유방암 환자에서 타목시펜 사용시 나타나는 부작용과 대처법

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Tamoxifen related side effects

- Long-term effect
  - Hot flushes
  - Changes in menstruation
  - Mood changes
  - Increased TG
- Late effect
  - Increased risk of stroke
  - Increased risk of endometrial cancer
  - Increased risk of blood clots
  - Osteopenia in premenopausal women

ASCO, 2016

Contents

- Endometrial cancer in TMX users
- Ovarian cyst
- Hot flush
- Vaginal dryness

Endometrial cancer

EM cancer following TMX

	Number randomised	Number of endometrial cancers		Hazard ratio	*p* value
		Tamoxifen arm	Control arm		
Adjuvant tamoxifen studies[2]	7085 vs 7085	41	12	3.4	0.0002
Prevention tamoxifen studies					
NSABP P1[3]	6681 vs 6707	36	15		
Royal Marsden Hospital[15]	1238 vs 1233	6	2	2.4	0.0005
IBIS-1[16]	3573 vs 3566	11	5		

- More advanced stage, p53 positive tumor, negative ER and poor 3-yr survival in TMX users…

Bergman, 2000, Lancet

- 타목시펜 사용 기간과 누적 용량에 비례해서 자궁내막암 위험이 증가

- 타목시펜으로 인한 자궁내막암은 임상적 특성과 예후가 일반 자궁내막암과 차이 없음
- 유방암과 자궁내막암이 같은 위험인자를 공유

Senkus-konefka, 2004, Cancer Treat Rev

Endometrial effects of TMX

- EM hyperplasia, endometric cystic atrophy (senile cystic atrophy), EM polyp, EM Ca
- EM Ca in 1.25% of 1,026 pts with TMX -spain

- Extensive fibrosis- difficulties in obtaining EM Tissue
- Endometriosis, adenomyosis, myoma in post-MP women
- EM Ca in 3.6% of aSx women with increased EM thickness (>50%) after TMX

Cohen, 2002, Cancer

- Hysteroscopic finding of 261 post-MP women with TMX
- Atrophic EM 75.5%, EM polyp 11.5%, EM HPL 4.2%, EM polyps with HPL 4.2%, EM Ca 0.4%

Cohen, 1999, Gynecol Obstet Invest

USG in TMX users

- TMX 사용자에서는 자궁내막두께가 증가
- 두께에 따라 조직검사를 해도 이상 없는 경우가 많음: high rate of false positive
- 초음파 자궁내막두께와 조직검사 결과에 discrepancy가 많음
- Stromal edema caused by TMX
  - Subendometrial sololucencies in adjacent myometrial tissue
  - thick miduterine structure resembling a thickened EM

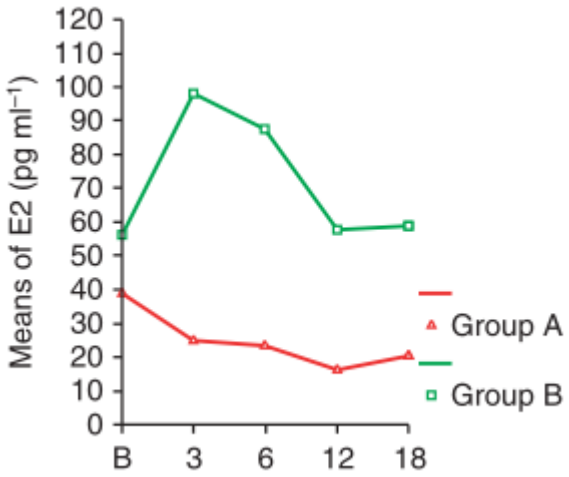
Cohen, 2002, Cancer

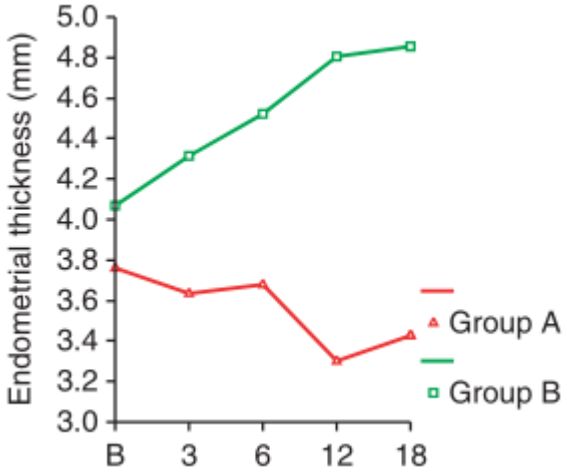
- 출혈이 없는 경우 routine gynecologic exam만 시행하도록 권고
- 출혈이 있는 경우 자궁내막두께가 정상이어도 (ex: 3mm) 자궁내막암이 진단되기도 함

