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Photobiomodulation - Perspectives in the Treatment of Genital Consequences of Cancer Therapies: Literature Review

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Introduction

In women, the cancer treatments (surgery, chemotherapy, radiation therapy, hormone therapy) and especially gynecological cancers treatments have a non-negligible impact [1]. Indeed, the damages to the reproductive organs and sexual activity can be transitory or permanent, early or delayed and even prolonged in time resulting an impaired quality of life [2,3]. Radiation therapy alone or combined with other anticancer treatments such as surgery and chemotherapy, induces early menopause or makes worse genitourinary symptoms of menopause in women of different ages [4]. The radiation therapy and some chemotherapy drugs can cause vaginal lesions starting with inflammation of the mucosa and submucosa leading to ulcerations, necrosis and then fibrosis. The vaginal wall becomes rigid, narrow, and short and can stenos, thus making sexual intercourse uncomfortable and even impossible in case of complete stenosis [5,6].

The early assessment and identification of disabling symptoms, the use of dilators associated with psycho-emotional or sexologist support, or even local hormonal therapy (when it is allowed), form an important part of the care provided to women who survived cancer [7,8]. However, these treatments are often restrictive (regular use and uncomfortable dilators, destruction of vaginal hormone receptors by the radiotherapy) and therefore with moderate effectiveness [9].

In addition, for many years, the light has been used on the female genital tract through so-called "ablative" lasers (treatment by excision) in various pathologies such as neoplastic intraepithelial lesions or endometriosis, or condylomas. Even more recently, so-called "non-ablative" lasers (fractional CO2, Yag, Erbium) are used to treat genitourinary menopause syndrome and urinary incontinence, or for vaginal rejuvenation [10-14]. These indications have been also extended to the genitourinary consequences of anti-cancer treatments in breast cancers in particular and gynecological cancers [15,16]. After the analysis of the studies which are heterogeneous and often have limitations, the European Society of Sexual Medicine has made no recommendations in favor of using the lasers in these indications. The Food Drug Association has also issued a safety warning for these indications [17,18]. The Photobiomodulation treatment (PBM) which also uses the light's effects can be proposed as an alternative to the use of fractional laser, whose safety of use appears to be controversial.

This article reviews the biological basis, the symptoms and management of genitourinary complications which are secondary to anti-cancer therapies and examines the current status and justification for the use of PBM in these indications.

Toxicity of Anti-Cancer Treatments on the Genitourinary Sphere

The anti-cancer treatments can cause damages to the feminine reproductive organs and sexual activity:

- Surgery is a great purveyor of rigid and painful scars;
- Chemotherapy is responsible for mastitis, peripheral neuropathies and premature ovarian failure;
- Hormonal therapy is making worse the climacteric symptoms;

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- Radiation therapy is responsible for long-term fibrosis and vaginal stenosis by direct involvement of the mucosa and submucosa.

Therefore, we will review the cancers whose treatments are likely to cause toxicity on the genital sphere, which is responsible in the long term for an impaired quality of life.

Gynecological cancers

The gynecological cancers include cancers of the cervix, endometrium, vagina and vulva.

The cervical cancer is the 12th most common female cancer in France, but its incidence is decreasing in this country. His predilection is the cervical ostium even if there is also a vaginal involvement. It is viro-induced by the Human Papillomavirus (HPV) oncogene and affects young patients between 25 to 64 years old [19].

The endometrial cancer is the 4th most common female cancer in developed countries. Its incidence is increasing in France. Its main causes are hyperoestrogenism, aging and genetic transmission, in a low percentage. The patients are older with an average at 63 years [20].

The vaginal cancer is rarer, 2% of gynecological cancers, mainly viro-induced by oncogene HPV. He occurs rather in post menopause, but in 15% of cases it affects women under age of 40 (in utero exposures to Diethylstilbesterol) [21].

The vulvar cancer is also rare, 4% to 5% of gynecological cancers. There are 2 different epidemiologies: young female cancer that is viro-induced to HPV oncogene and favored by immuno-depression and tobacco and cancer of older women occurring in the context of prolonged chronic inflammatory vulvar disease [22].

In the early stages, the treatment of these tumors mainly involves surgery combined with external beam radiation therapy or brachytherapy, or chemotherapy alone, or radio-chemotherapy depending on the stage and type of disease, the patient's condition and comorbidities [23-27].

