DEFINIZIONE DI STATO MENOPAUSALE

Scenario 1

Donna in pre-menopausa prima dell'avvio dei trattamenti oncologici, in amenorrea durante il trattamento con tamoxifene e che ha completato 5 anni di trattamento con il farmaco

Scenario 2

Donna in pre-menopausa prima dell'avvio dei trattamenti oncologici, in amenorrea durante il trattamento con tamoxifene e che ha completato 2-3 anni di trattamento con il farmaco

?

TAMOXIFENE

INIBITORI DELL'AROMATASI

DEFINIZIONE DI STATO MENOPAUSALE

Come posso monitorizzare la persistenza dello stato menopausale?

<u>Scenario 3</u>

Donna da poco in menopausa in trattamento con inibitori dell'aromatasi

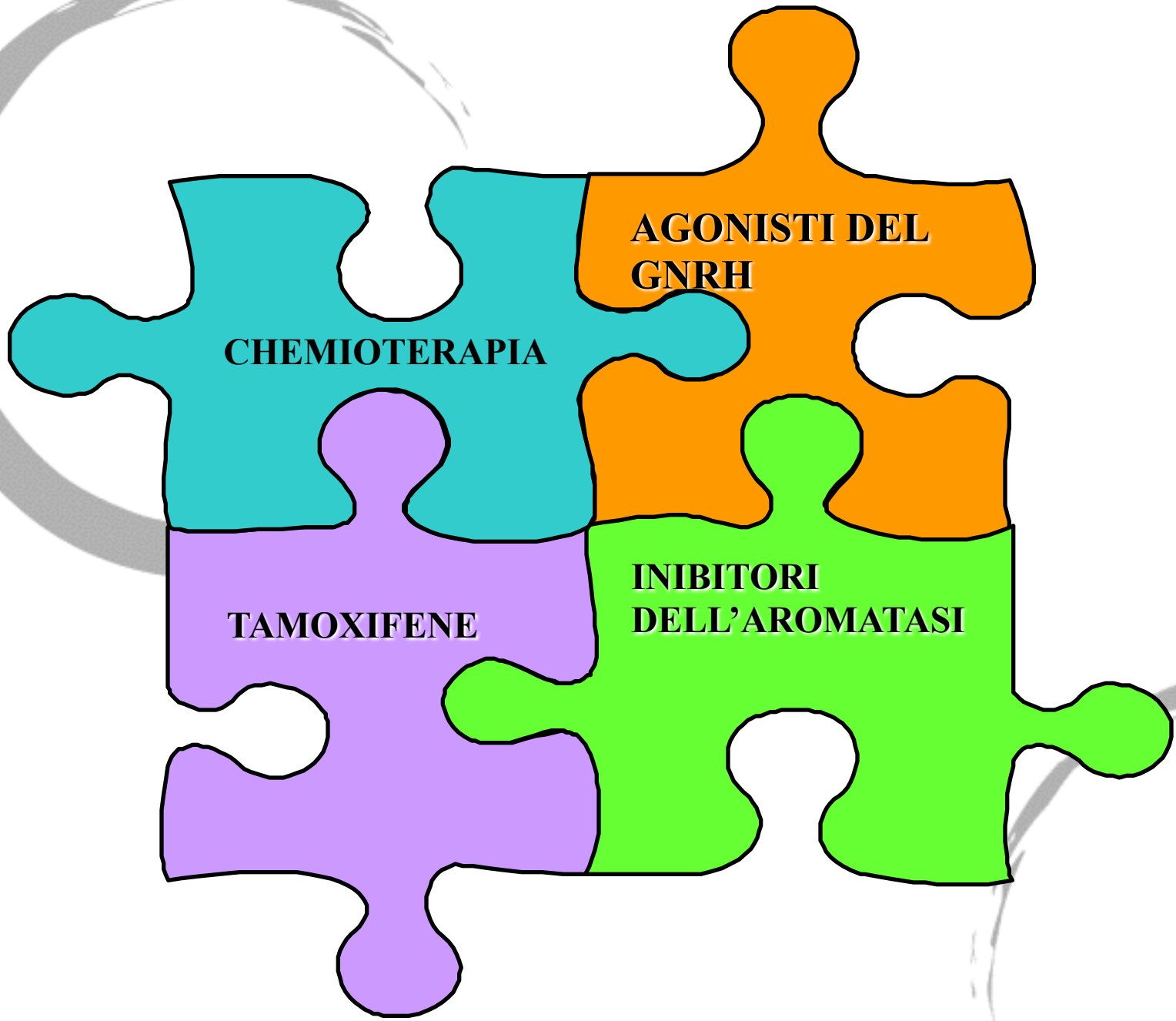
DEFINIZIONI

INSUFFICIENZA OVARICA:
- **amenorrea da 3 mesi**
- **due riscontri in un mese di FSH>40 UI/L ed Estradiolo (E2) <10 pg/ml**
- **età<40 aa**

AMENORREA SECONDARIA:
- **assenza di flusso mestruale per più di 3 cicli o per 6 mesi**
- **dosaggi di gonadotropine non indicativi**

MENOPAUSA (*NCCN*):
- **annessiectomia bilaterale**
- **età ≥ 60 aa**
- **età < 60 aa con amenorrea di almeno 12 mesi in assenza di trattamenti adiuvanti e dosaggio di FSH ed E2 in range post-menopausale (FSH> 40UI/L ed E2<10 pg/ml)**
- **età < 60 aa in donne in trattamento con tamoxifene e dosaggio di FSH ed E2 in range post-menopausale**