Combined effects of Goserelin and TMX

- Pre- and peri-menopausal women (n=110) with ER (+) early stage breast Ca

	Goserelin + TMX	TMX alone
Age (years)	42.4 ± 5.2	42.5 ± 5.2
E2 (pg/ml)	41.8 ± 108.9	52.4 ± 95.9
FSH (mIU/ml)	20.6 ± 16.3	28.6 ± 24.4





Group A: Gosereline + TMX
Group B: TMX alone

Yang H, Br J Cancer, 2013

LNG-IUD in Breast cancer survivors

- Levonorgestrel의 자궁내막증식 억제 효과로 자궁내막병변에 대한 검사, 시술 빈도가 줄어들 것이다.

Strom BL, Contraception, 2004
Backman T, Obstet Gynecol, 2005
Dinger J, Contraception, 2011
McNaught J, J Obstet Gynecol, 2006

- 유방암 진단 당시 이미 LNG-IUD를 가지고 있었던 여성에서 높은 재발율
- In subgroup analysis, women using LNG-IUD at the time of Dx and continued showed higher recurrence rate than women who did not have it at the time of Dx (HR 3.4, 95% CI:1.01-11.35)

Trinh XB, Fertil Steril, 2008

Author (year of publication)	Population	Design and Outcomes	Findings
Trinh XB (2008) [45]	Breast cancer survivors	Case control study of breast cancer recurrence	increased recurrence among women with a levonorgestrel-IUD at time of diagnosis
Kesim MD (2008)[71]	Breast cancer patients taking tamoxifen	Cohort followed for 36 months for lipid and endometrial changes	Improvement of endometrium, no effect on lipids
Chan SS (2007) [39]	Breast cancer patients taking tamoxifen	Cohort followed for 12 months for endometrial changes	Improvement of endometrium
Gardner FJ (2000)[40]	Breast cancer patients taking tamoxifen	Cohort followed for 12 months for endometrial changes	Improvement of endometrium

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

Screening for second primary cancers

Cancer screenings in the average-risk patient

Recommendation 2.1: It is recommended that primary care clinicians

(a) should screen for other cancers as they would for patients in the general population; and

(b) should provide an annual gynecologic assessment for postmenopausal women on selective estrogen receptor modulator therapies.

Postmenopausal women who are taking SERMS, such as tamoxifen, should be advised to report any vaginal spotting or bleeding, because these drugs slightly increase the risk of endometrial cancer in postmenopausal women.

In the absence of abnormal vaginal spotting or bleeding, periodic imaging is not of value and may lead to unwarranted biopsies.

Discuss the risks, benefits and limitations of screening modalities with your patients.

Ovarian cyst

Ovarian cyst

- Simple cyst, normal serum CA 125
- Torsion, rupture, cystic necrosis
- DDx with ovarian metastasis, primary ovarian cancer

Cohen I, 1999, Gynecol Oncol

- Spontaneous regression in 72.7% (12months f/u)

Kourounis G, The Breast J, 2005

- Higher incidence of ovarian malignancy in breast cancer pts : primary or metastatic cancer
- About 12~26% incidence of malignancy among breast cancer pts. Who undergone surgery for adnexal mass.

Simpkins F, Obstet Gynecol, 2005

Hann LE, Radiology, 2000

- TMX prevents premalignant changes of breast but not ovarian cancer in rats.

Ting AY, Cancer Prev Res, 2008

Ovarian cyst

Incidence

- Women without TMX: 8.5%
- Women with TMX: 80%
  - Overall 19.3% ~ 25%, 0.83% in STAR trial (postmenopausal)
  - 1.1~10% in women with amenorrhea, 33.3±18mon
  - 43.8~80% in women with menstruation, 50.7±6.2mon
  - Significantly higher serum 17β-E_2 on MCD #14-#21

	MCD #14	MCD #21
With TMX	757.7±372.0	300.0±134.5
Without TMX	206.5±275.5	96.5±71.5

Cohen I, 1999, Gynecol Oncol

Seoud, 2001, European J Obstet Gynecol Reprod Biol

TMX induced massive ovarian steroidogenesis

- 17β-E_2 up to 2500pg/ml
- TMX acts directly on the ovary
- Hypothalamic negative feedback? - No change in FSH, LH level

- Supraphysiologic estrogen level may inhibit the effect of TMX
- TMX is a competitive inhibitor of estrogen
- TMX must be present in a conc. 100-1,000 times higher than E_2

Cohen I, 1999, Gynecol Oncol

- High estradiol level in premenopausal women has been related to increased incidence of contra-lateral Breast Ca

Baum, 1992, Act Oncol

Mx of ovarian cyst in TMX users

- No specific recommendations regarding the Tx for ovarian cysts in premenopausal TMX users

- F/U without intervention : q3-4-6 mon
- Surgical removal of large complex ovarian cyst
- Cessation of TMX Tx? : better Px with TMX in breast Ca

- USG guided cyst aspiration: high false negative, high recurrence rate, malignancy…
- GnRHa: mainly spontaneous regression, no RCT.. cost-effectiveness?