The toxicity's severity on the urogenital sphere is more important if the treatments are combined, the doses are high and if the patient has risk factors like an advanced age, obesity, and diabetes or tobacco consumption. It depends also on the technique used for radiotherapy [28-30]. For chemotherapies such as Taxanes or Platinum agents, there is a neurological toxicity (Chemo-Induced Peripheral Neuropathy), which can lead to pain of the urogenital sphere [31,32].

For radiotherapy there are 2 phases that can explain the observed symptoms:

- In the acute phase (0 to 3 months): Edema and inflammation lead to dysfunctional bladders (dysuria, instabilities, pollakiuria, incontinence) but also hematuria or even fistulas;

- In the late phase (> 3 months): The micro-avascularization disorders are the cause of an arterio-capillary fibrosis responsible for cellular hypoxia by decreasing the infusion in the healthy tissues. As consequence, the increased lactate levels leads to low collagen production by fibroblasts and therefore tissues hypoplasia, atrophy, fibrosis and therefore functional deficit. Especially during this phase, we see the complications in the genital sphere that affects the woman's sexual health (bleeding, inflammatory pain, dyspareunia, xerosis, and vulvo-vaginal stenosis responsible for a low libido) and therefore the quality of their life [33-35].

Other cancers

In young women treated for breast cancer, the adjuvant hormonal therapy has proven benefits in terms of survival. However, these agents represented by Tamoxifen, anti-aromatases, and LHRH analogues, develop important side effects, especially in the genital sphere (vaginal dryness, sexual disorders with the decline of libido) that can lead to poor adherence to the treatment [36,37]. In addition, the implementation of a prophylactic bilateral salpingo-oophorectomy in young patients with BRCA mutation reduces the risk of developing breast or ovarian cancer, but is causing also the early menopause with its side effects on the sexual health and quality of life [38].

After an allograft of hematopoietic stem cells there are gynecological complications such as premature ovarian insufficiency (gonadotoxicity of the pre-transplant conditioning regimen), chronic Graft-*vs.*-Host Disease (cGVHD) of the anogenital zone (cGVHDgyn) and secondary neoplasms (prolonged immunosuppression after transplantation) [39,40]. cGVHD remains a common toxicity and a major cause of morbidity and mortality in patients who have had an allo-stem cell transplant. Genital involvement can be associated with ocular, oral, digestive and cutaneous injuries. It can lead to a complete obliteration of the vagina, therefore to hematometra, inability to sexual intercourse and inability to perform cervical screening for neoplasms (higher in this context) and can take the aspect of another inflammatory vulvar pathology [41].

Toxicities treatment in the uro-gynecological sphere

Currently, the treatments of urogenital toxicities secondary to anticancer treatments include:

- Local or general hormonal treatments (hormone replacement therapy) when they are not contraindicated and when the patient accepts to take them;

- Vaginal use of lubricants, moisturizers and hyaluronic acid that improve xerosis and dyspareunia [42,43];

- Regular use of dilators fights against consecutive vulvo-vaginal stenosis, late sequela of radiotherapy or cGVHD (then in combination with oestrogens);

- Topical immunosuppressants and local corticosteroids improve the symptoms of cGVHD but may induce the appearance or recurrence of HPV lesions [39];

- Prasterone is a local treatment that can be proposed as an effective alternative for the management of dyspareunia and sexual function disorders;

- Analgesics and Gabapentin can be used in the treatment of vulvodynia or pain genital neuropathies with more or less success [44];

- Surgery can be useful in the treatment of fistulas, certain scars painful or rigid as well as in the treatment of complete vaginal obliterations secondary to cGVHD [39];

- Recently fractional laser has been used in the treatment of dyspareunia with same results as in the treatment of Genitourinary Menopause Syndrome (EMS) and the same discussions [16].

All these treatments are offered in combination with psycho-emotional support or even with a sexologist work. However, they will have to be practiced regularly because their interruption leads

to worsening symptoms, which often leads to fatigue as well as an impaired quality of life.

Photobiomodulation: Mechanisms and Application

Hamblin MR defines Photobiomodulation therapy (PBM) as "A form of light therapy that uses non-ionizing forms of light sources, including lasers, LEDs and wideband light, in the visible and infrared spectrum. These is a non-thermal process involving endogenous chromophores that cause photo physical (i.e. linear and nonlinear) and photochemical events at various biological scales. This process leads to beneficial therapeutic results, including, but not limited to, pain or inflammation, immuno-modulation and promotion of wound healing and tissue regeneration" [45].

Light induces the action of a photon on a photo-acceptor: The chromophore. It has been demonstrated that Cytochrome C Oxidase (CCO), an enzyme in the mitochondrial oxidative respiratory chain, plays an essential role in the light absorption. The stimulation of the ORC increases the synthesis of Adenosine Triphosphate (ATP), modulates Reactive Species of Oxygen (ROS), ultimately leading to an upward regulation of the transcription of genes.

