Nut TDM en farmacogenetics van tamoxifen en endoxifen

11/3/2014

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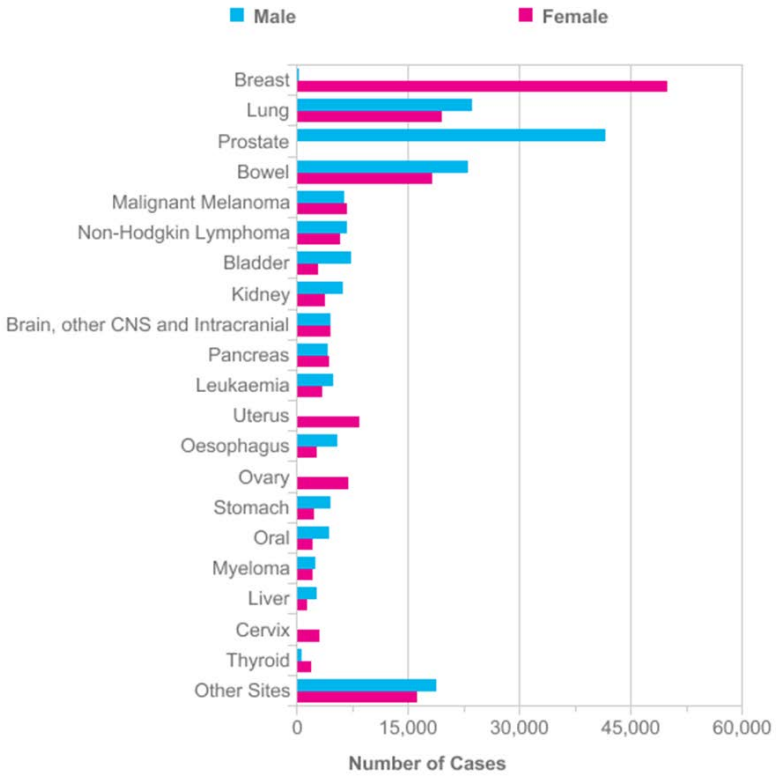
Overzicht

- Inleiding
- *CYP2D6* genotypering
  - concentratie
  - effectiviteit
- *CYP2D6* inhibitoren
- TDM
- Fenotypering
- Besluit & To Do

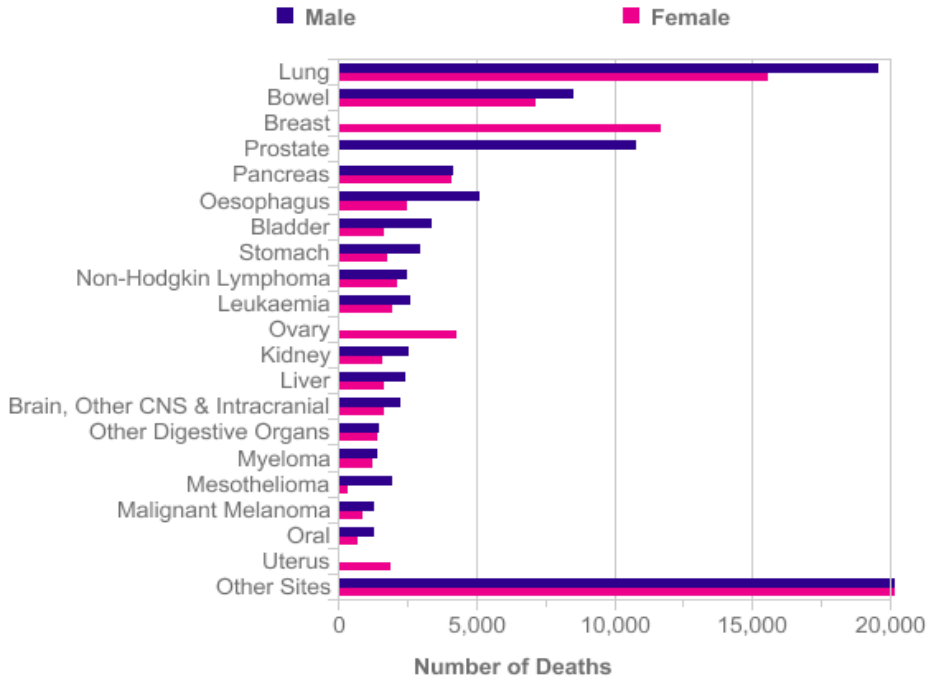
INLEIDING

Inleiding: borstca

The 20 Most Common Cancers in 2011



The 20 Most Common Causes of Cancer Death in 2011



Number of New Cases, UK

Inleiding: borstca

World cancer statistics: Breast cancer

This section lists the 50 countries with the highest breast cancer rates in the world.

Belgium has the highest rate of breast cancer in the world. The UK has the 11th highest breast cancer rate and every year 89.1 of every 100,000 women in the UK develop breast cancer.

Scientists estimate about 42% of breast cancer cases in the UK could be prevented through drinking less alcohol, being physically active and maintaining a healthy weight.

You can find out more by downloading our Reducing Your Risk of Breast Cancer publication.

Rank	Country	Cases per 100,000 women
1	Belgium	109.2
2	Denmark	101.1
3	France (Metropolitan)	99.7
4	The Netherlands	98.5
5	Israel	96.8
6	Iceland	95.5
7	Ireland	93.9
8	Uruguay	90.7
9	Switzerland	89.4
9	New Zealand	89.4
11	**UK**	**89.1**
12	Finland	86.3
12	Italy	86.3
14	Australia	84.8

World Cancer Research Fund

Inleiding: borstca

Behandeling borstca

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)®

Breast Cancer
Version 1.2014

- Chirurgie
- Radiotherapie
- Chemotherapie
- Gerichte therapie
- Hormonale therapie
  - Selectieve oestrogen-receptor modulatoren (SERM)
    - *Bv. tamoxifen*
  - Aromatase inhibitoren
    - *Bv. anastrozol, letrozol, exemestan*
  - Anti-oestrogenen
    - *Bv. fulvestrant*

Inleiding: borstca

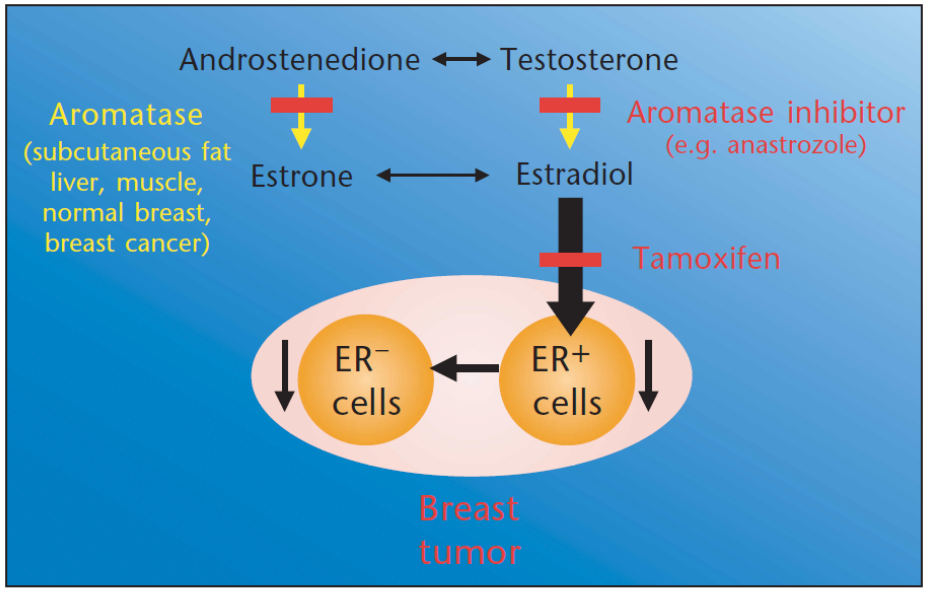


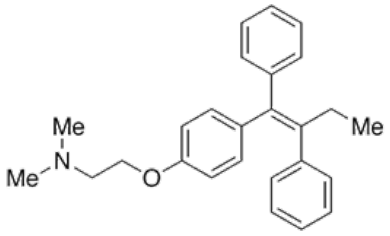
Fig. 1 Estrogen synthesis and the basic mechanisms of action of tamoxifen and aromatase inhibitors. Breast tumors most frequently present as a mixture of estrogen receptor (ER)–positive and estrogen receptor–negative cancer cells. The effects of the drugs may occur by direct antiproliferative mechanisms in estrogen receptor–positive cells or by paracrine influences of estrogen receptor–positive cells on neighboring estrogen receptor–negative cells. Tumors are complex lesions involving a stroma that includes fibroblasts, endothelial cells and inflammatory cells, which may influence the degree of clinical response seen.