GnRHa in ovarian cyst with TMX

- Six TMX-treated premenopausal women with ovarian cyst
- Mean age 44yrs (37-51yrs)
- Mean duration of TMX use 15 mo (3-40 mo)
- Serum E_2 939-1796 pg/ml
- All cysts disappeared after 3-6 monthly inj. of GnRHa
- Serum E_2 was also suppressed
- No recurrence during 6 mons of follow up
- GnRHa maybe inhibit the effect of TMX at the level of ovary

Shushan, 1996, Int J Gynecol Obstet

- Long-term cumulative failure rate was 7.4% after 12 months since the Tx with GnRHa.

Kourounis G, The Breast J, 2005

Ovarian cyst in postMP women with TMX

- 32/332 (9.6%) with simple cyst by USG
- No associated clinical factors – no predictive factor
- Decreasing size of cyst over time
- 3/32 pt underwent surgery (9%)
  - Simple ovarian cyst : pelvic pain with 4.6cm cyst
  - Well-differentiated ovarian Ca: increasing size up to 6cm
  - Metastatic adenoCa: increased up to 3.8cm with solid portion
  - Malignant change d/t TMX?
- 11/32 (34%) no change in size
- 9/32 (28%) additional cyst
- Normal serum CA 125

Cohen I, 2003, Radiology

Pathologic result of ovarian mass in breast cancer pts I/II

- N=45

Table 1 Histopathologic findings of adnexal masses in women with breast cancer

Histopathology	*n*	%
Benign	35	77.7
Simple ovarian cyst	25	71.4
Mucinous cystadenoma	2	4.4
Dermoid cyst	2	4.4
Serous fibroadenoma	1	2.2
Endometrioma	1	2.2
Malignant	10	22.2
Primary ovarian cancer	5	11.1
Serous papillary adenocarcinoma	2	4.4
Endometrioid adenocarcinoma	1	2.2
Borderline mucinous tumour	1	2.2
Granulosa cell tumour	1	2.2
Metastatic breast cancer	5	11.1
Lobular carcinoma	3	4.4
Ductal carcinoma	2	6.7

Table 2 Correlation of clinical parameters with ovarian pathology

	Benign mass	Malignant mass	*P*
Age (years)			
≤ 50	27	6	0.438
>50	8	4	
Oestrogen receptor			
(−)	5	5	0.029*
(+)	30	5	
Tamoxifen use			
No	7	3	0.668
Yes	28	7	
Interval to oophorectomy			
≤ 3 years	23	4	0.166
>3 years	12	6	
Ultrasound characteristics			
Simple	25	0	0.000*
Complex	10	10	
Mass size			
≤ 5 cm	22	3	0.83
>5 cm	13	7	
Bilaterality			
Unilateral	29	6	0.194
Bilateral	6	4	
CA 125 level			
Normal	30	2	0.000*
Increased	5	8	

Tuncer ZS, ANZJOG, 2012

Pathologic result of ovarian mass in breast cancer pts II/II

- N=129
- 88% benign and 12% malignancy.

Ovarian Histopathology	n	%
Benign	113/129	88
Serous cystadenoma	39	35
Simple/functional	37	32
Endometrioma	11	10
Fibroma/thecoma	10	9
Mucinous	7	6
Brenner	4	4
Teratoma	2	2
Sertoli-Leydig cell	2	2
Tuboovarian abscess	1	0.1
Malignant	16/129	12
Primary ovarian cancer	14/129	11
Low malignant potential	7	
Epithelial	7	
Metastatic breast cancer	2/129	1.5
Infiltrating ductal	2	

	Odds Ratio	95% Confidence Interval	*P*
Breast cancer hormone receptor			
Estrogen positive	1.00		.003
Estrogen negative	12.4	(2.36–65.1)	
CA-125			
Not elevated			
Elevated	6.29	(1.26–31.46)	.02
Mass size			
≤ 5 cm	1.00		
> 5 cm	4.62	(1.23–17.25)	.02
Adnexal Mass			
Not complex	1.00		
Complex	29.2	(4.77–∞)	< .001