Calcium ion channels (possibly mediated by the absorption of light by opsins) could also be a chromophore, just like flavoproteins (they have a role in the repair of bacterial DNA) as well as the water present in the mitochondria (reacting to Infrared Radiation (IR)) [46].

The action of light on the chromophores leads to a cascade of biological effects. Being able to modulate signaling pathways, the production of ROS that act on balance Redox through NFkB, ATP (adenosine triphosphate), Ca, NO and the group of inositol phosphates. It has been also observed a modulation of cytokines pro inflammatory as well as a change in the phenotype of activated macrophages [46,47].

The clinical areas of PBM applications are therefore numerous and varied [48]. The first researches and studies, focused on the treatment of pain, inflammation and the acceleration of healing [49-53]. But there are many others areas such as cell proliferation, angiogenesis, and apoptosis [54-56].

As a result, PBM is a treatment increasingly used in oncology. Studies have reported an improvement in wound healing with pain reduction, in inflammatory conditions such as radio dermatitis, mucitis and lymphedema. However, a controversy has arisen in front of the disparity of studies, the poor results and the fact that PBM could promote the proliferation of tumor cells. But the literature review seems to show that the benefit in oncology is in favor of the use of the PBM [57,58]. In any case, almost all the articles studied consider that it is essential to perform additional research to find the optimal parameters irradiation by LEDs to improve the results of the studies and the passage of laboratory to clinical applications.

Applications in Gyneco-Oncology

On PubMed, if we enter the term "Photobiomodulation", we get 1713 results; of which 1 article in 1992 and 1 in 1997 then almost nothing until 2012, year from which the scientific production has continued to grow until today (515 publications for 2020). The fields represented are varied, from veterinary medicine to oncology, neurology, sports, dermatology etc. If we search by adding the term "mucitis" 85 results are obtained, and 15 for "xerostomia". Now, if we associate the word "menopause" we find only 9 articles (against 154 by replacing PBM by Laser). This explains why we will list the perspectives for the application of PBM in onco-gynecology.

By taking the different toxicities and extrapolating from existing studies for organs very close to the genitals, we can make the following proposals.

Application to xerosis and vulvovaginal atrophy

Whether it is radiation-induced, (arterio-capillary fibrosis of the mucosa and submucosa, destruction of the hormone receptors), chemo or hormone-induced (allograft ovarian failure, anti-aromatase in breast cancer hormone receptors positive), or surgical (prophylactic annexectomy in BRCA mutated patients, surgical treatment in endometrial or cervical cancers), the physiopathology of this complications shows fragmentation of elastin, and collagen, thinning of smooth muscles, disappearance of glycogen cells (decrease in vaginal secretions) and a reduction in blood flow that leads to an decreased lubrication, similar to that observed in SGUM [59]. Various studies show the effectiveness of the fractionated CO2 laser in this indication, especially after gynecological cancer in terms of histological analysis, improvement of symptoms, decreased pain or improved sexual health score, such as Female Sexual Function Index (FSFI) [15,60,61].

Only one study with the PBM was found and it shows efficiency similar to the CO2 laser. Lanzafame et al. [62] realize in postmenopausal women, 1 vaginal biopsy before and 3 months after 8 sessions of PBM performed to a small endovaginal device. Histological analysis shows an epithelial tissue with an increased number in keratinocytes and glucogenic load. Changes were also observed in lamina propria: Marked angiogenesis, signs of tissue congestion with red blood cells in the new vessels, a collagenesis and an increased cellularity. The PBM restores the vaginal function that is maintained at least 3 months after the treatment [62].

In addition, the work of Thompson et al. has demonstrated that the vaginal and buccal epithelium are microscopically similar, that there are no differences statistically significant between the maximum and minimum number of layers of epithelial cells, that the surface keratinization models as well as the distribution and appearance of the lipidic slats in intercellular spaces are similar. Based on these results, Thompson et al. have concluded that the vaginal epithelium can be used as a substitute for oral epithelium in certain *in vitro* studies and possibly for studies *in vivo* [63]. Therefore, from studies showing a beneficial action of PBM on the oral sphere, in the treatment of pathologies following anti-cancer therapies, we can imagine, by extrapolation, the same results on the genital sphere [64,65].

