Ovarian Supression/Ablation in Breast Cancer: a brief history

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“There are things enclosed within the walls that, if suddenly go out to the street and shout, would fill the world”.
Federico García Lorca

In 1866, Astley Cooper said that some breast malignant tumors became notorious during the premenstrual period. Paradoxically, Thomas W. Nunn in 1882 noted that many patients, beginning the menopause, presented a important reduction of the tumor size. Albert Schinzinger in 1889 proposes carrying out oophorectomies as part of breast cancer treatment, however the presentation of its observations at the Congress of Berlin that same year failed to convince his colleagues.

George Beatson in Scotland, knowing the tradition of farmers who castrated cows, after delivery, in order to maintain milk secretion, was convinced that breastfeeding was controlled from the central nervous system. He devoted himself to find the nerve connecting the brain with the breast, making sections of the spinal nerves and sympathetic branches in sheep that were breastfeeding, without being able to suppress lactation. Beatson, argued that the breast histopathological changes during breastfeeding were almost identical to those seen in malignant neoplasms and raised in his publication in The Lancet during 1896. Ensuring that menstruation during breastfeeding is inhibited temporarily, decided to try suppressing menstrual cycles by oophorectomy and thus eliminating tissue proliferation in breast. He makes his first observations in breastfeeding does and noticed that when removing the ovaries, could suspend breastfeeding and at autopsy, months later, observed a proliferation of adipose tissue, i.e. as he expressed it in his work: "the milk turned into fat". In that same publication describes three cases of premenopausal patients with locally advanced breast cancer who recorded a remission after oophorectomy, communicating that one of them survived the surgery four years. For 1928,
Striggard would discover that the nerve that Beatson sought in a feverish way was a hormone that we know today as prolactin.

At the beginning of 1900, oophorectomy was gaining popularity slowly despite very encouraging results. The mortality of this intervention, which was not insignificant, was their main impediment. In 1905, Fouveau of Cournelles and Wintz in 1924 proposed radiant ablation. Using a dose of about 1,550 rads, produces suppression of ovarian function that was achieved at three months. Starts a struggle between the two methods of ovarian ablation and for the beginning of the 1960's many centers in Europe, among them the Institute Gustave Roussy, had replaced the oophorectomy by radiant ablation.

But despite the suppression of ovarian function, many patients did not present a sustained response and relapse frequently. In 1950 Huggins and Dao propose adrenalectomy in patients previously castrated, with active disease and that the Pap smear showed signs compatible with estrogenic activity. This method was also used in patients with active disease and more than five years of menopause. Adrenalectomy was made possible thanks to the fact that patients could then receive substitution treatment with cortisone, which had been isolated shortly before by Kendall, Hench and Reichstein, work which had granted the Nobel Prize in Physiology and Medicine in 1950. Adrenalectomy had a short life as a therapeutic measure for breast cancer mainly by high morbidity and operative mortality. At the beginning of 1960 aminoglutethimide, an anticonvulsant is discovered with powerful non-selective inhibitor of adrenal steroidogenesis properties, together with the replacement cortisone definitely displaced adrenalectomy. In 1956 Huggins shared the Nobel Prize in Physiology and Medicine with Peyton Rous.

In 1953 Olivercrona, disciple of Harvey Cushing one of the most brilliant students of Williams Halsted, and Luft introduced transfrontal and transphenoidal hypophysectomy as endocrine ablation in breast cancer. With this new intervention, as Junqued Avello well described: “...are determined the adrenal and estrogen suppression at the gonadal level eliminating the respective trophic or stimulating hormones (- FSH and LH - gonadotropin and adrenocorticotrophic -ACTH-) as well as the growth hormone, TSH and prolactin”. As can be seen, in the field of endocrine surgery, hypophysectomy was the best expression of the predominant ultra-radical thought in breast cancer treatment in the early 1950's. In Venezuela, in the Instituto de Oncología Luis Razetti, Samuel Darío Urdaneta was one of the pioneers of this technique.

At the end of the 1960's, profound changes occur, among them the introduction of oral contraceptives (OC). In the search for the best formulation for these drugs tamoxifen and
clomiphene grabbed attention as estrogens candidates. Clomiphene, which did not function as estrogen, began to be used as an effective inducer of ovulation since 1982. Meanwhile the tamoxifen, a no steroid and synthetic component that acts as a selective modulator of the estrogen receptor, considered a failure as an estrogen component within a formulation of OCs, was tested in patients with advanced breast cancer by its creator Arthur Walpole at the Christie Hospital in Manchester in the United Kingdom in the mid-1960. In 1973, Craig Jordan in Massachusetts demonstrated its efficacy in ER+ tumors. As it is described in the article Tamoxifen: 50 years later... long life to the king, this drug became from being a disappointing drug in the opinion of many, to convert it in one of the more important drugs in the treatment of the cancer of breast.

The essays begin in the treatment of advanced breast cancer, then in adjuvant therapy, coinciding with Gockermann tests to compare tamoxifen with the controversial diethylstilbestrol. The tamoxifen came to constitute a new option in patients with metastatic disease or as adjuvant in early tumors and, from 1998, as a breast cancer prevention measure. Its introduction meant a huge change in the perception of the treatment. Thanks to a well-structured and understandable bio-based, adjuvant endocrine therapy is today one of the major research fields and tamoxifen remains, for almost three decades, as the adjuvant endocrine therapy of choice in premenopausal patients with ER+ tumors.