M. Dowsett et al, Nature 2012, 8(12): 1341-1344

Inleiding: Tamoxifen

Tamoxifen

- Nolvadex®
- Pre- als postmenopauzele pt
- ER+ borsttumoren
- Selectieve Oestrogeen Receptor Modulator (SERM)
  - inhibitie oestrogeen effecten (borstweefsel)
  - oestrogene werking (bot, cardiovasculair, uterus)
- Nevenwerkingen
  - warmteopwellingen (3% - 80%), vochtretentie (32%), hyper-triglyceridemie, neurologische symptomen (19%), depressie (>2%)
- Toediening
  - PO, 20 mg/dag



Inleiding: Tamoxifen

Tamoxifen metabolisme

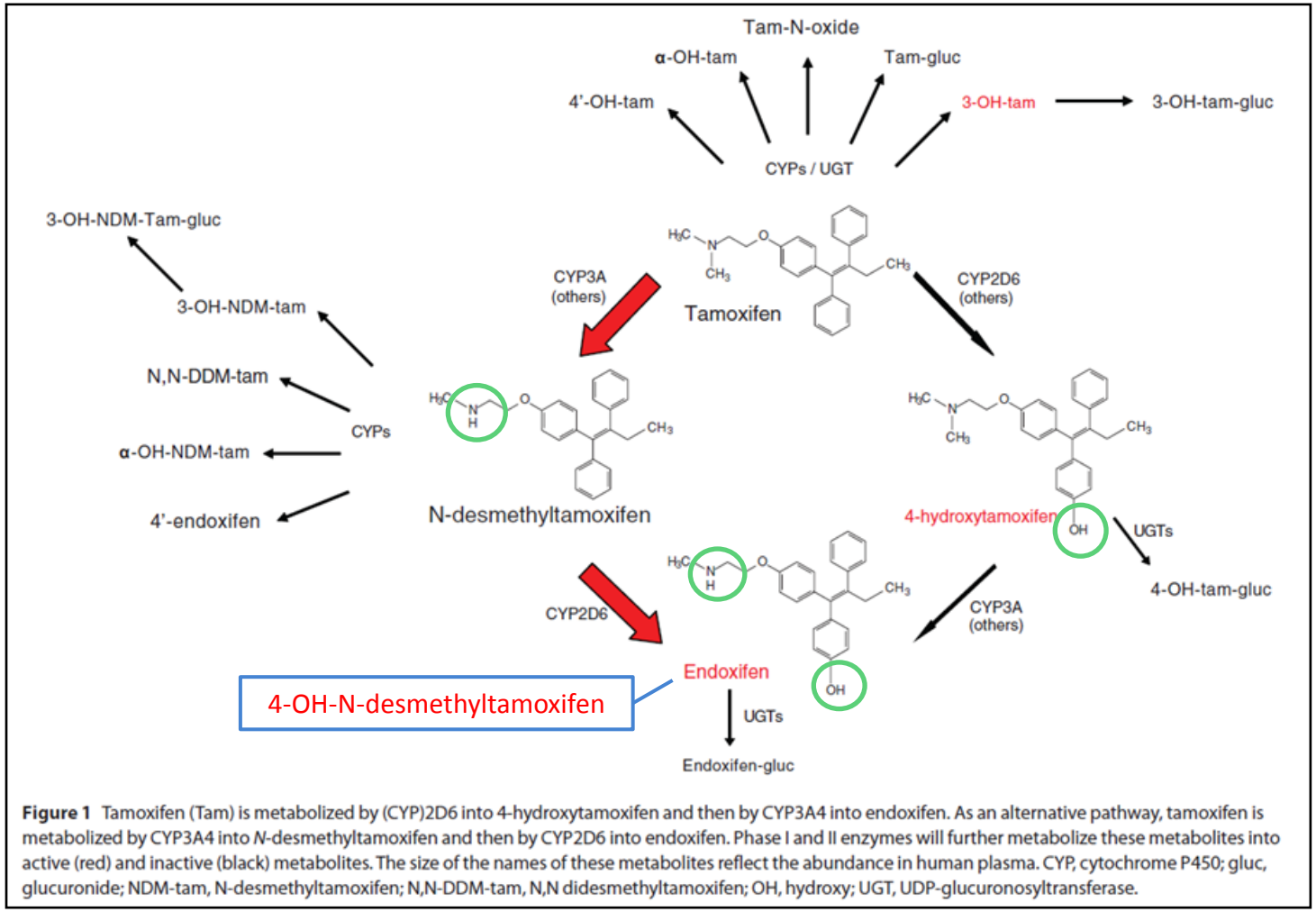


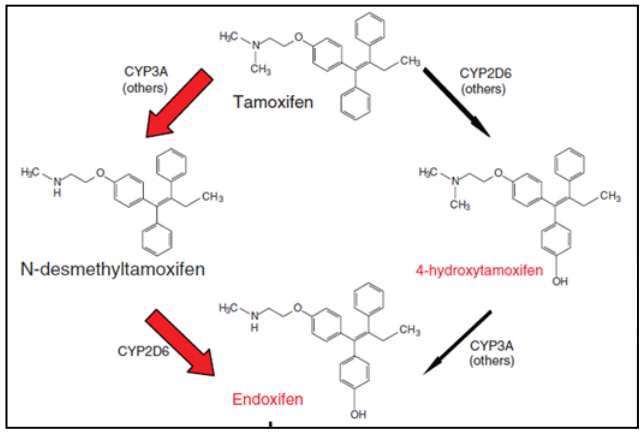
Figure 1 Tamoxifen (Tam) is metabolized by (CYP)2D6 into 4-hydroxytamoxifen and then by CYP3A4 into endoxifen. As an alternative pathway, tamoxifen is metabolized by CYP3A4 into *N*-desmethyltamoxifen and then by CYP2D6 into endoxifen. Phase I and II enzymes will further metabolize these metabolites into active (red) and inactive (black) metabolites. The size of the names of these metabolites reflect the abundance in human plasma. CYP, cytochrome P450; gluc, glucuronide; NDM-tam, N-desmethyltamoxifen; N,N-DDM-tam, N,N didesmethyltamoxifen; OH, hydroxy; UGT, UDP-glucuronosyltransferase.

[Binkhorst L. et al, Clinical pharmacology & therapeutics 2012]

Inleiding: Tamoxifen

Metabolisatie

- Tamoxifen (TM) = prodrug
- Metabolisatie
  - *CYP2D6*
  - *CYP3A4*
- Actieve metabolieten
  - 4-OH-N-desmethyltamoxifen = **endoxifen**
  - **4-OH-tamoxifen**



- **Affiniteit ER** endoxifen en 4-OH-tamoxifen [Mürdter et al, 2011]
  - 30-100x meer dan TM
- Endoxifen **plasma concentrations**
  - 5-10x hoger dan 4-OH-tamoxifen

→ Belangrijkste actieve metaboliet = endoxifen

Inleiding: Tamoxifen

Metabolisatie

- Sterke interindividuele farmacokinetiek

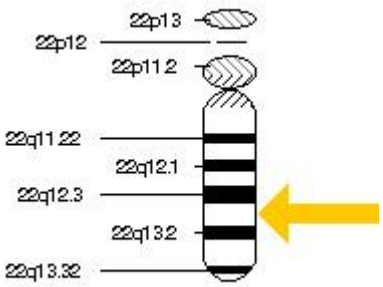
- *CYP2D6*
  - chromosoom 22
  - >80 SNPs
  - hoog polymorf gen

  → variante allelen

  → *copy number*

  ✓ genotype → fenotype
    - *poor metabolizer (PM)*
    - *intermediate metabolizer (IM)*
    - *extensive metabolizer (EM)*
    - *ultra-rapid metabolizer (UM)*

  ✓ prevalentie ≠ etnische groepen



http://ghr.nlm.nih.gov/gene/CYP2D6

Inleiding: *CYP2D6*

Frequenties van de meeste prevalente *CYP2D6* allelen in verschillende etnische groepen

CYP2D6 allele	Enzymatic activity	Caucasian (%)	African–American (%)	Asian (%)
*1	Functional	30–40	28–50	20–40
*2	Functional	20–35	10–80	9–20
*35	Functional	4–6	—	—
*3	Nonfunctional	1–4	0–0,5	0.8–1
*4	Nonfunctional	12–23	2–7	0.5–3
*5	Nonfunctional	1.5–7	0.5–6	4–6
*6	Nonfunctional	0.5–1	0	–
*4×n	Nonfunctional	0.1–0.5	0.9	–
*9	Reduced	0–3	0	3
*10	Reduced	2–8	3–8	40–70
*17	Reduced	0.1–0.3	10–30	0.5
*41	Reduced	8	–	–
*1×n	Increased	0.2–1	2–5	0.5
*2×n	Increased	0.5–1.5	1.5–2.5	0–1

[Ramón y Cajal T. et al, 2010]

Inleiding: *CYP2D6*

Classificatie *CYP2D6* fenotypes

	Metaboliser status	Activity	Genotype and CYP2D6 inhibitor status[a]
± 8%	Poor metabolisers	No activity	Two null alleles (*CYP2D6*3, *4, *5, *6, *11*), or one null allele and a strong inhibitor
± 20%	Intermediate metabolisers	Reduced activity	One null allele (*CYP2D6*3, *4, *5, *6, *11*) or one or two variants **9, *10, *17, *41*, and/or a moderate inhibitor
± 70%	Extensive metabolisers	Normal activity	Two 'wild-type' or normal alleles (*CYP2D6*1, *2, *35*) and no inhibitor
± 2%	Ultrarapid metabolisers	Excess activity	**1xN, *2xN, *35xN, *41xN* and no inhibitor

[a]Inhibitor staus refers to the coadministration of drugs that may affect CYP2D6 activity (see Table 2).
Abbreviation: *N*, number of gene duplication alleles.

