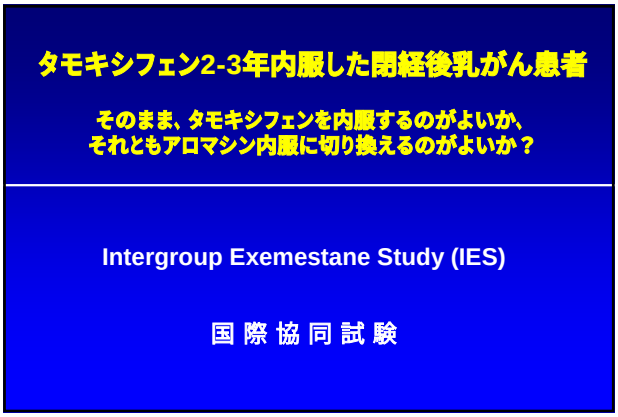
AROMATASE ACTION



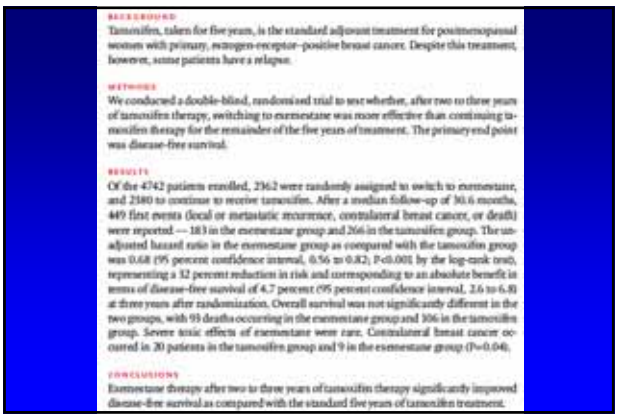

閉経後乳がん女性の体の中
乳がん
アロマターゼ
男性ホルモン
女性ホルモン　= エストロゲン


アロマターゼ阻害剤治療中の
閉経後乳がん女性の体の中
乳がん
アロマターゼ
男性ホルモン
女性ホルモン　= エストロゲン


アロマターゼ阻害剤の構造
steroidal inactivators
androgen substrate
exemestane
formestane
androstenedione
non-steroidal inhibitors
aminoglutethimide
fadrozole
letrozole
anastrozole


タモキシフェン2-3年内服した閉経後乳がん患者
そのまま、タモキシフェンを内服するのがよいか、
それともアロマシン内服に切り換えるのがよいか？
Intergroup Exemestane Study (IES)
国 際 協 同 試 験


The NEW ENGLAND JOURNAL of MEDICINE
A Randomized Trial of Exemestane after Two to Three Years of Tamoxifen Therapy in Postmenopausal Women with Primary Breast Cancer


BACKGROUND
Tamoxifen, taken for five years, is the standard adjuvant treatment for postmenopausal women with primary, estrogen-receptor–positive breast cancer. Despite this treatment, however, some patients have a relapse.
METHODS
We conducted a double-blind, randomized trial to test whether, after two to three years of tamoxifen therapy, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the five years of treatment. The primary end point was disease-free survival.
RESULTS
Of the 4742 patients enrolled, 2362 were randomly assigned to switch to exemestane, and 2380 to continue to receive tamoxifen. After a median follow-up of 30.6 months, 449 first events (local or metastatic recurrence, contralateral breast cancer, or death) were reported — 183 in the exemestane group and 266 in the tamoxifen group. The unadjusted hazard ratio in the exemestane group as compared with the tamoxifen group was 0.68 (95 percent confidence interval, 0.56 to 0.82; P<0.001 by the log-rank test), representing a 32 percent reduction in risk and corresponding to an absolute benefit in terms of disease-free survival of 4.7 percent (95 percent confidence interval, 2.6 to 6.8) at three years after randomization. Overall survival was not significantly different in the two groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group. Severe toxic effects of exemestane were rare. Contralateral breast cancer occurred in 20 patients in the tamoxifen group and 9 in the exemestane group (P=0.04).
CONCLUSIONS
Exemestane therapy after two to three years of tamoxifen therapy significantly improved disease-free survival as compared with the standard five years of tamoxifen treatment.

IES: Collaboration between 20 international trials groups

A total of 367 hospitals in 37 countries from 5 continents

Intergroup Exemestane Study

55才以上、過去2年以上生理のない女性乳癌
十分な初期治療（術前・術後化学療法、手術、放射線治療）
ER　陽性、不明

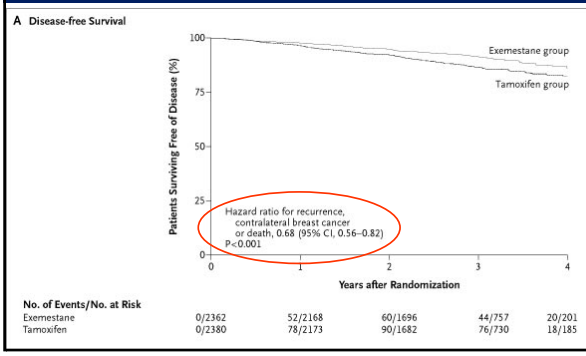
タモキシフェン 2-3年内服

ランダム化割付

合計
5年間

タモキシフェン 2-3年内服	エクセメスタン 2-3年内服
n = 2362	n = 2380

DISEASE-FREE SURVIVAL



次回の講義
2005年6月14日（火）

EBMと臨床試験
（evidenceを創る、伝える、使う）