COMPARISONS BETWEEN THE NON-PROLIFERATIVE AND PROLIFERATIVE THERAPY IN FIBROCYSTIC MASTOSIS

A. Carauleanu¹, R. Socolov¹, V. Rugina², O. Gabia², Daniela Mihaela Carauleanu², Ivona Anghelache Lupascu², Demetra Socolov¹
University of Medicine and Pharmacy “Grigore T. Popa”- Iasi
Faculty of Medicine
1. Department of Mother and Child Medicine
2. “Cuza-Vodă” Obstetrics and Gynecology Clinical Hospital, Iasi
* Corresponding author: E-mail: drcarauleanu@yahoo.com

COMPARASIONS BETWEEN THE NON-PROLIFERATIVE AND PROLIFERATIVE THERAPY IN FIBROCYSTIC MASTOSIS (Abstract) Aim: Fibrocystic mastosis (FCM) is the most frequent benign breast lesion. Most treatments for fibrocystic mastosis are: hormonal, with beneficial results and non-hormonal, with fluctuating results.

Material and methods: A number of 210 cases were studied, which were divided into 7 groups. The study lasted for 9 months and it was carried out on the basis of a personal examination sheet. The following were monitored: age groups, mastodynia, reducing breast nodules, a significant reduction in the volume of the mastosic cysts, reduction of the fibrous tissue, medication tolerance.

Results: Mastodynia has declined by 90% in the cases treated with Tamoxifen and Danazol, by 70% in the case of Lynestrenol and Bromocriptine, by 50% in the 15 patients who were given Utrogestan. Knowing the advantages and disadvantages of drugs (contraindications, side effects), age category, breast pain reduction, antiproliferative activity, tolerability, relapse allow us to assess the benefit-risk. Even in those circumstances that remained incompletely clarified for objective reasons, related to the inaccurate/incorrect reporting by the patients, there is a significant difference (p <0.05) between the frequency of relapses following the treatment with Tamoxifen and the other categories of drugs who were administered.

Conclusions: Our study shows that in the groups that were administered Logest, Utrogestan and Bromocriptine, only antalgic effects were achieved (disappearance or only decrease of mastodynia) and no anti-proliferative effects were obtained. Basically, hormone treatment should be made based on a histopathological examination. Keywords: BENIGN BREAST DISEASE, PROLIFERATIVE, MASTOSIS.

Histopathologically, the fibrocystic mastosis (FCM) is defined as all the dystrophic changes in the breast tissue, the gathering under the form of fibrosis of the epithelial, cystic, metaplastic and hiperplastic modifications. The disease classification is different; the French authors consider it as mammary distrophy: fibrocystic mastosis (FCM), while the American authors consider it as a benign breast disease (benign breast disease). There is no current consensus on the content of this notion.

Both the diagnosis and the treatment of the benign breast diseases remain a challenge, and the indication for surgery is not clearly defined.
Any of the 3 categories of histopathological lesions has a different risk with regard to the possibility of occurrence of the breast cancer in the next 15 years, so that the non-proliferative do not increase the risk of a breast cancer, even if there is a family history of breast cancer, the proliferative lesions without epithelial atypia are risk around 2 for the appearance of a breast cancer, taking into account the associated epidemiological factors (1).

In order to assess the therapeutic value of a medicine we must take into account the risk/benefit ratio, and the risk is determined according to the contra-indications and adverse side effects(8).

Hormonal treatments are justified by hormonally dependent character, and possibly regressive, of the parenchymatous breast proliferations: cysts, apocrine metaplasia, ductal epithelial hyperplasia (epitheliosis), lobular epithelial hyperplasia (adenosis) (7).

For some drugs with hormonal action it has been demonstrated that they have an anti-proliferative activity, e.g.: Lynestrenol (which is a norsteroid), Tamoxifen and Danazol.

Cupceanu reported that 48 women with benign breast disease (BBD) were treated with Tamoxifen + Lynestrenol, and that the combination of these medicines has reduced substantially the size of adenomas, fibroadenomas, cysts and dysplastic lesions. Thus it was showed that Tamoxifen also had an antiproliferative action (2).