[Stearns V. et al, 2008]

Inleiding: *CYP2D6*

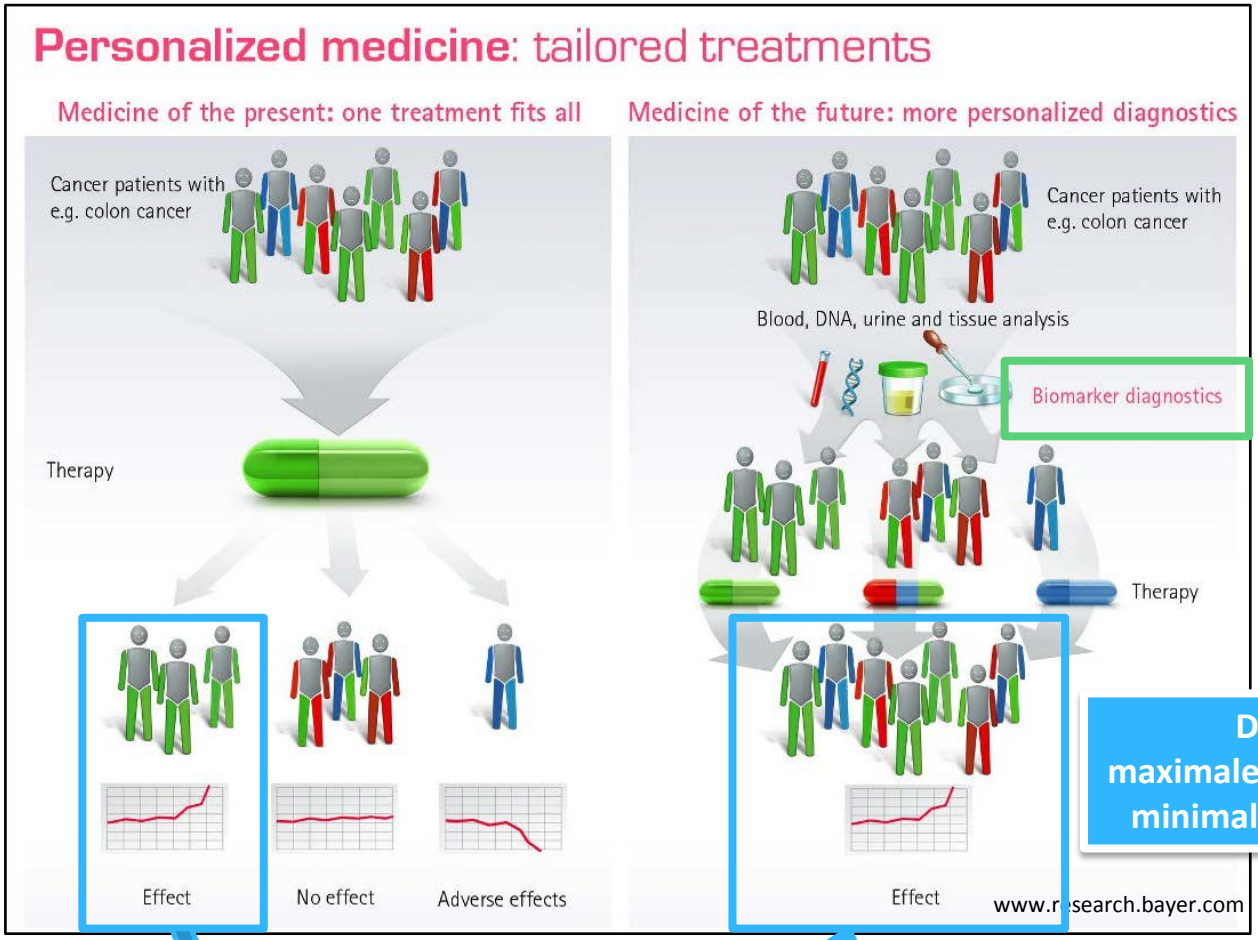
Table 1 Summary of *CYP2D6* variants and alleles detected by three commercial platforms

Allele	Protein effect	Luminex xTag V3	Roche Amplichip	Autogenomics INFINITI
**1*	F	Presumed	Presumed	Presumed
**2*	F	**–1584G**, 1661G>C, **2850C>T**, 4180G>C	**–1584G**, 1039C>T, 1661G>C, **2850C>T**, **4180G>C**	**2850C>T**
**3*	NF	**2549delA**	**2549delA**	**2549delA**
**4*	NF	100C>T, 1661G>C, **1846G>A**, 4180G>C	100C>T, 1039C>T, 1661G>C, **1846G>A**, 2850C>T, 4180G>C	**1846G>A**
**5*	NF	Deletion	Deletion	Deletion
**6*	NF	**1707delT**	**1707delT**, 1976G>A, 4180G>C	**1707delT**
**7*	NF	**2935A>C**	**2935A>C**	**2935A>C**
**8*	NF	1661G>C, **1758G>T**, 2850C>T, 4180G>C	1661G>C, **1758G>T**, 2850C>T, 4180G>C	**1758G>T**
**9*	DF	**2613–2615delAGA**	**2613–2615delAGA**	**2615_7delAAG**
**10*	DF	**100C>T**, 1661G>C, 4180G>C	**100C>T**, 1039C>T, 1661G>C, 4180G>C	**100C>T**
**11*	NF	**883G>C**, 1661G>C, 2850C>T, 4180G>C	**883G>C**, 1661G>C, 2850C>T, 4180G>C	Not tested
**12*	NF	**124G>A**, 1661G>C, 2850C>T, 4180G>C	Not tested	**124G>A**
**14*	NF	**1758G>A**, 2850C>T, 4180G>C	Not tested	**1758G>A**
**15*	NF	**138insT**	**138insT**	Not tested
**17*	DF	**1023C>T**, 1661G>C, 2850C>T, 4180G>C	**1023C>T**, 1661G>C, 2850C>T, 4180G>C	1023C>T
**19*	NF	Not tested	1661G>C, 2539-**2542delAACT**, 2850C>T, 4180G>C	Not tested
**20*	NF	Not tested	1661G>C, **1973insG**, 1978C>T, 1979T>C, 2850C>T, 4180G>C	Not tested
**29*	DF	**1659G>A**, 1661G>C, 2850C>T, **3183G>A**, 4180G>C	**1659G>A**, 1661G>C, 2850C>T, **3183G>A**, 4180G>C	1659G>A
**35*	F	–1584C, **31G>A**, 1661G>C, 2850C>T, 4180G>C	–1584C, **31G>A**, 1661G>C, 2850C>T, 4180G>C	Not tested
**36*	NF	Not tested	100C>T, 1039C>T, 1661G>C, 4180G>C, gene conversion to CYP2D7 in exon 9	Not tested
**40*	NF	Not tested	**1023C>T**, 1661G>C, **1863ins(TTT CGC CCC)2**, 2850C>T, 4180G>C	Not tested
**41*	DF	1661G>C, 2850C>T, **2988G>A**, 4180G>C	**–1584C**, 1661G>C, **2850C>T, 4180G>C**	2988G>A
Duplication	IF			

Nucleotide changes in bold define the allele.
DF, decreased function; F, functional; IF, increased function; NF, nonfunctional.

[Lyon et al., 2012]

Inleiding: gepersonaliseerde GK



DOEL
maximale effectiviteit
minimale toxiciteit

"the right patient, with the right drug, at the right dose, at the right time"

Questions

- Verband *CYP2D6* genotype en tamoxifen/endoxifen concentratie?
- Verband *CYP2D6* genotype en klinische outcome tamoxifen behandeling?
- Plaats TDM tamoxifen/endoxifen?

CYP2D6 GENOTYPERING

concentratie

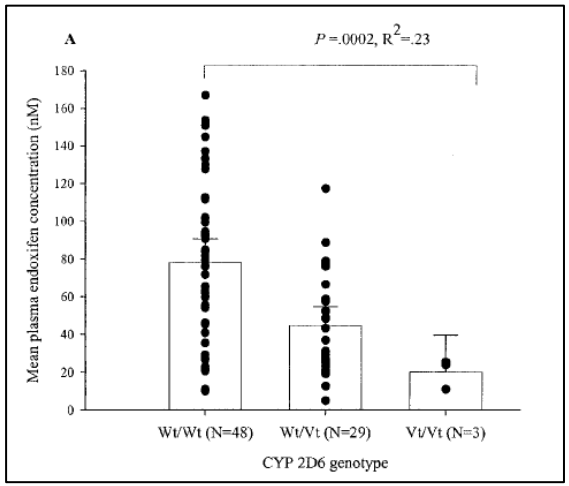
klinische effectiviteit

CYP2D6 vs. concentratie

Jin et al., 2005 (n=80)

CYP2D6 genotype – gem. $[endoxifen]_{pl}$ (95% CI) (P<0.001)

- Wt/Wt: 78.0 nM (65.9-90.1)
- Wt/Vt: 43.1 nM (33.3-52.9)
- Vt/Vt: 20.0 nM (11.1-28.9)



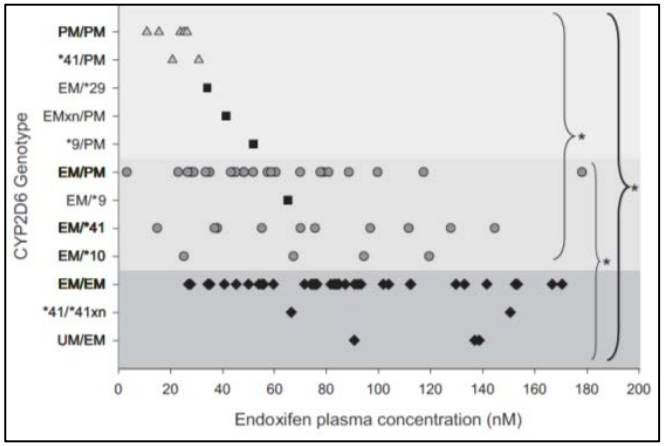
Verband CYP2D6 genotype en gelijktijdig gebruik van CYP2D6 inhibitoren op plasma endoxifen concentraties [Jin et al., 2005]
Punten: individuele plasma concentraties, error bars: 95% CI.