Application to stenosis and vulvo-vaginal fibrosis

The fibrosis is an important consequence of radiation therapy. The PBM is an emerging therapeutic modality for the treatment of cutaneous fibrosis. The PBM would act on the cellular plan, as a modulator of reactions, would reduce the speed of proliferation and migration of fibroblasts, would inhibit pro-fibrotic cytokines and their related pathways such as that of TGF-beta and would decrease the synthesis and deposition of collagen [66,67].

In the article on the use of PBM to reduce fibrosis tissue associated with cGVHD, Epstein et al. are discussing the understanding of the molecular mechanisms involved in inflammatory phenomenon such

as the induction of TGF-beta and NFκB. The clinical benefit found in the two cases presented needs further investigations to determine the therapeutic efficacy of PBM [68]. In another study, patients with oral cGVHD are treated long-term with PBM. Here, JB Epstein shows that PBM therapy represents an additional approach for the ongoing management of oral HDSC and that the frequency of treatment should be individualized (weekly or monthly or bimonthly) for each patient in order to provide the best control of oral outcome [69].

The vaginal involvement in cGVHD is an inflammatory process that can lead to erosive lesions with scars complicated by vulvovaginal stenosis and complete agglutination of the vagina [70]. The treatment then becomes difficult and is associating surgery, immunosuppressive and dilators. However, given the histological similarity of the vaginal and oral mucosa, the successful use of PBM in the treatment of oral cGVHD, here too we can think that the PBM is an additional promising option to consider for the management of stenoses and fibrosis in the future, in order to evaluate its effectiveness and to define the appropriate treatment and irradiation parameters for each condition.

Application to vulvo-vaginal pain

As many articles showed, one of the main areas of application of the PBM is pain, whether acute (e.g. post-surgery and then related to inflammation), or chronic (rather neuropathic) [44,50,52,71-73]. The pain is a major symptom and extremely frequent and very difficult to treat since it is multifactorial. Only one article was found studying the use of PBM on a small cohort of woman with essential vestibulodynia (a complex disorder of sexual pain characterized by vulvar vestibule pain in response to contact or pressure). It shows an efficiency of nearly 78% (against 44%) compared with the placebo and 57% of patients kept the benefit of treatment at one year [74]. Because of the poor literature on the contribution of the PBM in this indication, we can only extrapolate its use in the treatment of pain induced by the cancer therapy.

The vulvar pain is often consecutive to chronic inflammation and (leading to nociceptive pain resulting from peripheral sensitization, and then to a central sensitization) resembles to neuropathic pain [75]. In these last years, articles showing the effectiveness of PBM in neuropathic pain diabetics, burning mouth syndrome, nerve compression following a nerve inflammation such as the carpal tunnel, gives hope for the same results on pain radio/chemo-induced and requires equally more studies [76,77].

Application in sexual dysfunctions

Sexual disorders are common during cancer treatment and especially when its affects directly the genital sphere with consequences on the organ function or on the "femininity external signs". Sexual dysfunctions may include a decreased sexual desire (libido), insufficient sexual arousal, lack of lubrication vaginal and delayed or absent sexual orgasm (anorgasmia), or a combination of these elements. The causes of sexual dysfunction are multifactorial (psychiatric, neurological, endocrine, cardiovascular and pelvic disorders, side effects of drugs commonly prescribed, depression) [78].

The brain suffers from many different disorders that can be classified into three major groups: Traumatic events (stroke, traumatic brain injury and global ischemia), degenerative diseases (dementia, Alzheimer's disease and Parkinson's disease) and psychiatric disorders (depression, anxiety, and posttraumatic stress syndrome). There are evidences that applying light on the head can have a beneficial effect on all these diverse [79]. The PBM therapy of the brain improves the metabolic capacity of neurons and stimulates anti-inflammatory, antiapoptotic and antioxidant responses, as well as neurogenesis and synaptogenesis [80].

Cassano et al. [78] reports the effects of PBM on sexual dysfunction in a depressed patient's cohort with medical and psychiatric comorbidity and concomitant pharmacological treatments. The results indicate that repeated sessions of PBM can be associated with therapeutic effects on sexual dysfunction, but they do not seem to be related on the antidepressant effect of PBM in the cohort [78].

Of course, here again it is necessary to carry on further studies to evaluate, the effectiveness and the administration protocols.

Conclusion

After reviewing the impact on the uro-gynecological sphere of anticancer therapies, and more particularly those used in gynecological cancers, as well as the currently available treatments that can solve them, it appears that the PBM is a promising option for the management of these side effects. However, it is still important to define appropriate treatment and irradiation parameters for each condition to ensure the effectiveness of the PBM.

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