NON E' POSSIBILE DEFINIRE LO STATO MENOPAUSALE NELLE DONNE IN TRATTAMENTO CON AGONISTI O ANTAGONISTI DEL GNRH


AGONISTI DEL GNRH
CHEMIOTERAPIA
TAMOXIFENE
INIBITORI DELL'AROMATASI

CHEMIOTERAPIA E MENOPAUSA

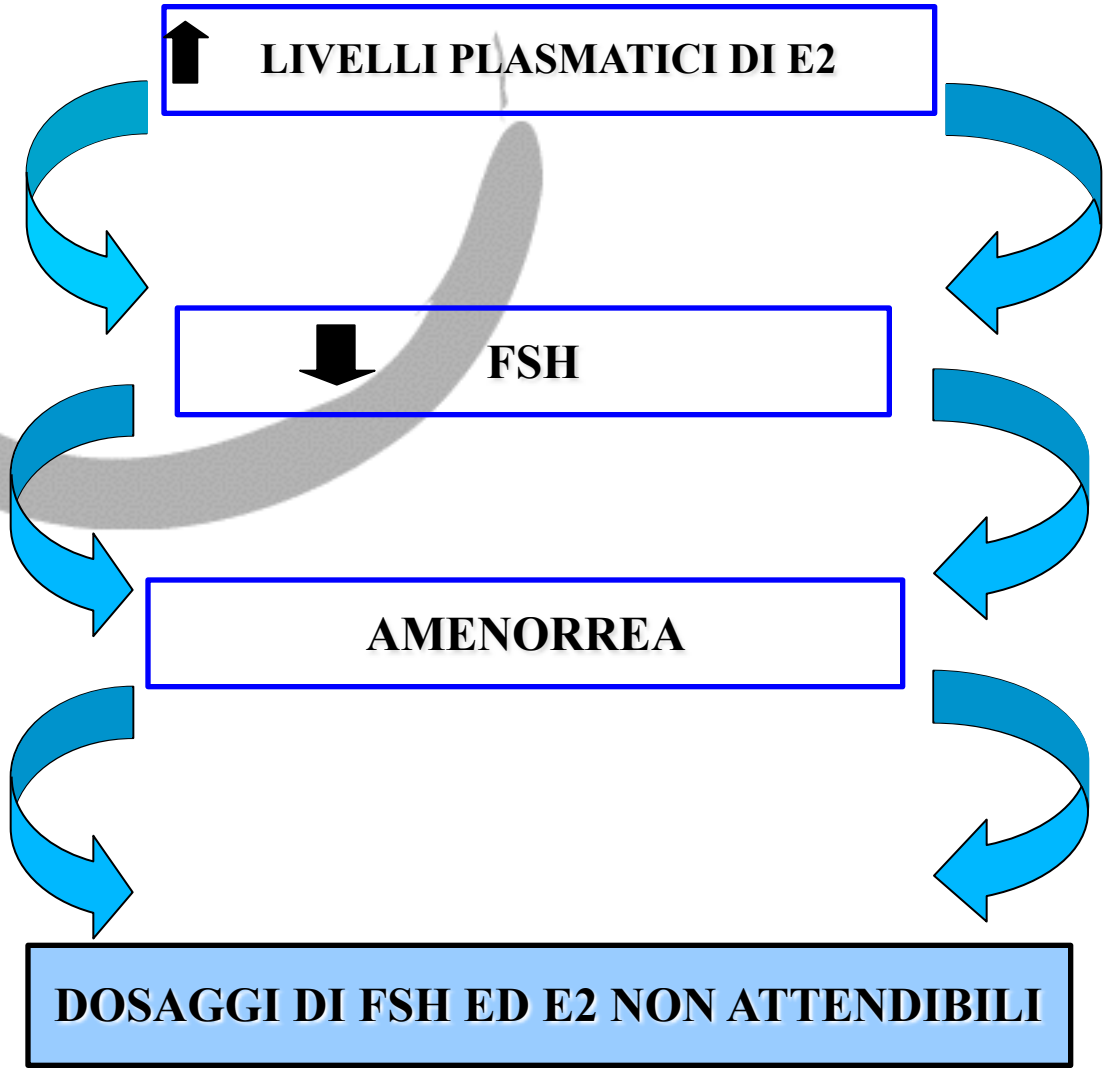
Età <40 aa: 22-61%

Età >40 aa: 61-97%

Single drug	Adjuvant regimens
High risk (>80%)	
Cyclophosphamide	CMF, FEC and FAC×six cycles in women aged ≥40 years
Ifosfamide	
Chlorambucil	
Melphalan, Busulfan	
Nitrogen mustard	
Procarbazine	
Thiotepa	
Intermediate risk	
Cisplatin	CMF, FEC and FAC×six cycles in women aged 30–39 years
Carboplatin	AC and EC×four cycles in women aged ≥40 years
Adriamycin	Taxane-containing combinations
Taxanes	
Low risk (<20%) or no risk	