Borges et al., 2006 (n=158)

endoxifen/NDM plasma ratio (P<0.001)

- 0 functioneel allel: 0.04 ± 0.02
- 1 functioneel allel: 0.08 ± 0.04
- ≥2 actieve allelen: 0.15 ± 0.09

CYP2D6 genotype vs. $[endoxifen]_{pl}$



Effect CYP2D6 genotype op endoxifen plasma concentraties (nM) 4 mnd tamoxifen en geen concomitant gebruikt van CYP2D6 inh. [Borges et al., 2006]

CYP2D6 vs. concentratie

Madlensky et al., 2011 (n=1370)

CYP2D6 phenotype		Concentration (ng/ml) Endoxifen	Tamoxifen	4OH-tam	ND-tam
Ultrarapid metabolizer	Mean	**22.8**	**143.4**	**2.7**	**230.8**
N = 27	SD	11.3	58.4	1.2	71.1
	Median	24.5	137.0	2.7	226.0
Extensive metabolizer	Mean	**15.9**	**136.4**	**2.3**	**242.1**
N = 1,097	SD	9.2	64.3	1.1	95.3
	Median	14.3	127.0	2.1	230.0
Intermediate metabolizer	Mean	**8.1**	**142.9**	**1.7**	**295.7**
N = 164	SD	4.9	70.8	0.8	112.6
	Median	6.7	134.0	1.6	286.0
Poor metabolizer	Mean	**5.6**	**142.3**	**1.7**	**312.7**
N = 82	SD	3.8	63.1	0.9	114.2
	Median	4.7	140.5	1.5	291.5
ANOVA F statistic		77.1	0.69	20.6	25.3
P		<0.001	0.55	<0.001	<0.001

Tamoxifen en metabolieten concentraties (ng/mL) vs.CYP2D6 fenotypes [Madlensky et al., 2011]

Mürdter et al., 2011 (n=236)

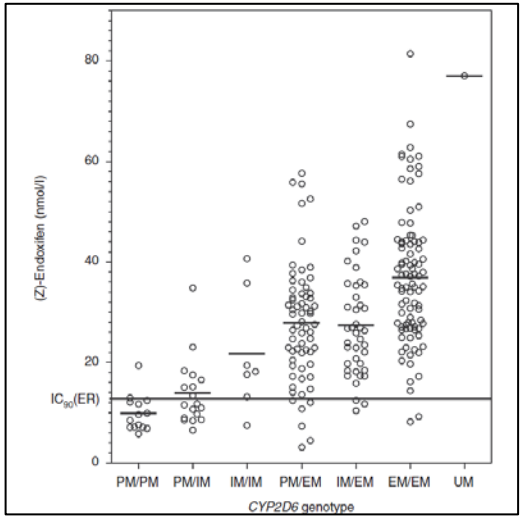
correlatie (Z)-endoxifen gen-plasma concentratie ($P < 10^{-16}$)

- PM/PM: 9.9 ± 3.6 nmol/L
- EM/EM: 36.9 ± 13.4 nmol/L
- EM/UM: 77 nmol/L

(Z)-endoxifen plasmaconcentratie tov IC90

- PM/PM: 93% $[(Z)\text{-endoxifen}]_{pl}$ <IC90
- EM/EM: >99% $[(Z)\text{-endoxifen}]_{pl}$ >IC90

CYP2D6 genotype geassoiceerde (Z)-$[endoxifen]_{pl}$ levels en ER-inhiberende act. [Mürdter et al., 2011]



CYP2D6 vs. concentratie

Besluit

- Associatie *CYP2D6* genotype / fenotype en metabolisatie van tamoxifen
- Minder / niet-functioneel allel

  → lagere gemiddelde endoxifen plasma concentraties

CYP2D6 vs. effectiviteit

Claim

The Food and Drug Administration recommended an update in the tamoxifen package insert in 2006 to reflect the increased risk of breast cancer recurrence in postmenopausal ER+ patients who are CYP2D6 poor metabolizers. This recommendation, however, was based on only a few studies at that time. Whether and how to implement CYP2D6 genotyping in daily practice was not exemplified. [www.fda.org]

CYP2D6 vs. effectiviteit

Trials

- Goetz et al., 2005 (n=223)

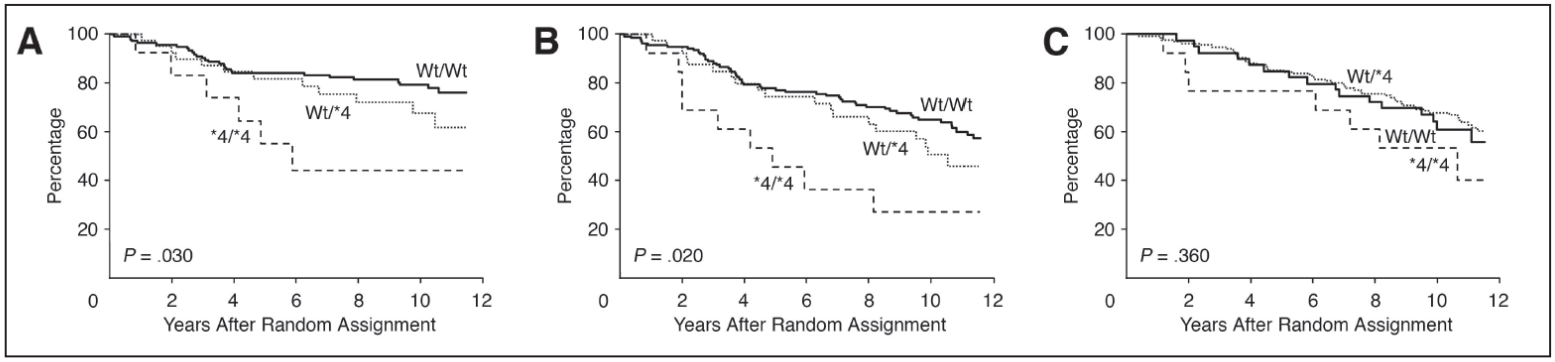


Fig 2. Kaplan-Meier estimates of (A) relapse-free time, (B) disease-free survival, and (C) overall survival for patients with the CYP2D6*4 genotype.

Table 3. Unadjusted and Adjusted Hazard Ratios and Corresponding 95% CI and *P* Values Comparing Patients With the CYP2D6*4/*4 Genotype With the wt/wt or *4/wt Genotypes

	Unadjusted			Adjusted*		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Relapse-free time	2.71	1.15 to 6.41	.023	1.85	0.76 to 4.52	.176
Disease-free survival	2.44	1.22 to 4.90	.012	1.86	0.91 to 3.82	.089
Overall survival	1.73	0.79 to 3.76	.169	1.12	0.50 to 2.50	.780

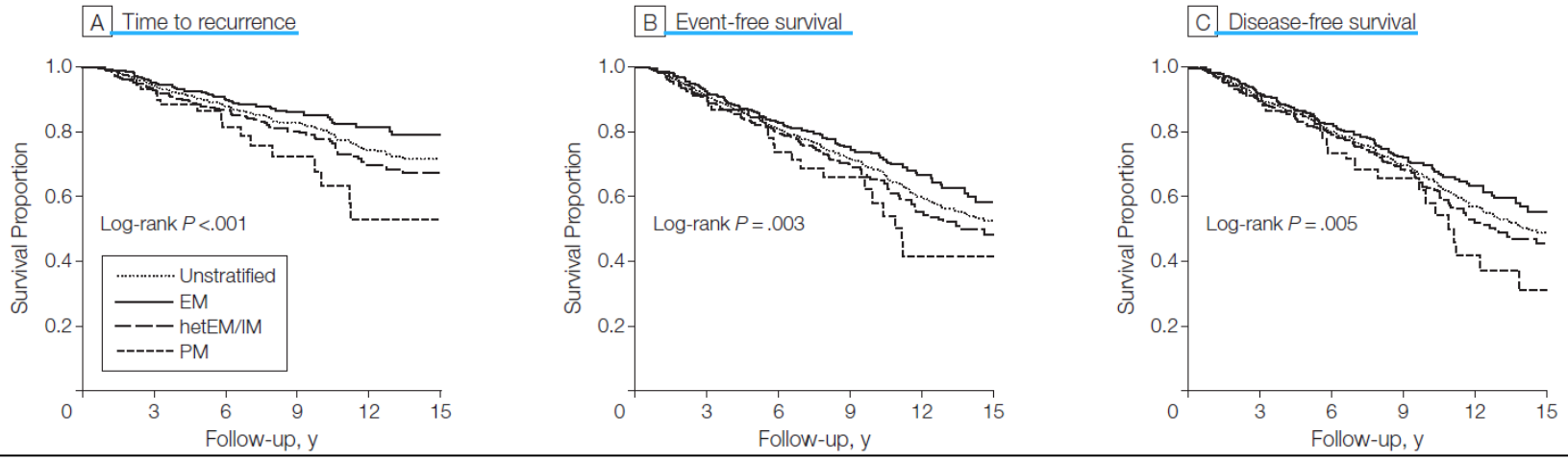
CYP2D6 vs. effectiviteit

Trials

- Schroth et al., 2009
  - DNA (tumor weefsel of bloed)
  - genotype *CYP2D6*: verminderde (*10,*41), geen (*3,*4,*5) enzymatische activiteit

    → extensive (n=609), heterozygous extensive/intermediate (n=637), poor (n=79) met.

