ORIGINAL ARTICLE

Non-conventional hormone therapy - Tissue-specific Tibolone-Caution

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ABSTRACT

Objectives: The present retrospective study was undertaken to assess safety profile of long term Tibolone therapy when one of my patients developed carcinoma breast.
Methods: Fifty patients who were put on Tibolone were studied as regards the indication for Tibolone therapy, age distribution, duration of therapy and side effects.
Results: Although most subjects responded well to therapy without significant side effects two patients developed breast lump. One of the breast lumps was malignant, the other benign. It is possible that prolonged Tibolone therapy may have caused carcinoma breast as against the notion that Tibolone is breast protective. Few of recent studies like Million Women Study and LIBERATE study which was concluded in April 2010, have shown that Tibolone also increases risk of carcinoma breast.
Conclusion: Tibolone when used for management of menopausal symptoms should be given for less than 4 years and regular follow up with mammography is must.

Key Words: Breast cancer (Ca), menopause, Tibolone

INTRODUCTION

Conventional hormonal replacement therapy with estrogen and estrogen-progesterone found a place in the management of menopause. Clear-cut follow-up schedules are in place for conventional hormone replacement therapy.

With passage of time we have more therapies in the basket, for example, a widely acting gonadomimetic hormone (with combination of all estrogenic, progestrogenic and androgenic actions) known as Tibolone.

The Women's Health Initiative Randomized Control Trial,[1] Million Women Study[2] brought out what was already known to us that conventional hormone replacement therapy slightly increases the risk of cancer breast, cancer endometrium, if estrogen alone therapy is used. Therefore careful follow-up is recommended by regular general examination, breast examination, mammography, pelvic examination, pelvic sonography and lipid profile.

With the introduction of tissue-specific menopausal therapy by Tibolone which was highlighted to reduce risk of breast cancer (Ca) and Ca endometrium, we encouraged its use. But with increasing usage and experience we realized that Tibolone is not breast and endometrium-safe. So today I take the opportunity to share my experience of Tibolone with you.

MATERIAL AND METHODS

The present study analyzed 50 women who were put on Tibolone for management of menopausal symptoms. The study period was from April 2002 to April 2010. Women received 2.5 mg of Tibolone at night with dinner orally for variable period of time depending on

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their need [Tables 1-5]. The study included the analysis of a range of variants such as:

a. Indication for Tibolone therapy
b. Age of woman
c. Duration of therapy
d. Effectiveness
e. Side-effects

A. The indications for Tibolone therapy included
   a. Prophylactic use
   b. Urological problems
   c. Vulvovaginal symptoms
   d. Skeletal symptoms
   e. Reduced libido
   f. Psychological symptoms
   g. Vasomotor symptoms

B. The age groups were as follows -
   a. 25 - 30 years
   b. 31 - 40 years
   c. 41 - 50 years
   d. 51 - 60 years
   e. 61 - 70 years
   f. Above 70

C. Duration of therapy was recorded.

D. Effectiveness of Tibolone therapy was categorized as follows:
   a. Excellent
   b. Good
   c. Satisfactory
   d. Poor
   e. Side-effects were recorded.

OBSERVATION

The observations have been recorded in tabular form. The total number of women studied was 50 from April 2002 to April 2010 at the Potdar Hospital.

Most women i.e. 94% had excellent response to their symptoms with Tibolone therapy. The patients who responded poorly had medical problems like hyperthyroidism and endogenous depression.

Side-effects of Tibolone therapy

Surprisingly nobody reported side-effects, the ones mentioned here have been noted due to high degree of suspicion.

DISCUSSION

Pharmacology of Tibolone - 2.5 mg Tibolone when

Table 1: Indications for Tibolne therapy

Indications	Number of women
Prophylactic use	20
Urological symptoms	15
Vulvovaginal symptoms	4
Skeletal symptoms	8
Reduced libido	3
Psychological symptoms	9
Vasomotor symptoms	7
Total	66

Total number is more because one subject may have multiple symptoms

Table 2: Age distribution of women

Age group in years	Number of women
25 - 30	3
31 - 40	17
41 - 50	20
51 - 60	5
61 - 70	4
Above 70	1
Total	50

Table 3: Duration of therapy

Duration	Number of women
Less than 6 months	3
6 months to 1 year	10
1 year to 2 years	30
2 years to 3 years	4
3 years to 4 years	2
4 years to 5 years	Nil
More than 5 years	1
Total	50

Table 4: Effectiveness of Tibolone therapy

Effectiveness	Number of women	Percentage
Excellent	47	94
Good	1	2
Satisfactory	Nil	0
Poor	2	4
Total	50	100

Table 5: Analysis of side-effects

Side-effects	Number of women
Gastrointestinal symptoms	Nil
Headache	Nil
Edema	Nil
Acne	Nil
Weight gain	44
Breast tenderness / heaviness	Nil
Breast lump - carcinoma	1
Breast lump - benign	1
Total	46

Four women showed no side-effects

taken orally is quickly metabolized to 3-alpha and 3-beta hydroxy metabolites which bind solely to estrogen receptors, whereas delta-4 isomer has affinity for both progesterone and androgen receptors but not for estrogen receptors.