Not significant according to:

Breast cancer stage, LN status, recurrence, pathology

Pt's age, TMX use, FHx of breast cancer

Sx of adnexal mass, bilaterality of adnexal mass

Simpkins F, ACOG, 2005

Hot flush

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

Premature menopause/hot flashes

Recommendation 3.12: It is recommended that primary care clinicians should offer SNRI (selective serotonin-norepinephrine reuptake inhibitors), SSRI (selective serotonin reuptake inhibitors), gabapentin, lifestyle modifications, and/or environmental modifications to help mitigate vasomotor symptoms of premature menopausal symptoms (LOE 5 IA).

- For younger women on endocrine therapies, 50% to 70% will likely experience hot flushes while on tamoxifen.
- The SNRI venlafaxine has been found to be safe and effective in reducing hot flushes.
- There is concern that SSRIs that inhibit the CYP2D6 (CYP450 2D6) enzyme pathway, such as paroxetine, may reduce the conversion of tamoxifen to active metabolites, although a negative impact on breast cancer outcomes has not been conclusively demonstrated.

Non-hormonal treatment

- Non-hormonal medication
  - Antidepressant: venlafaxine, paroxetine, fluoxetine…
  - Gabapentin (anticonvulsant)
  - Clonidine (antihypertensive)

- Phytoestrogen
- Black cohosh – remifemin

- Non-pharmacological intervention

Antidepressants

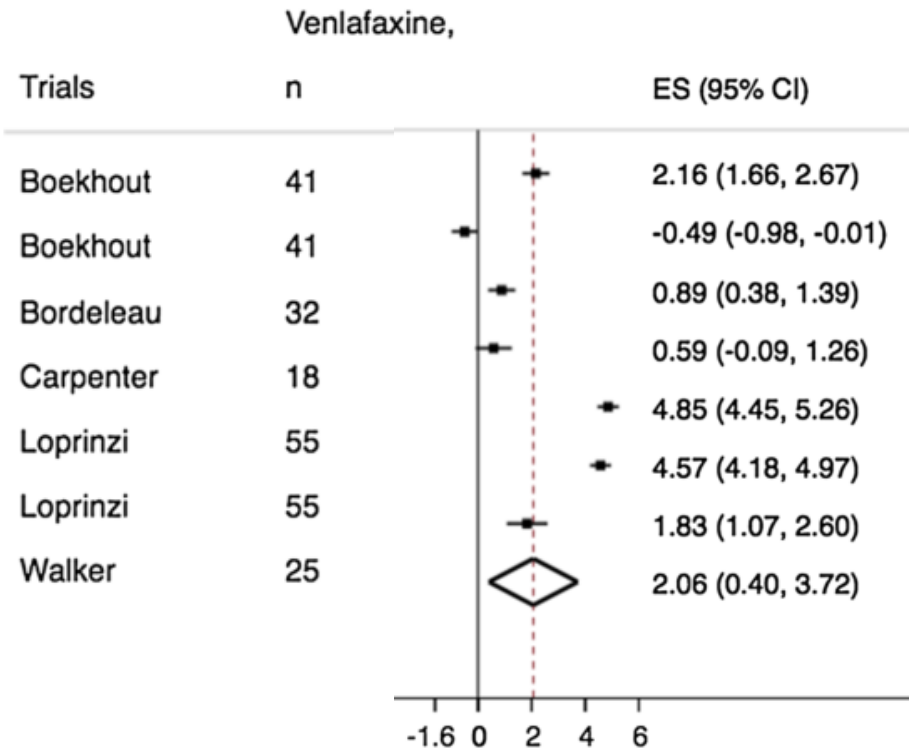
- Serotonin is involved in temperature control
- Venlafaxine, paroxetine, fluoxetine and citalopram all effective in RCTs
- Effect dose dependent
- But most studies short i.e. 3 months
- Longer term studies no effect
- Do not work in all women
- No evidence that these drugs increase the risk of breast cancer
- Common cytochrome P450 CYP2D6: co-administration of SSRI and TMX can decrease active metabolite of TMX

Suvanto-Luukkonen et al. Menopause 2005;12:18-26.

Nelson et al. JAMA 2006;295:2057-71.