Figure 1. Kaplan-Meier Estimates of Time to Recurrence, Event-Free Survival, and Disease-Free Survival



CYP2D6 vs. effectiviteit

Reviews

- **Stearns et al., 2008** - 9 studies
  - *CYP2D6* null-allelen slechtere prognose in vergelijking met 1 / 2 normale allelen
  - data studies niet consistent

- **Seruga et al., 2010** - 10 studies
  - niet-significante trend in de richting van toegenomen risico voor herval en risico op overlijden verminderde *CYP2D6* functionaliteit
    - HR van 1.41 (95% CI 0.94-2.10, P=0.08) en HR van 1.25 (95% CI 0.93-1.67, P=0.14) respectievelijk

- **Health Technology Assessment, Fleeman et al., 2011**
  - niet mogelijk om routine *CYP2D6* genotypering in klinische praktijk aan te bevelen

- **Province en Goetz et al., 2013**
  - strenge inclusie criteria (postmenopauzale vrouwen met ER+ borstca, 20 mg TM/d, 5 jaar): significant verband *CYP2D6* PM status en slechtere IDFS (HR 1.25, 95% CI 1.06-1.47, P=0.009)
  - niet voldaan aan deze strikte inclusie criteria: invloed van de *CYP2D6* status niet statistisch significant

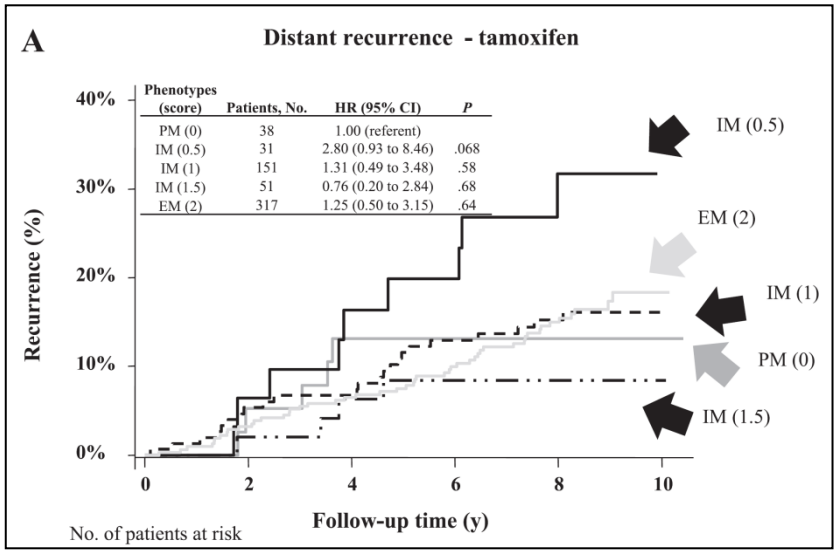
- **Lum et al., 2013** - 25 studies
  - tot nu toe onvoldoende evidentie aanbeveling *CYP2D6* genotypering bij tamoxifen therapie

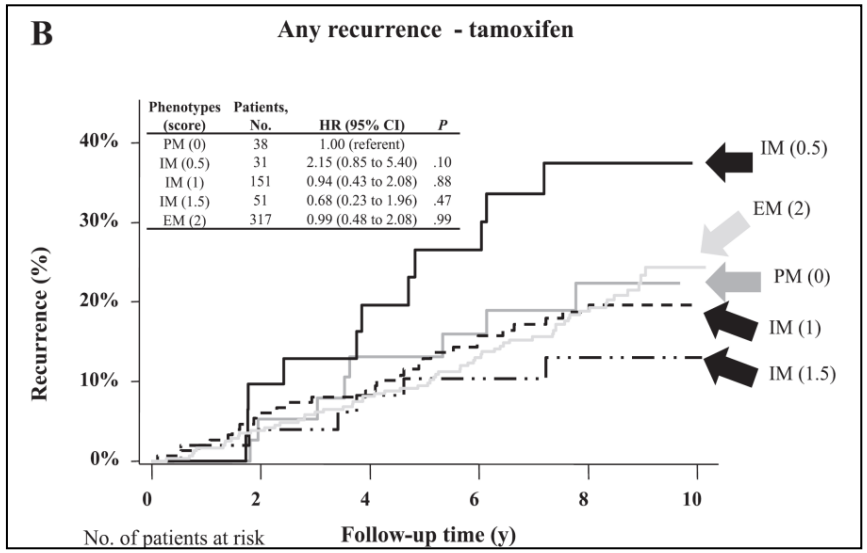
- **Zeng et al., 2013 -** 20 studies
  - “loss of function” *CYP2D6* allelen geassocieerd met een slechtere DFS in Aziatische pop.

CYP2D6 vs. effectiviteit

2 recente prospectieve studies

- **ATAC Trial (n=588)**
  - Arimidex, Tamoxifen, Alone or in Combination [Rae et al., 2012]

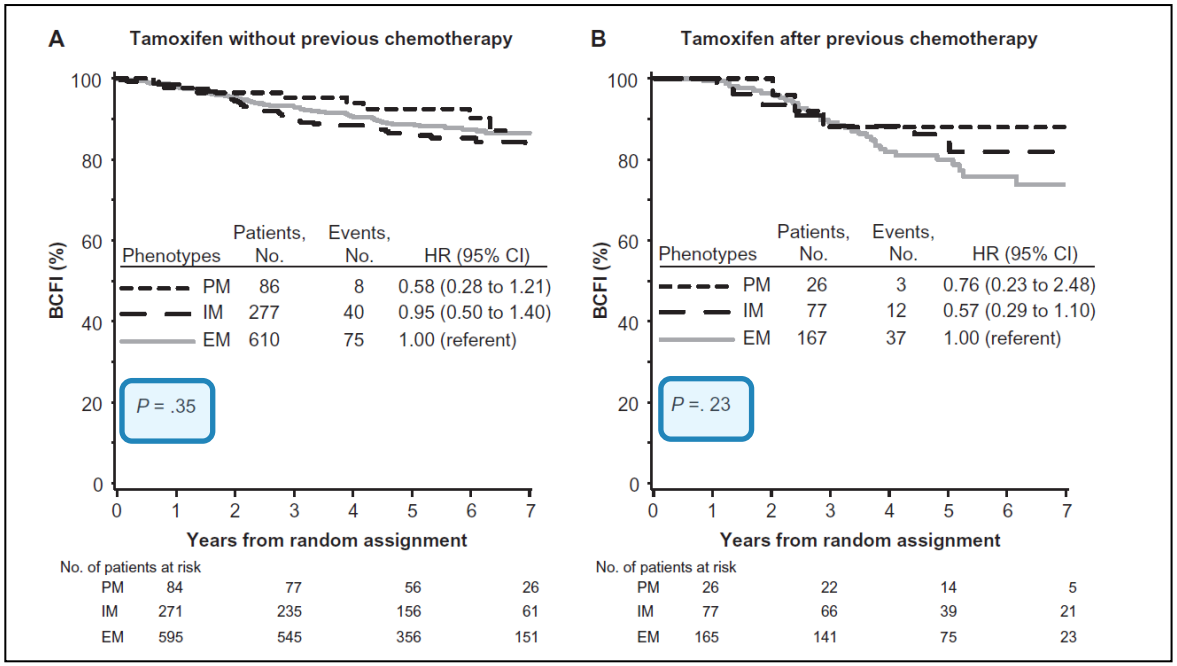




- **BIG 1-98 Trial (n=1243)**

CYP2D6 vs. effectiviteit

- **ATAC Trial (n=588)**
- **BIG 1-98 Trial (n=1243)**
  - Breast International Group 1-98 [Regan et al., 2012]
  - Postmenopauzale pt, borstca vrije periode (BCFI)



CYP2D6 vs. effectiviteit

- **ATAC Trial (n=588)**
- **BIG 1-98 Trial (n=1243)**

Geen significant verband tussen *CYP2D6* genotype en klinische outcome tamoxifen behandeling

CYP2D6 vs. effectiviteit

- Commentaar ATAC en BIG 1-98
  - BIG 1-98 trial
    - Geen Hardy-Weinberg evenwicht
      - frequentie *CYP2D6*4* allelen
      - 30.5% heterozygoten → echter beschreven frequentie = 19.7%
    - Tumorweefsel als bron DNA
  - ATAC trial
    - Slechts 19% van geïncludeerde patiënten genotypering beschikbaar (588 van 3116 pt)
      - studiepopulatie niet representatief voor originele populatie
      - mogelijk bias: alleen pt uit UK
    - Tumorweefsel als bron DNA

CYP2D6 vs. effectiviteit

Bemerkingen (1)

- ✓ Fenotypes
  - geen consensus definities *CYP2D6* metabolisatiefenotypes
  - gepoolde (bv. pool IM + PM) vs. niet-gepoolde resultaten

- ✓ Studieopzet
  - patiëntenpopulatie (pre- vs. postmenopauzale, etnische origine, primair vs. gemetastaseerd borstca, …)

- ✓ Genotypering
  - genotypering van *CYP2D6* is moeilijk door het grote aantal polymorfismen
  - studie van verschillende polymorfismen
  - bron DNA
    - bloed vs tumorweefsel (*fresh-frozen weefsel -formalin-fixed paraffin-embedded*)
    - DNA materiaal uit tumorweefsel: 'fouten' door *'loss of heterozygosity'* door somatische mutaties - locus 22q13 >25% van de borsttumoren 'aangetast'

CYP2D6 vs. effectiviteit

Bemerkingen (2)

- ✓ Complex metabolisme
  - klinische respons tamoxifen behandeling = resultaat zijn van een gecombineerd effect van verschillende metabolieten
    - eigen plasmaconcentratie, affiniteit voor ER en een agonist/antagonist effect

- ✓ *CYP2D6* inhibitoren
  - gebruik?
  - registratie?
  - evaluatie?