Tibolone has an estrogenic effect on bone and vaginal tissue. The delta-4 isomer functions as progesterone in endometrial tissue, whereas in brain and liver it is androgenic. In the breast tissue, the main action is strong inhibition of sulfatase activity and weak inhibition of 17-beta hydroxysteroid dehydrogenase activity which prevents conversion of estrone sulfate to estradiol. And thus it was thought to reduce breast pain and density helping better mammographic interpretation as well as protection of breast from cancer.[3,4]

Merits and Demerits of Tibolone

Tibolone has an advantage over other forms of hormone replacement therapy as it is easy to use and does not induce withdrawal bleeding in postmenopausal women. It is effective in preventing and reducing vasomotor, urogenital symptoms and osteoporosis. The androgenic action of Tibolone may help depression and libido more than any other form of hormone replacement therapy. Tibolone has been considered and promoted as safe for the endometrium and breast and may provide some cardiovascular protection to these women. Tibolone is the therapy of choice for postmenopausal women, more so in elderly women (65 years) with contraindication for estrogen therapy like breast and endometrial cancer, hypertriglyceridemia and endometriosis.[5] The only disadvantage probably is stroke which may occur in some elderly women.[6]

Incidence of Breast Cancer

The Mumbai cancer registry shows a sharp rise in the incidence of cancer with increasing age. In females the cancer of breast is by far the commonest cancer at all ages (21.2 / 1 lakh) but its incidence peaks in the age group 65-69 years (149.3 / 1 lakh).

Result from Present Study

The present study shows that Tibolone is very effective in the management of menopausal symptoms, 94% showing excellent response. It is a very well tolerated drug; only weight gain of 1.5 to 2 kg was seen in most women when the therapy period was of about two years [Table 6].

The significant finding of the present study was the development of carcinoma breast in one of the subjects who needed Tibolone for more than five years [Table 7]. This patient underwent hysterectomy at the age of

Table 6: Weight gain during Tibolone therapy

Weight change observed in grams	Number of women
Weight loss	3
Weight remained same	3
0-500	1
501-1000	2
1001-1500	1
1501-2000	30
2001-2500	Nil
2501-3000	1
Above 3000	9
Total	50

Table 7: Incidence of cancer breast in women who are nonusers of estrogen-progesterone therapy (EPRT) as against women who use this therapy for 5 to 15 years[7]

Years of Taking EPRT	Breast cancer over 20 years (50 - 70)	Excess breast cancer in EPRT
Non-user	45/1000	-
5 years	47/1000	2/1000
10 years	51/1000	6/1000
15 years	57/1000	12/1000

40 years in the year 1998. She was put on Tibolone for menopausal symptoms. Although tapering was repeatedly tried because of recurrence of menopausal symptoms, it had to be restarted. A lump was noted in the right breast in November 2009. Mammography and needle biopsy were negative. Repeat investigations in April 2010 were positive for malignancy. She was managed with surgery and chemotherapy.

It appears that this malignancy was as a consequence of prolonged Tibolone therapy. It is possible that aromatase in breast tissue which is not suppressed by Tibolone might have led to the formation of a significant amount of estradiol in the breast.[3] Similar findings were found in the LIBRATE study[8] where women treated for cancer breast were put on Tibolone therapy for management of menopausal symptoms. The study was completed in April 2010 and showed recurrence of cancer breast with no protection offered by Tibolone. The Million Women Study[1] also showed that Tibolone had nearly 1.5 times the risk of breast cancer as compared to women who never used hormone replacement therapy.

Whereas the THEBES study[4] showed that the Tibolone group had a 3.1fold decrease in risk of invasive breast cancer. The only drawback of this study is that the follow-up is only of two years which is not enough to give reliable results.

CONCLUSION

Tibolone is not without risk when taken beyond five years. In case it is essential to continue, frequent mammographic studies are required.

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