In recent years, treatment with tamoxifen has been object of new schemes. While it has maintained its dosage of intact form, with the publication in December of 2012 of the ATLAS trial (Adjuvant Tamoxifen: Longer Against Shorter), the extension to 10 years today is an available alternative especially for young patients who maintain their ovarian function after five years of treatment and adequately toleration of the drug. Another sub-group with indication for extension are the postmenopausal patients with intolerance or contraindication to be changed to an aromatase inhibitor. With a very discreet reduction in relapses (3.7%) and mortality (2.8%), even this option doesn’t fit as a routine therapy.

Another choice is to add, to tamoxifen treatment, an ovarian suppression/ablation procedure (OS). The oldest endocrine management measure in the treatment of the breast cancer in premenopausal patients returns to be explored. Since the publication of Beatson, 120 years have passed in when has not taken his eyes off of estrogen and especially of the ovaries. For the present time OS can be done by oophorectomy, ablation with radiation therapy or the administration of GnRH analogue agonist. Similarly, the temporary or permanent failure of ovarian
function occurring after administration of adjuvant chemotherapy, is also considered a form of OS.

The use of tamoxifen or an aromatase inhibitor (AI), as the exemestane, with OS fits perfectly with the concept of hormone total blockade, i.e. cancel the oestrogenic effect by modulating its receptor and also inhibiting its synthesis.

As for the oophorectomy, via a laparotomy or laparoscopic, is the more quickly OS. However it is an irreversible measure, which can be not indicated in patients younger than 40 years who wishes to keep her fertility once the treatment with tamoxifen for five years conclude. Additionally, in this group of patients with absolute contraindication to receive hormone replacement therapy, early menopause might decrease the quality of life for the impact on the emotional, sexual, bone and cardiovascular area. In patients before the age of 35, with proven BRCA1 or BRCA 2 mutation and later to a genetic counseling, performing a reducing bilateral adnexectomy of risk would be an indication which could envisage. In this case the OS and decreased risk of ovarian cancer, it would be done as an interesting added value.

Ablation by radiotherapy is perhaps less attractive measure. With a failure rate of around 35% and the side effects in the medium and long term at pelvic level, are the major arguments against. The OS, which is irreversible, is reached between 2 and 3 months of having received the radiant dosage, which limits even more its routine implementation. Perhaps the only indication on which stays as a rescue alternative, is in premenopausal patients with disease metastatic ER+ and whose clinical condition or for other reasons not possible other form of OS.

On the other hand the OS with GnRH analogues is perhaps the faster and more cost-efficient measurement now. Its excellent profile of tolerance, almost immediate effect and more importantly its reversibility makes it the most suitable option in young women. In addition, these drugs allow a better tolerance to tamoxifen, avoiding frequent menstrual disorders during treatment with tamoxifen only.

From the publication of the SOFT and TEXT studies, the need to suppress ovarian function has become an indication with a high level of evidence, thanks to a significant reduction of 22% in the risk of relapse in the tamoxifen group with OS (HR: 0.78, p = 0.03). At five years, 88.4% of patients with tamoxifen and OS remained relapse-free compared with 86.4% of patients with tamoxifen alone, with a significant difference, after adjusting for Cox analysis (HR: 0.75 p = 0.02). However, the overall survival at five years was 96.7% in patients taking tamoxifen with OS, compared to
95.1% in the tamoxifen only group, difference that was not statistically significant. However, in the subgroup of patients at increased risk of relapse, especially those undergoing previous chemotherapy, overall survival at five years was 94.5% in the tamoxifen group with OS and 90.9% in patients with tamoxifen only, a difference that was statistically significant (HR: 0.64 CI, 0.42-0.96). At the same time, in the analysis combined, is demonstrated that the exemestane added to OS reduced the recurrence in 34% in comparison with a reduction of 22% with tamoxifen with OS.

Today we can pharmacologically act on the synthesis estrogenic, well modulating the receptor or blocking its action in the cell tumor in an accurate way. We can inhibit the ovarian function, in a reversible way and with lower morbidity, selectively turning off the action of the hypophysary gonadotrophins using GnRH analogues, as Olivercrona and Luft proposed with hypophysectomy and Beatson with oophorectomy. Can be blocked, also reversibly, the conversion of androgens to estrogens, using an aromatase inhibitor, under the same driven force that were tried with adrenalectomy and aminoglutethimide, without paying the price of a syndrome of Addison. Even with the strong existing evidence, unable to achieve OS with GnRH analogues for the recurring failure of these drugs in Venezuela, oophorectomy is not ideal alternative in patients under 40 years because its irreversibility makes it a measure excessive and with effects that impact negatively the quality of life. Choose to keep the single treatment with tamoxifen is one of the more reasonable options. However in women to five or less years of the likely age of menopause, in the absence of GnRH analogues, oophorectomy may be a feasible option. Inhibit in a reversible way, quickly and efficiently the ovarian function with a drug is one of the greatest advances of our time. For this reason, back out because a necessity to oophorectomy in the XXI century, which brilliantly raised Beatson in 1896, will always mean a worrying setback.

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