Bleomycin	CMF, FEC and FAC×six cycles in women aged <30 years
Dactinomycin	AC and EC×four cycles in women aged <40 years
Vincristine	
Vinblastine	
Methotrexate	
Mercaptopurine	
5-Fluorouracil	
To be determined	
Trastuzumab	
Lapatinib	

Torino F, et al. Endocrine Related Cancer, 2012

TAMOXIFENE E MENOPAUSA



Guerrero A, et al. Annals of Oncology, 2013

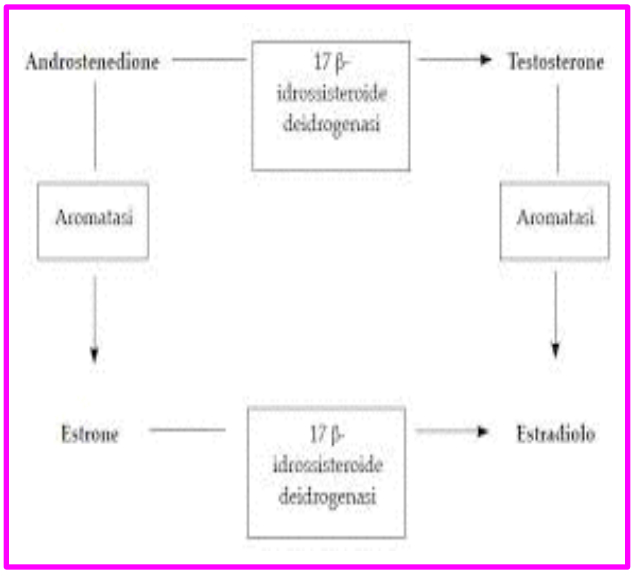
INIBITORI DELL'AROMATASI E MENOPAUSA

⬇ PRODUZIONE PERIFERICA DI E2

⬆ FSH

STIMOLO ALLA CRESCITA FOLLICOLARE

⬆ E2



Folkered EJ, et al. JCO, 2014

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Endocrine Effects of Adjuvant Letrozole Compared With Tamoxifen in Hormone-Responsive Postmenopausal Patients With Early Breast Cancer: The HOBOE Trial