- ✓ Compliance tamoxifen behandeling
  - Murphy et al., 2012
    - 15-20% onderbreken in het eerste jaar
    - 31-60% beëindigen op het einde van de 5 jaar behandeling
  - Chlebowski et al., 2006
    - 20-46% vroegtijdige beëindiging

CYP2D6 vs. effectiviteit

Besluit

- *CYP2D6* polymorfisme kan slechts 38% van de interindividuele variabiliteit in endoxifen plasma concentraties verklaren [Mürdter et al., 2011]
- trend naar invloed genotype op verminderde klinische outcome
- voornamelijk retrospectieve studies
- echter discordante resultaten
- voorlopig geen evidentie voor routinematige *CYP2D6* analyse

- ➢ grote, welomschreven, prospectieve studies met controle compliance en registratie *CYP2D6* inhibitoren vereist
- ➢ opstellen richtlijnen
- ➢ vgl nieuwe richtlijnen met huidige gang van zaken

CYP2D6 INHIBITOREN

CYP2D6 inhibitoren

+/- 25-30% van de borstkanker patiënten met tamoxifen behandeling nemen SSRI antidepressiva owv nevenwerkingen tamoxifen [Jin et al., 2005; Dusetzina et al., 2013]

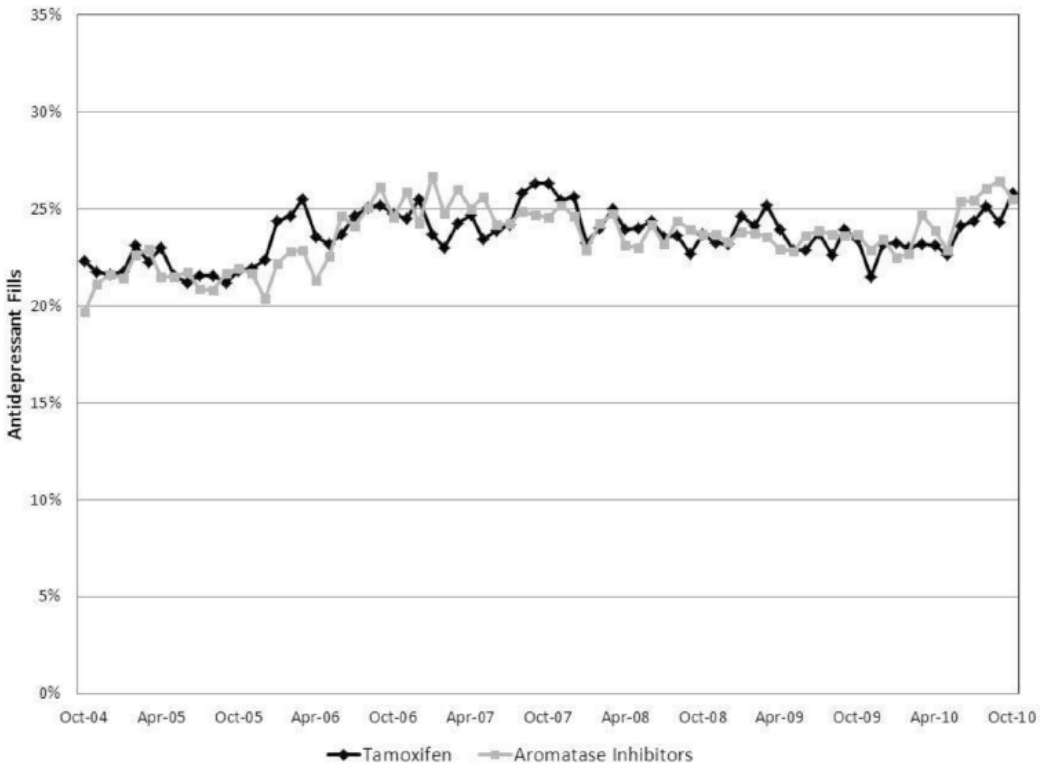


Figure 1. Proportion of Women Receiving Antidepressants and Endocrine Therapy by Month – Propensity Score Matched Sample

The figure demonstrates the proportion of women taking tamoxifen (black line) and aromatase inhibitors (gray line) who were also prescribed an antidepressant in each month of observation.

Dusetzina et al., 2013

CYP2D6 inhibitoren

Table 2

Select Common Drugs With CYP2D6 Inhibition Activity

Strong Inhibitors[a]
Paroxetine
Fluoxetine
Buproprion
Quinidine
Moderate Inhibitors
Duloxetine
Sertraline
Amiodarone
Thioridazine
Cimetidine
Diphenhydramine
Weak Inhibitors[b]
Venlafaxine
Citalopram
Escitalopram

[a]Strong CYP2D6 inhibitors should be avoided in women on tamoxifen.

[b]Weak CYP2D6 inhibitors appear to be safe in women on tamoxifen.

Kuderer et al., 2009, 13 (14): 1223-1232

CYP2D6 inhibitoren

Jin et al., 2005 (n=80)

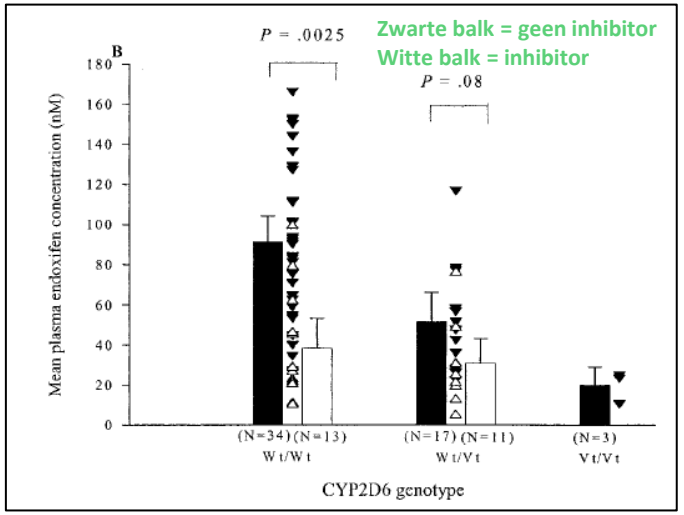
- prospectieve, observationele trial
- TM + *CYP2D6* inhibitor

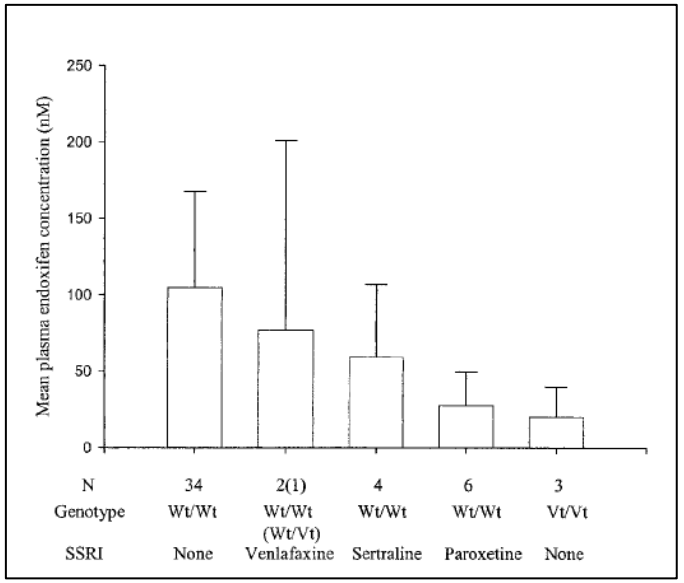
→ reductie gemiddelde $[endoxifen]_{pl}$

- *Wt/Wt* genotype + *CYP2D6* inhibitor
  - reductie 58% (P=0.0025)
- *Wt/Vt* genotype + *CYP2D6* inhibitor
  - reductie 38% (P=0.08)

→ inhiberende werking *CYP2D6* inhibitor ≈ reducerende invloed $[endoxifen]_{pl}$

- venlafaxine (zwakke inh.)
  - lichte daling $[endoxifen]_{pl}$
- paroxetine (sterke inh.)
  - sterke daling $[endoxifen]_{pl}$
  - vgl met *CYP2D6 Vt/Vt* genotype





CYP2D6 inhibitoren

Borges et al., 2006 (n=158)

- prospectieve trial, 4 mnd tamoxifen (20 mg/dag)

→ TM + venlafaxine

- geen significant effect op $[endoxifen]_{pl}$
  - gehele studiepopulatie

  71.7 ± 41.3 nmol/L vs. 80.8 ± 39.3 nmol/L, P=0.60
  - EM/EM genotype

  93.6 ± 38.6 nmol/L vs. 84.1 ± 39.4 nmol/L, P=0.72

→ TM + zwakke (citalopram en sertraline) vs. sterke (paroxetine) *CYP2D6* inhibitoren

- daling $[endoxifen]_{pl}$ zwakke inh < sterke inh

  24.6 ± 16.6 nmol/L vs. 50.1 ± 30.4 nmol/L, P<0.01)
- sterke *CYP2D6* inhibitoren

  ≈ *CYP2D6* EM fenotype → PM fenotype

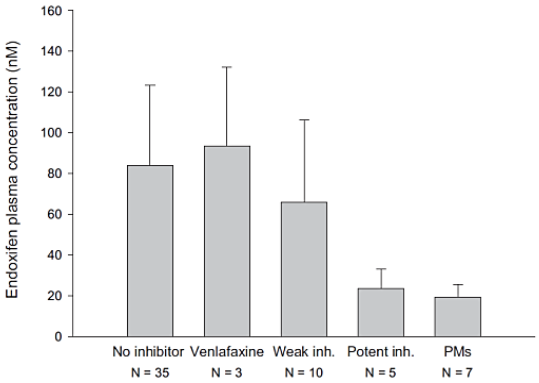


Fig 6. Effect of concomitant use of CYP2D6 inhibitors (inh) on endoxifen plasma concentration after 4 months of tamoxifen treatment (20 mg/d). *Solid bars* represent mean + SD. From left to right, groups are composed o EM/EMs who were receiving neither CYP2D6 inhibitors nor venlafaxine, EM/EMs who were receiving venlafaxine, EM/EMs who were receiving weak CYP2D6 inhibitors, EM/EMs who were receiving potent CYP2D6 inhibitors, and PM/PMs who were not receiving any CYP2D6 inhibitors.