Hurst et al. (3) argued that Tamoxifen produces significant regression of the breast cysts. Viviani et al (4) in the study "Ultrasound evaluation of the volume of breast fibroadenoma in women treated with Tamoxifen" conclue that this drug significantly reduces the volume of fibroadenoma when administered for 50 days at a dose of 20 mg per day.

Tan Chiu et al. (5) stated that, in 1998, the National Surgical Adjuvant Breast and Bowel Project had demonstrated that the treatment with Tamoxifen reduces the incidence of noninvasive and invasive breast cancer in the woman at high risk for this disease (thus Tamoxifen is recognized as having a prevention effect on the breast cancer).

The same authors had found that Tamoxifen reduced not only the risk of non-invasive and invasive breast cancer, but it also reduced the risk of benign breast disease relapses (BBD) and morbidity and the costs of repeated diagnoses and treatments that are associated with them. Thus, Tamoxifen is recognized as having a prevention action of the BBD relapses, including FCM.

Pricop et al. (6) states that Danazol can accomplish the disappearance of the cysts smaller than one inch in diameter, but that doesn't seem to diminish the fibrous tissue. Le Franc et al. (1990) specifies that, for the objective amelioration of the FCM "tumour plaques", 6 months are required and these results are not superior to those who followed a treatment with progestagens or with birth control pills, with progestagen predominance.

On the other hand, progestagens and bromocriptine are effective in the treatment of mastodynia (especially in cyclical mastalgia) and, to some extent, in fighting against breast nodes.

Currently there is no encoding in the use of these broad categories of hormonal medications: oral contraceptives, progestagens (Utrogestan), norsteroids (Lynestrenol), antiprolactinics (Bromocriptine), antgonadotrope drugs (Danazol, LHRH
Comparisons between the non-proliferative and proliferative therapy in fibrocystic mastosis

agonists) and antiestrogens (Tamoxifen).

However, in the literature (1) it was mentioned that, because of the adverse side effects of the norsteroids, in practice it is recommended to start preferably with progesterone, locally and/or general, and in the event of inefficiency to resort to other treatments, first the norsteroids (Lynestrenol), then Danazol or antiestrogens (Tamoxifen).

MATERIAL AND METHODS

A number of 210 cases were studied, which were divided into 7 groups. The study lasted for 9 months and it was carried out on the basis of a personal examination sheet (fig. 1).

The data collected as study material and considered refer to: the total number of cases under investigation and diagnosed with fibrocystic mastosis, the division of cases into age groups, admission reasons, clinical examination, pathological personal history of clinical relevance for the basic disease (main diagnosis), family history relevant for the basic disease, anatomo-pathological diagnosis, the treatment followed.

The local administration of Diclofenac gel in the first 10 days after menstruation has been justified by the chronic inflammatory process due to the breaking up of the cysts and the release of their contents in the surrounding stroma.

Fig. 1. Structure according to categories of patients included in the study
In 6 of the lots (of 30 patients each) a local background treatment with diclofenac gel and progestogel. Lot 7 was made of patients who refused any treatment (control group).

Each of the 6 groups were given, in addition to diclofenac gel and progestogel, one of the following drugs: Logest- 21 cp per month, 6 months; Utrogestan 10 days per month, 6 months; Lynestrenol 10 days per month, 3-6 months; Bromocriptine (parlodel), 3 months; Danazol 200 mg/day - 3 months; Tamoxifen 6 months. We have not had cases with LHRH (gonadotropin releasing hormone) treatment.

They were studied under this treatment, at first, after 3 months and after 6 months, by imaging (ultrasound and mammography) and FNAC - fine-needle aspiration cytology (sporadically). Further on, we studied, at 9 months, the possible relapses and some histo-pathological examinations after these hormonal treatments.

The following were monitored: age groups, mastodynia, reducing breast nodules, a significant reduction in the volume of the mastosic cysts (which has been made by ultrasonography), reduction of the fibrous tissue, medication tolerance (frequency of relapses; risk/benefit ratio).