Emanuela Rossi, Alessandro Morabito, Francesca Di Rella, Giuseppe Esposito, Adriano Gravina, Vincenzo Labonia, Gabriella Landi, Francesco Nuzzo, Carmen Pacilio, Ermelinda De Maio, Massimo Di Maio, Maria Carmela Piccirillo, Gianfranco De Feo, Giuseppe D'Aiuto, Gerardo Botti, Paolo Chiodini, Ciro Gallo, Francesco Perrone, and Andrea de Matteis

Table 1. Comparisons of Hormonal Levels Between Tamoxifen and Letrozole Groups

	Baseline Values					Change at 6 Months					Change at 12 Months				
	Tamoxifen (n = 43)		Letrozole (n = 96)			Tamoxifen (n = 41)		Letrozole (n = 89)			Tamoxifen (n = 39)		Letrozole (n = 84)		
Hormone	Median	Range	Median	Range	*P*	Median	Range	Median	Range	*P*	Median	Range	Median	Range	*P*
Estradiol, pg/mL	9.7	< 5.0-21.6	9.3	< 5.0-30.9	.80	2.6	−8.2-20.4	−3.2	−23.8-13.4	.0004	2.8	−10.7-16.4	−3.7	−28.4-14.6	< .0001
Progesterone, ng/mL	0.13	< 0.03-0.50	0.20	< 0.03-0.90	.18	0.00	−0.24-0.30	0.04	−0.30-0.50	.029	−0.02	−0.22-0.20	0.05	−0.27-0.33	.009
FSH, mU/mL	57.9	34.2-131.7	64.9	27.6-158.7	.61	−18.6	−63.7-31.3	6.5	−42.8-61.1	< .0001	−25.8	−85.8-−1.5	5.0	−46.4-46.2	< .000
LH, mU/mL	28.6	10.2-64.4	30.3	6.2-85.3	.56	−8.3	−29.7-11.1	−2.5	−26.3-35.9	< .0001	−12.0	−30.3-1.3	−3.55	−44.4-20.6	< .0001
Testosterone, ng/mL	0.13	< 0.02-0.51	0.18	< 0.02-0.61	.055	0.03	−0.29-0.4	0.05	−0.34-0.42	.36	0.03	−0.28-0.29	0.06	−0.36-0.42	.40
DHEA-S, μg/dL	59.0	15.8-241.5	68.1	4.2-306.0	.24	10.2	−78.9-100.9	7.2	−126.0-95.1	.71	5.0	−34.8-66.4	6.5	−59.5-159.0	.53
Cortisol, μg/dL	10.2	3.3-21.1	12.1	0.7-83.0	.10	4.6	−8.5-19.2	0.9	−75.2-13.8	< .0001	4.8	−3.0-16.2	0.0	−77.3-11.6	< .0001

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEA-S, dehydroepiandrosterone-sulphate.

ETA'

Incidence and predictors of ovarian function recovery (OFR) in breast cancer (BC) patients with chemotherapy-induced amenorrhea (CIA) who switched from tamoxifen to exemestane

A. Guerrero[1], J. Gavilá[1], E. Folkerd[2], B. Ortiz[3], F. Martínez[4], A. García[5], M. A. Climent[1], V. Guillem[1] & A. Ruíz[1]

[1]Department of Medical Oncology; [2]Department of Biochemistry, Royal Marsden Hospital, London, UK; Departments of [3]Biochemistry; [4]Radiodiagnostic; [5]Gynecology, Instituto Valenciano de Oncología, Valencia, Spain

Background: Aromatase inhibitors (AIs) may promote ovarian function recovery (OFR). True incidence, predictors and impact on the outcome of OFR are unknown.

Patients and methods: We carried out a prospective study to assess ovarian function in estrogen receptor (ER)-positive BC patients on tamoxifen who had at least 2 years of chemotherapy-induced amenorrhea (CIA) and postmenopausal E2 levels. Patients switched to exemestane and underwent a series of investigations including vaginal ultrasound, antimullerian hormone, follicle stimulating hormone (FSH), and E2. E2 measurements were made using a clinical assay (direct) and a highly sensitive (indirect) immunoassay for comparison.