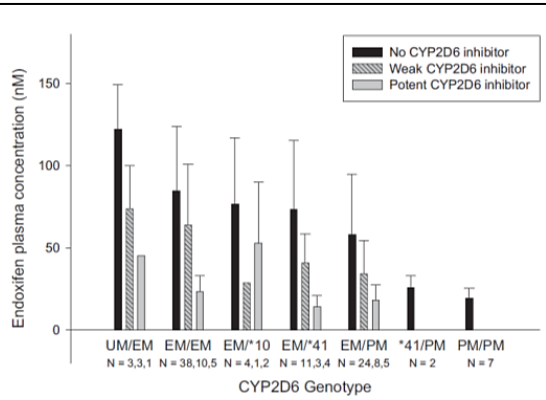
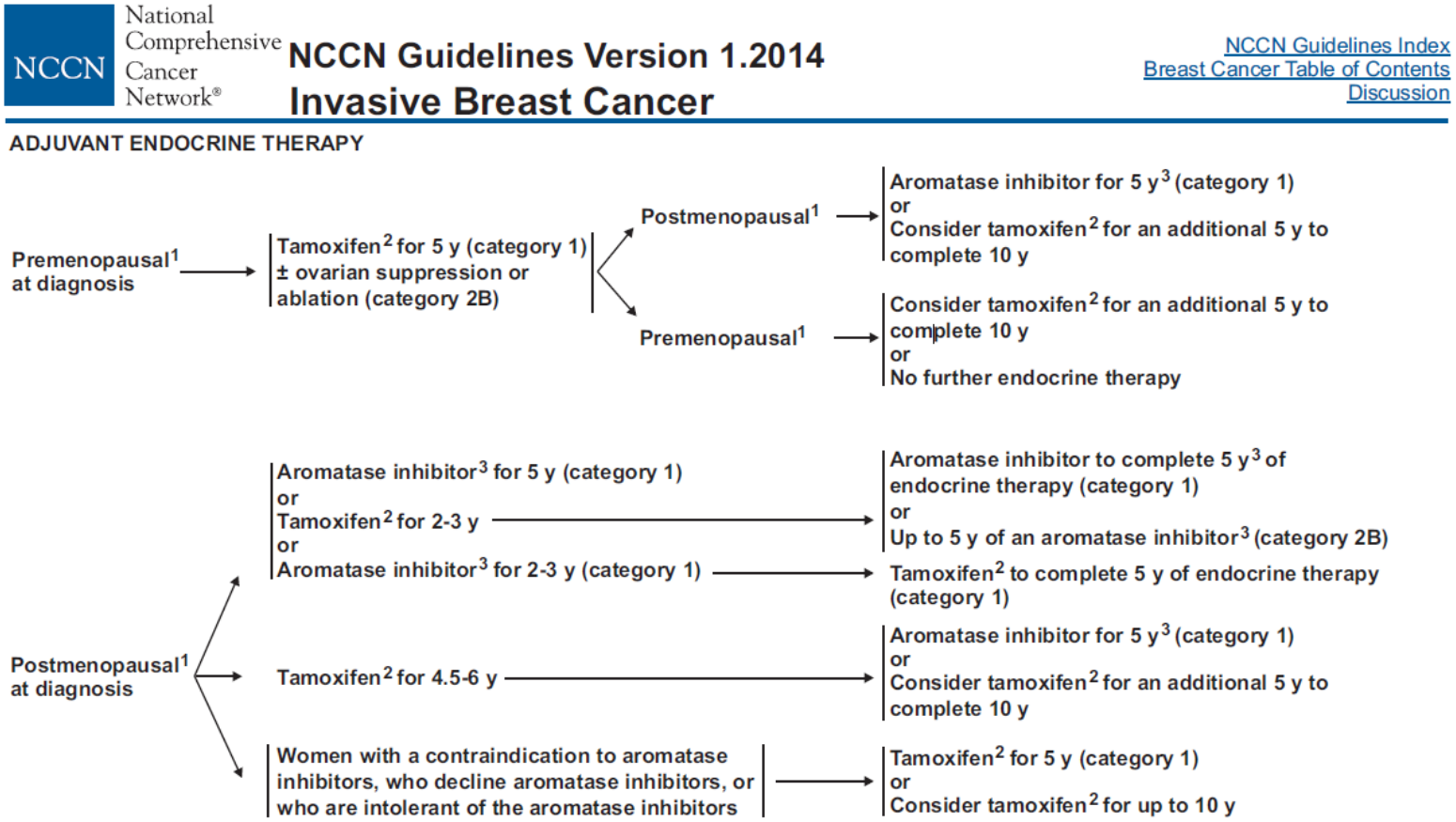


Fig 7. Effect of *CYP2D6* genotype and concomitant use of CYP2D6 inhibitors on plasma endoxifen concentration after 4 months of tamoxifen treatment. Data are presented as mean + SD. *Black bars*, Group means for patients who were not receiving any CYP2D6 inhibitors; *striped bars*, group means for patients who were taking weak CYP2D6 inhibitors; *gray bars*, group means for patients who were taking potent CYP2D6 inhibitors.

CYP2D6 inhibitoren



TDM

TDM

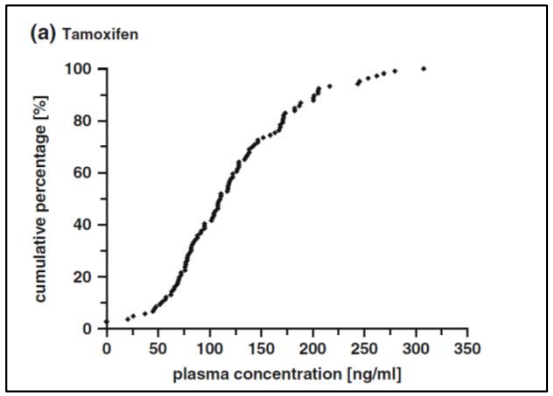
TDM tamoxifen / endoxifen

- TDM?
  - Sterk variabele metabolisatie
  - Comedicatie - SSRI
  - Compliance problematiek
  - Moeilijke objectieve waarneming nevenwerkingen
- Doel: optimalisatie therapie
- Literatuur TDM tamoxifen/endoxifen beperkt

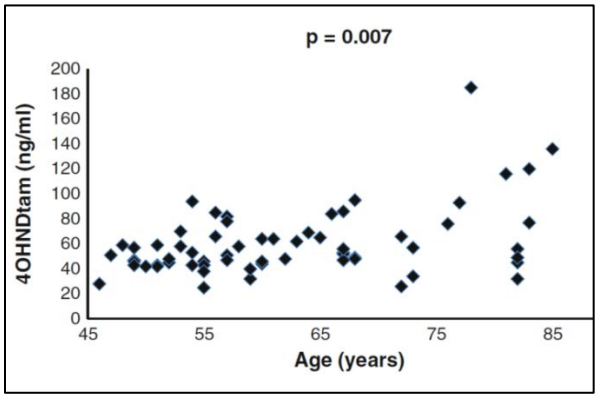
TDM

TDM tamoxifen / endoxifen

- Problemen plasmaconcentraties
  - ✓ sterk variabele concentraties tamoxifen [Beer at al., 2010]
    - LC-MS/MS: steady-state $[tamoxifen]_{pl:}$ 20 tot 377 ng/mL
  - ✓ invloed
    - leeftijd: $[endoxifen]_{pl}$ ↑als leeftijd ↑ [Lien et al., 2013]
    - BMI >24.4kg/m² ≈ hogere 4-OH-tamoxifen en endoxifen plasma concentraties (P=0.080, P=0.080) [Madlensky et al., 2011; Wu et al., 2007]



Cumulatieve frequenties tamoxifen concentraties (n=106) [Beer et al., 2010]



Serum concentraties van 4OHNDtam (endoxifen) in functie van de leeftijd bij postmenopauzale patiënten met Wt/Wt CYP2D6 allelen (EM) [Lien et al., 2013]

TDM

Tamoxifen? Endoxifen?