RESULTS
The FCM incidence is estimated in over 60% of women. It is frequent in women of ages between 30 and 60 years. For the data in our study, we calculated the FCM incidence signalled in relevant personal history to 20%; obviously, values were lower after referring to the entire batch under study, namely 6.68%.

Most part of the patients who attended our unit came from the urban environment (66.9%), and the ones from the rural environment were only 1/3 of the reported cases (33.1%).

Depending on the age of the lot, the women aged between 20-30 years were administered, in an equal number of cases, namely 30 cases (out of a total of 90 cases), Logest or Utrogestan or Lynestrenol, and the women aged 26-40, i.e. 30 cases, were given Bromocriptine. In other 30 cases, the women aged between 30-40, were given Danazol, and Tamoxifen was administered to 30 patients placed in perimenopause, although Tamoxifen is recommended as the first-line treatment.

Mastodynia has declined by 90% in the cases treated with Tamoxifen (27 patients) and Danazol (27 patients), by 70% in the case of Lynestrenol (21 patients) and Bromocriptine (21 patients), by 50% in the 15 patients who were given Utrogestan. In only 9 patients (30%), mastodynia was reduced in case of the treatment with Logest.

Another aspect that was had in view was the reduction of the nodules. This reduction was present in 80% of cases treated with Tamoxifen and Danazol in 50% of the cases treated with Lynestrenol, 40% of the cases receiving Bromocriptine, 30% of the cases treated with Utrogestan and 20% of those treated with Logest.

The volume of mastosic cysts, according to the diameter of the cysts measured by ultrasound, was reduced in a percentage of 80% in the cases treated with Tamoxifen and in those treated with Danazol. In the case of the treatment with Tamoxifen, the volume of the mastosic cysts was reduced by 50% in the case of the cysts with the diameter greater than 1 cm and reduced in full in the case of the cysts with a diameter smaller than 1 cm. As for the Bromocriptine and Logest, in none of the cases there has been a reduction of the volume of the mas-
Comparisons between the non-proliferative and proliferative therapy in fibrocystic mastosis

totic cysts.

According to the reduction of the fibrous tissue under therapy, the influences (actions) of the physiotherapy treatments (ultra-rays, ultrasound, etc.) on the fibrous tissue have not been studied. No hormonal drug has reduced the fibrous tissue. This is an argument for the usefulness (or necessity) to prevent the formation of the fibrous tissue, via the early treatment of the fibrocystic mastosis. The fibrous tissue is not hormone-dependent.

The case distribution according to the tolerability of the treatment was of 100% in the cases treated with Logest and Utrogestan, with a very good degree of tolerability. The degree of tolerability is good in the cases treated with the other treatments.

In terms of the frequency of relapses, the results we obtained were as follows: for patients receiving treatment with Logest, Progestogel, Utrogestan (Duphaston) or Bromocriptine, the frequency of relapses was of 70%. In the case of the treatment with Lynestrenol, we noticed a presence of relapses in 50% of the cases. Danazol caused a lower frequency of relapses in only 30% of the cases. The best results were achieved following the treatment with Tamoxifen for which relapses were mentioned in only 20% of the cases.

After the experience of Pricop et al.-2003 and of Tan Chiu et al, 2003, and also after our personal experience, the risk-benefit ratio is most favorably inclined towards Tamoxifen, that does not represent any hazard at the dose of 10 mg/day (3 months).

DISCUSSION

Knowing the advantages and disadvantages of drugs (contraindications, side effects), age category, breast pain reduction, antiproliferative activity, tolerability, relapse allow us to assess the benefit-risk.

In order to assess the risk/benefit ratio, we must know the risks, which are represented by the contraindications and adverse side reactions.

It is known that if a drug, at a specific dose, has a favorable action in a certain direction but it has adverse side effects of high intensity, the risk/benefit ratio is low and the use of such drug is more limited.

In these cases the therapeutic strategy means associating more drugs with the same desired beneficial action, but with different adverse side effects (which are not cumulative). In this way drugs can be administered in low doses because the beneficial effects are cumulative and the adverse side effects are different and of low intensity, and they are not cumulative because they are not identical. The combination of drugs that have the same adverse side effects or similar side effects is contraindicated, as they will be cumulative.