Results: Both E2 assays (indirect versus direct) showed a similar incidence of OFR 32% (95% CI 19.5–44.5) versus 30% (95% CI 17.7–42.3) and median time to OFR 5.4 months (95% CI 1.2–9.6) versus 6.0 months (95% CI 4.8–7.1). On multivariate analysis, the mean age at the start of exemestane treatment was the only marker associated with probability of OFR (OR: 0.44, 0.24–0.78; $P = 0.006$). According to a receiver operating characteristic (ROC) analysis, age <48 years predicted for OFR (sensitivity: 59%; 1-specificity: 17%; AUC: 0.796; $P = 0.001$). Patients with OFR had higher mean E2 levels (43.6 versus 5.76 pmol/l; $P = 0.001$) and a reduced disease-free survival [DFS; HR 9.3 (95% CI 3.3–48.0; $P = 0.04$)] than those without it.

Conclusion: Even with a clinical and biochemical profile compatible with menopause, switching from tamoxifen to an AI should be avoided in patients <48 with CIA.

Key words: amenorrhea/chemically induced, aromatase inhibitor, estradiol/blood, ovarian function

Adjuvant Aromatase Inhibitors for Early Breast Cancer After Chemotherapy-Induced Amenorrhoea: Caution and Suggested Guidelines

Ian E. Smith, Mitch Dowsett, Yoon-Sim Yap, Geraldine Walsh, Per E. Lønning, Richard J. Santen, and Daniel Hayes

Purpose
Aromatase inhibitors (AIs) are now established as adjuvant therapy for early hormone receptor–positive breast cancer in postmenopausal women. Their use is sometimes extended to younger women after chemotherapy-induced amenorrhoea; we have audited this in one institution's breast unit, and we propose guidelines for use in such circumstances.

Patients and Methods
The use of aromatase inhibitors as adjuvant therapy in younger women age ≥ 40 with hormone receptor–positive early breast cancer and chemotherapy-induced amenorrhea has been audited clinically and biochemically.

Results
A total of 45 such women were identified in the audit, with a median age of 47 years (range, 39 to 52 years). Twelve women (27%) showed a return of ovarian function (10 renewed menses, one pregnancy, one biochemically premenopausal) after starting an AI. Median age at restart of ovarian function was 44 years (range, 40 to 50 years).

Conclusion
AIs may promote recovery of ovarian function in some women with chemotherapy-induced amenorrhea and should be used with caution. Biochemical monitoring of ovarian function requires highly sensitive immunoassays. Guidelines for the selection and delivery of adjuvant endocrine therapy in such patients are proposed.