- Suggestie therapeutische cut-off waarde (Z)-endoxifen: 5.9 ng/mL [Madlensky et al., 2011]
- Gebruik (Z)-endoxifen serum concentraties in de optimalisatie tamoxifen behandeling [Jager et al., 2014]
  - dosis tamoxifen ≈ steady-state (Z)-endoxifen serum concentratie
  - tamoxifen 20 mg/d → 30 of 40 mg/d, als (Z)-endoxifen serum concentratie <5.9 ng/mL
    → significante stijging van gemiddelde serum concentraties ($p<0.001$)

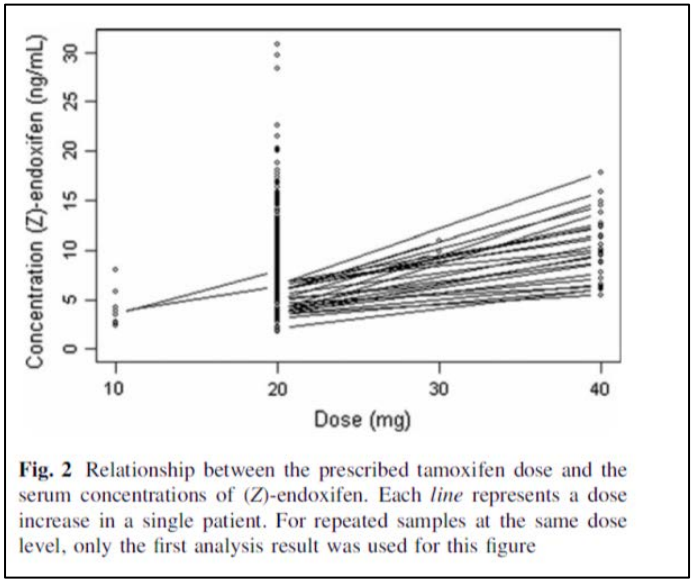


Fig. 2 Relationship between the prescribed tamoxifen dose and the serum concentrations of (Z)-endoxifen. Each *line* represents a dose increase in a single patient. For repeated samples at the same dose level, only the first analysis result was used for this figure

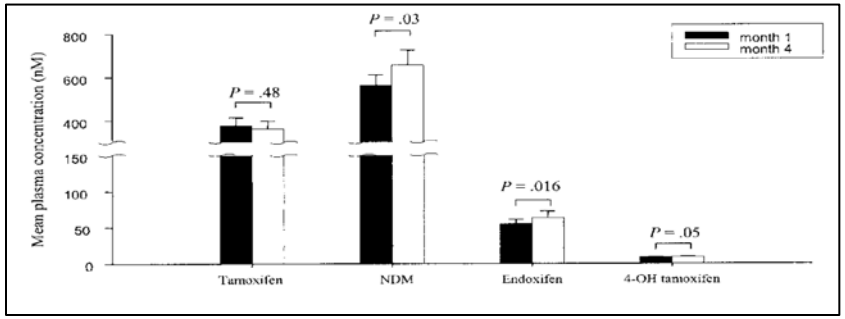
[Jager et al., 2014]

TDM

TDM tamoxifen / endoxifen

- Meerdere gerichte studies zijn vereist
  - tamoxifen? endoxifen?
  - optimale plasma concentratie optimaal therapeutisch effect vs. nevenwerkingen?
  - correlatie plasma concentraties en klinische outcome?
  - correlatie plasma concentraties vs. doelweefsel?

- Praktijk?
  - steady-state concentraties$_{pl}$ [Jin et al., 2005]
    - 4 mnd na start / aanpassing behandeling - tijd metabolieten > tamoxifen



  - concentratie bepaling op specifiek vastgestelde tijdstippen
  - compliance belangrijke rol interpretatie van de plasmaconcentraties

FENOTYPISCHE TESTEN

Fenotypische testen

Fenotypering

- probe geneesmiddel dat farmacokinetiek tamoxifen metabolisme zal voorspellen
- dextromethorfan

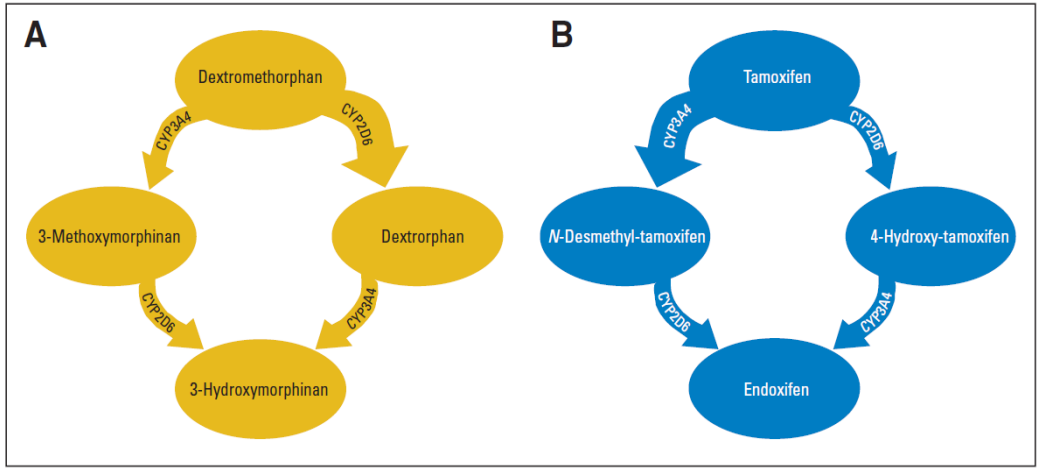


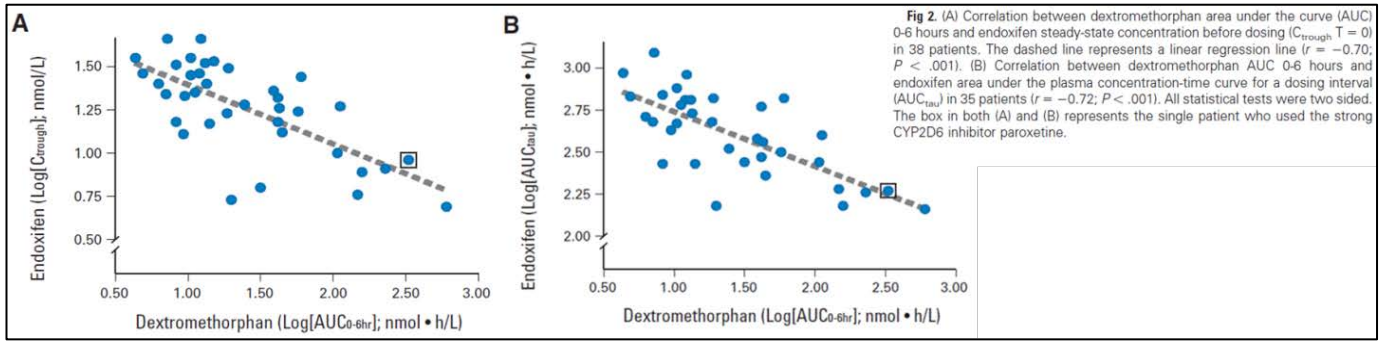
Fig 1. Scheme for both dextromethorphan and tamoxifen metabolism. (A) Dextromethorphan is mainly converted by CYP2D6 to dextrorphan, and (B) tamoxifen is mainly converted by CYP3A4 into *N*-desmethyl tamoxifen. Afterward, dextrorphan is converted by CYP3A4 into 3-hydroxymorphinan and *N*-desmethyl tamoxifen is converted by CYP2D6 into endoxifen.

Schematische voorstelling dextromethorfan en tamoxifen metabolisme [de Graan et al., 2011]

Fenotypische testen

Fenotypering

- dextromethorfan
  - de Graan et al., 2011 (n=40):
    - dextromethorfan AUC concentraties 0 tot 6 u na inname ≈ AUCtau voor tamoxifen (P<0.001)
    - dextromethorfan blootstelling ≈ steady-state AUC_{tau} endoxifen en dal-concentraties (P<0.001)
    - analyses over 6 uur kunnen gebruikt worden de voorspelling van $[endoxifen]_{pl}$



Correlatie dextromethorfan AUC 0-6u en endoxifen dal-concentratie (A) en endoxifen AUC_{tau} (B) [de Graan et al., 2011]

- ✓ echter opstelling optimaal protocol voor staalafname + interpretatie
- ✓ later gebruik co-medicatie, compliance?

CONCLUSIE

Besluit

CYP2D6 genotypering

- nog geen consensus over routine testen
- suggestief voor voorspelling klinische outcome, echter discordante resultaten
- slechts beperkte rol voor invloed farmacokinetiek tamoxifen
- geen rekening met andere, niet-genetische factoren

TDM

\+ compliance / andere effecten / comedicatie / beperkte verklaring *CYP2D6* farmacokinetiek

\- optimaal therapeutisch venster / steady-state / tijdstip monitorring / tamoxifen vs. metabolieten

Besluit

→ monitoring van endoxifen plasma concentraties in plaats van de voorspelling ervan aan de hand van *CYP2D6* genotypering lijkt voorlopig de meest optimale methode in de individualisatie van tamoxifen behandeling

→ voorstel

→ eventueel bij start behandeling *CYP2D6* genotypering

(instellen optimale dosering, beslissingen omtrent comedicatie, '*switching*' strategie)

→ lange termijn follow-up: TDM

To Do

- Prospectieve studies ivm verband tussen *CYP2D6* genotypering en klinische outcome?
- TDM: optimale therapeutische minimale endoxifen plasma/serum concentratie?
- Rol andere enzymen: *CYP3A4?*
- Gebruik endoxifen?
  - Lopende trial: *Phase I Study of Z-Endoxifen as a Hormonal Therapy for Breast Cancer - National Cancer Institute*

VRAGEN?