Therefore, in treating FCM, the association of Lynestrenol with Danazol is not indicated because they have virilising side effects and adverse effects (on the liver) in liver diseases. The association of Danazol and Tamoxifen is not found in the literature, likely because both can cause prolonged amenorrhoea (though perhaps not by the same mechanism) and due to weight gain (fluid retention).

Moreover, except for the combination of Progestogel with an oral progestagen, and the combinaton of Tamoxifen with Lynestrenol (2), we have not found in the literature any other drug combination for the treatment of FCM.

Since the administration of Progestogel is relatively efficient and the most anodyne, we maintained the administration preceded
by Diclofenac gel in all cases, whether we associated it to Utrogestan, Lynestrenol, Bromocriptine, Danazol or Tamoxifen (the latter two at the minimum effective dose to reduce the adverse side effects that limit their use).

Another problem is the main drug choice based on age. Thus, in young patients, progestins were used, like simple Progestogel or combined with Utrogestan, or in rebel cases, Utrogestan was replaced by Lynestrenol (norsteroid progestagen).

Over time, the mastosic cysts can increase in size and number, accompanied by fibrous elements whose provenance is insufficiently known. This is why in our series the treatment, in all the groups, maintains the local use of Diclofenac gel.

In patients over 30-35 years old and in premenopause patients we used Danazol or Tamoxifen. By administrating Utrogestan, Bromocriptine, Danazol, Tamoxifen, under the same conditions, we have created the opportunity to compare their effectiveness.

The fibrous tissue prevents the access of drugs to the mastosic cysts and it is more resistant to treatment, if not even far from any effect, therefore much more effective drugs are necessary (even if they have more important adverse side effects) (9).

Even in those circumstances that remained incompletely clarified for objective reasons, related to the inaccurate/incorrect reporting by the patients, there is a significant difference (p <0.05) between the frequency of relapses following the treatment with Tamoxifen and the other categories of drugs who were administered.

The intent of obtaining histopathological results after the hormonal treatments administered for 3-6 months has not been achieved because the patients refused the biopsy and even the fine needle aspiration cytopunction (10).

Following these results, there is the issue of choosing, between these drugs, the most beneficial hormonal treatment, taking into account the benefit/risk ratio, or possibly the individualization of these treatments.

CONCLUSIONS

Our study shows that in the groups that were administered Logest, Utrogestan and Bromocriptine, only antalgic effects were achieved (disappearance or only decrease of mastodynia) and no anti-proliferative effects were obtained.

In correspondence to the literature data, we found that, in a number of cases, relapse occurred.

In the group under Bromocriptine, tolerability was average, while it was very good in the other two groups. In the groups that were administered Lynestrenol, Danazol and Tamoxifen anti-proliferative effects were achieved (beside the disappearance of mastodynia).

Therefore, under Lynestrenol, the nodules (tumour plaques) disappeared, along with some of the mastosic cysts under 1 cm, and the mastosic cysts larger than 1 cm reduced their size. Tolerability was good.

Under Danazol, the nodules (tumor plaques) disappeared, along with many of the mastosic cysts under 1 cm, and the mastosic cysts larger than 1 cm reduced their size. Tolerability was average.

Under Tamoxifen, the nodules (tumor plaques) disappeared, along with many of the mastosic cysts under 1 cm, and the mastosic cysts larger than 1 cm reduced their size. Tolerability was good.

Further on, we found that after the treatment with Tamoxifen the relapses were the fewest.
Comparisons between the non-proliferative and proliferative therapy in fibrocystic mastosis

Before beginning the hormone treatment for FCM, malignancy should be excluded, as we must not forget (1) that a malignant lesion can simulate a benign one. According to our personal experience, and to the experience of Pricop et al. (6) and Tan Chiu et al. (5), the most favorable benefit-risk ratio refers to tamoxifen, which in the dose of 10 mg/day (3 months) is not dangerous for the patient.

REFERENCES