J Clin Oncol 24:2444-2447. © 2006 by American Society of Clinical Oncology

27%

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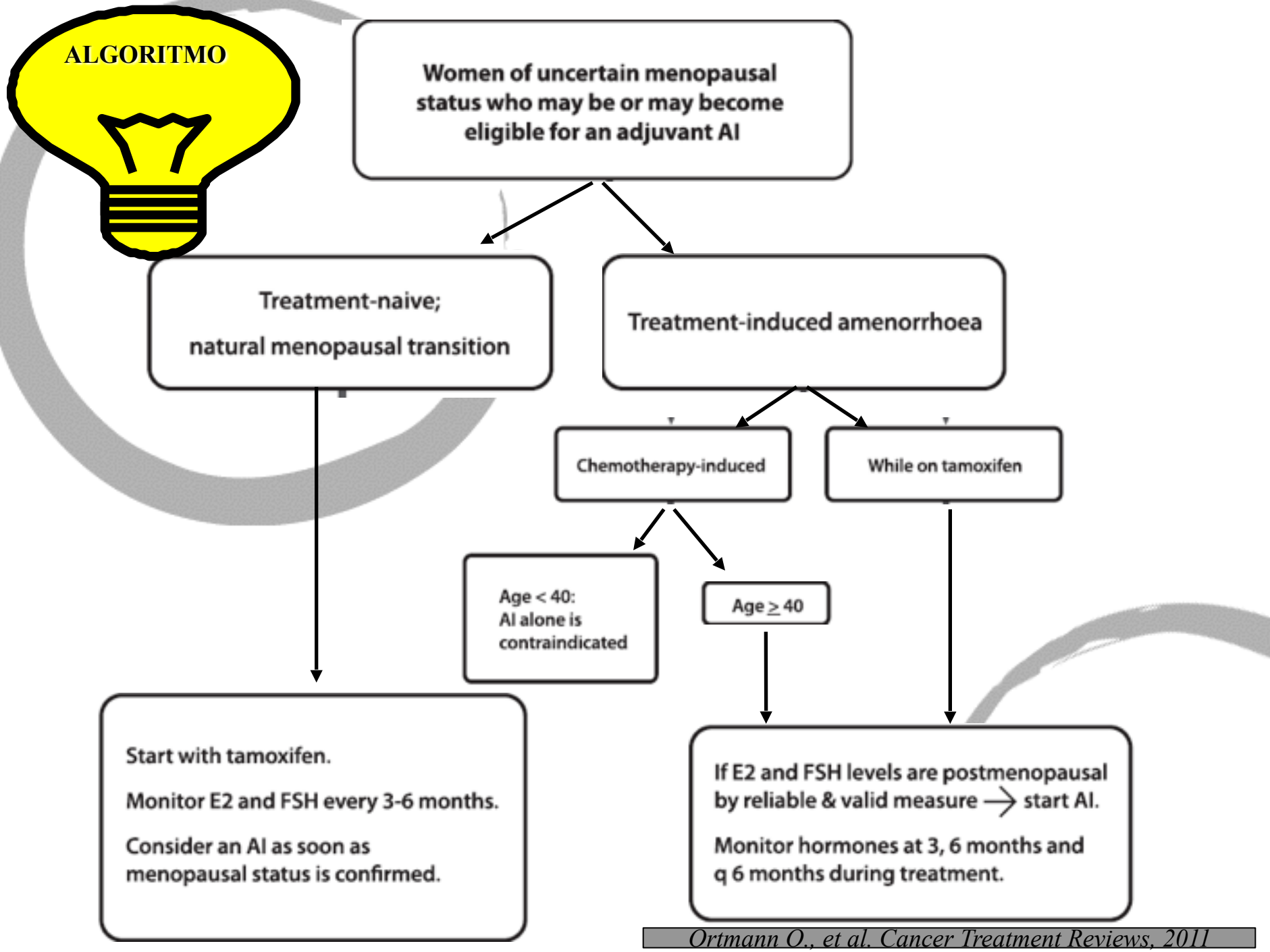
Ian E. Smith, Mitch Dowsett, Yoon-Sim Yap, Geraldine Walsh, Per E. Lønning, Richard J. Santen, and Daniel Hayes

1. **Età <40 aa** → **No AI (o solo in associazione ad Analoghi del GnRH)**
2. **Età >40 aa e dosaggi non disponibili** → **AI utilizzabili solo con cautela**
3. **Età >40 aa e dosaggi SERIATI di E2 e FSH in range post-menopausale** → **utilizzo di AI appropriato MA PROSEGUIRE CON DOSAGGI SERIATI DI FSH ED E2 PER 6 MESI**
4. **Terapia con AI dopo terapia con tamoxifene (late o early switch)** → **DOSAGGI SERIATI DI FSH ED E2 PER OLTRE 6 MESI CON E2 IN PROGRESSIVA RIDUZIONE (FINO A STABILIZZAZIONE <10 pmmol/L)**



Ortmann O., et al. Cancer Treatment Reviews, 2011

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Scenario 3

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Se età > 40 aa e dosaggio di FSH, LH ed E2

↓

FSH >40 UI/L ed E2<10 pg/ml

↓

Avviare trattamento con AI

↓

Monitoraggio di FSH ed E2 ogni 3 mesi per oltre 6 mesi

DISCUSSIONE

SOSPENSIONE DEL TAMOXIFENE PER EFFETTUARE I DOSAGGI?

DOSAGGI BORDERLINE?

MONITORAGGIO DI FSH ED E2 O ANCHE SOLO DI E2?

MONITORAGGI DI 6-12 MESI O MAGGIORI?