Antidepressant

- Venlafaxine (Effexor®)
  - SNRI: selective norepinephrine reuptake inhibitor
  - 37.5 ~ 75mg/day
  - Within 1~2 weeks
  - Reduce hot flash in breast cancer Pt by 61% compared with 27% with placebo
  - S/E: dry mouth, decreased appetite, constipation
  - ContraIx: MAO inhibitor, high BP



Ramaswani R, Breast Cancer Res Treat, 2015

Gabapentin

- Y-aminobutyric acid analogue primarily used as an anticonvulsant, but can also be used for the treatment of neuropathic pain and migraine

- Effectiveness is dose dependent (30-50% reduction hot flush scores, 300-900mg daily)
- 저녁에 300mg으로 시작해서 4-7일 간격으로 증량
- Up to 2700mg/day

- Effective in 50% compared with 29% in placebo
- S/E: somnolence, dizziness, ataxia, fatigue, nystagmus, lightheadedness
- ContraIx: hypersensitivity

Guttoso et al. Obstet Gynecol 2003;191:337-45.

Pandya et al. Lancet 2005;366:818-24.

- Antidepressant + gabapentin: showed better control for flush

Loprinzi CL, J Clin Oncol, 2007

Clonidine

- Centrally acting α_2-adrenergic agonist
- Antihypertensive
- Transdermally (0.1mg patch) or orally (0.05mg bid ~ 0.1mg bid)

- Limited effect on hot flushes
- Reduction of hot flushes in breast cancer patients by 37-46% compared to placebo

- Side effects (10-15%): nervousness, headache, agitation, dry mouth, dizziness, sleeping difficulties, constipation, interaction with other anti-hypertensives

Goldberg et al. J Clin Oncol 1996;12:155-8.

Pandya et al. Ann Intern Med 2000;132:788-93.

Phytoestrogens

- No evidence about efficacy and safety to support the use of phytoestrogens in the Tx of menopausal Sx after breast cancer
- RCTs conflicting evidence on menopause Sxs
- Studies: too short or wrong dose, small N number
- Variable metabolism and production of active aglycone form (35% excrete equol) and may be reduced by high fat intake and increased by raised carbohydrate intake

- Estrogen effect on breast? – relative contraindication for breast cancer survivors?

Non-pharmacological intervention

- Lifestyle modification
  - Rhythmic breathing
  - Vitamins
  - Exercise
  - Avoiding spicy foods, caffeine, alcohol
- Environmental modification
  - Cool rooms
  - Dressing in layer
- Acupuncture

ACS, ASCO guideline, 2016

Vaginal dryness

Vaginal dryness

- Topical vaginal estrogen therapy
  - No association with the increased risk of recurrence of breast cancer in a cohort study
- The serum concentration of estradiol is probably a major determinant of breast cancer risk.
- The issue of blood absorption of vaginal estrogen in breast cancer Pt.
- Variability of systemic absorption of vaginal estrogen according to the duration of Tx
- Very low doses (≤10μg/d) of E_2 provide good local Sx control and virturally no elevation of serum E2 levels in breast cancer patients

Ponzone R, Eur J Cancer, 2005

Vaginal moisturizer in Breast Ca Pts

- Replens®
  - Purified water, glycerine, mineral oil, polycarbophil, carbopol, hydrogenated palm oil glyceride, sorbic acid
  - Vaginal dryness: 62% in placebo, 64% in Repens®
  - Dyspareunia decreased in: 41% in placebo, 60% in Replens®
- Local cream, gels, douches: as substitute for the acidify of the normal pre-menopausal vagina and to provide protection against infection
- Vaginal moisturizers applied on a regular basis have an efficacy equivalent to local hormone therapy for the Tx of local urogenital Sxs (vaginal itching, irritation, dyspareunia)

Castelo-Branco C, Maturitas, 2005

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

Sexual health: Rec. 3.11: It is recommended that primary care clinicians

(a) should assess for signs and symptoms of sexual dysfunction or problems with sexual intimacy (LOE 5 0);
(b) should assess for reversible contributing factors to sexual dysfunction and treat, when appropriate (LOE 5 0);
(c) should offer non-hormonal, water-based lubricants and moisturizers for vaginal dryness (LOE 5 IA); and
(d) should refer for psychoeducational support, group therapy, sexual counseling, marital counseling, or intensive psychotherapy when appropriate (LOE 5 IA).

- Non-hormonal, water-based lubricants and moisturizers remain the primary treatment. Silicone-based products may last longer than water-based or glycerin-based products.
- Hormonal therapies, such as a low-dose estrogen vaginal tablets or an estradiol vaginal ring, may be recommended for vaginal dryness because of urogenital atrophy, although results commonly take approximately 6 to 12 weeks.
- The safety of hormonal therapies in women with a history of breast cancer is not well established at this time. The level of estrogen absorption is variable, which raises concerns in patients who have a history of breast cancer.
- Use of hormonal therapies for women on aromatase inhibitors is not recommended.

Thank you for your attention