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Ovarian Cancer: Causes and Possible Treatments

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ABSTRACT

About 10% to 15% of patients with ovarian cancer carry a mutation in a gene that promotes its development. These hereditary cancers occur at an earlier age than the average ovarian cancer, most often around the age of 50/55 years. In about half of these patients with a predisposing mutation for ovarian cancer, there is a family history of ovarian or breast cancer in a mother, grandmother, aunt or sister. This mutation is transmitted to children (one in two is at risk of being affected). Depending on the type of cancer the patient is suffering from, she is offered the standard treatment for this type of cancer. The reference treatment, as its name suggests, because it has been tried and tested and is therefore the reference for all patients affected by the disease in cause. The standard treatments used in cancer have been the subject of prior clinical trials. The patient may therefore be offered to participate in a clinical trial. Not all patients are affected by clinical trials and the proposal will be made on a case-by-case basis depending, for example, on the type of tumor, its size or any other criterion. Participation in a clinical trial allows the patient to benefit from the most innovative treatments while advancing medical research. If the patient wishes to inquire, or if the patient is offered to participate in a clinical trial, she can consult the register of open clinical trials.

Keywords: *Ovary, cancer, treatment, surgery, chemotherapy, immunotherapy.*

INTRODUCTION

The incidence of ovarian cancer in Europe is 12 new cases per 100,000 per year; ovarian cancer is responsible for 5.8% of cancer deaths. Ovarian cancers represent 4% of cancers in women and are the 5th leading cause of death from malignant tumors. This frequency may seem low, but these tumors are the leading cause of death from gynecological cancer. In addition, their incidence has been steadily increasing for 25 years. (**Zhang, 2019**) Treatment is based on surgery, which can be conservative for early-stage tumors in a young woman, most often followed by chemotherapy. Monitoring of treated patients is important in an attempt to detect and treat a possible recurrence earlier and therefore, ideally, to improve survival. The methods of this monitoring depend on the prognostic factors of the tumor. The European experience suggests that routine screening may reduce ovarian cancer mortality. The 22,000 women enrolled in the "screening" arm were compared 22,000 women who have not received a systematic paraclinical examination. 16 cancers were observed in the "screening" arm and 20 in the "no screening" arm. (**Reid, 2017**)

LITERATURE REVIEW

1. Risk factors for ovarian cancer

a) Hereditary risk factors

Epidemiological studies show that the cumulative risk of developing ovarian cancer is around 1%: 1 in 100 women will develop ovarian cancer during her lifetime (life time risk). In first-degree relatives (daughter, sister or mother) with a subject with ovarian cancer, the risk is 4%. If two first degree parents have been reached, the risk increases to 15%. The same is true if the first-degree parentage includes one case of ovarian cancer and one case of breast cancer occurring before the age of 50 or two cases of breast cancer occurring before the age of 60. In women, finally, related in the first degree with three women with ovarian cancer, the risk reaches 25%. These epidemiological notions do not have great individual significance. Their interest is above all to allow the identification of "families at risk". (**Hirst,**

2018) When in a family in first-degree related subjects, either two cases of ovarian cancer, or one case of ovarian cancer and one case of breast cancer appearing before the age of 50 or two case of ovarian cancer, we must consider that we are in the presence of a family at risk and we must suspect a "breast-ovary" syndrome, that is to say a "site specific ovary" syndrome, syndromes which can be linked to a mutation in the BRCA1 gene or the BRCA2 gene.

The most frequent mutations are those:

• BRCA1 or BRCA2 genes (75% of cases). This mutation promotes the occurrence of breast and / or ovarian cancer.

• Linked to Lynch syndrome (less than 5% of cases). This genetic predisposition can lead to colorectal and / or ovarian and / or uterine (endometrial) cancer.

• Linked to other mutations not yet identified but which are suspected due to a history of ovarian cancer in the family. (**Salehi, 2008**)

In the presence of a mutation in the BRAC1 gene, the cumulative risk (life time risk) of ovarian cancer is 45% (and the risk of breast cancer 80%). In the presence of a mutation in the BRCA2 gene, the cumulative risk is 25%. In the absence of a BRAC1 or BRCA2 mutation, the risk is that observed in the general population. (**McLemore, 2019**)

From a practical standpoint, testing for a mutation should be offered in all cases where there is a reasonable suspicion of breast syndrome or site-specific ovarian syndrome. We must add subjects belonging to a family classified as HNPCC (Hereditary Non Polypous Colorectal Cancer). The genetic test can identify the real subjects at risk who are not necessarily the first degree relatives of a woman with ovarian cancer. After genetic testing, two situations can be distinguished. If the person is a carrier of a mutation, it is necessary, from the age of 30, to submit to twice a semi-annual screening (ultrasound and CA125 assay every 6 months) and to propose, at the age of 40 years at most late, bilateral adnexectomy. If the person does not have a mutation, their risk is in principle the same as that seen in the general population. But it can be difficult to get people to accept no screening. The same is true for women in whom only one first-degree relative, most often the mother, has had ovarian cancer. (**Momenimovahed, 2019**)

b) Other risk factors

• Age: Ovarian cancer is most often diagnosed after the age of 60 although there are cases in young women.

• First menstruation before the age of 12 and / or late menopause (after 52) because more menstrual cycles (and therefore ovulations) in a woman's life would increase the risk of getting ovarian cancer.

• No pregnancy or first pregnancy after 30 years

• Infertility and in vitro fertilization (IVF), endometriosis, endometriotic cyst.

• Frequent use of talcum powder on the genitals in childhood. (**Adaranijo, 2018**)

Other factors have been implicated but their role in the risk of ovarian cancer remains debated. However, certain factors reduce the risk of developing ovarian cancer, such as: Prolonged oral contraception, multiple pregnancies and feeding with milk

All these elements will intervene in the strong presumption of ovarian cancer and at the end of this first assessment, specific management, by professionals specializing in ovarian pathology, will be offered to the patient.

2. Possible treatments of ovarian cancer

a) General considerations

Management must be done specifically by ovarian cancer specialists. The patient should therefore be referred to an establishment or a group of establishments equipped with this specialized medical staff but also with all the equipment necessary for the treatment and monitoring of the disease. This specialization is essential for the treatment of the disease and the improvement of its prognosis. This is why the search for medico-surgical competence should be given priority as much as possible over hotel comfort or proximity to home. (**Lugani, 2016**)

*The European recommendations in force, issued by the ESGO (**European Society of Gynecologic Oncology, 2016**) specify that the surgeon must perform at least 10 ovarian cancer surgeries per year, that the center in which he practices performs at least 20 surgeries of this type per year and that it has an appropriate platform (intensive care unit, multidisciplinary consultation meetings or RCP, technical platform, close liaison with a medical oncology team).*

b) Surgical treatment of ovarian cancer

A first assessment has led patient attending physician and / or gynecologist to a strong suspicion of ovarian cancer and in all probability; he then refers her to a surgical consultation. (**Bharathan, 2018**) *Surgery is a major part of the treatment for ovarian cancer.*

a) *The surgical consultation***:** The surgeon will explain to the patient in detail what the procedure is and the risks involved. He may order other examinations to complete the initial assessment and will set a date for the procedure. He will analyze the patient personal and family medical history. (**Amanda, 2007**)

b) *The anesthesia consultation:* A few days before the operation, the patient will meet the anesthesiologist. He will review her medical documents and ask what medications she is taking in order to take the necessary steps to keep the patient anesthesia going well. He must report the products or substances to which the patient is allergic. He will discuss with her any associated illnesses (diabetes, heart, respiratory, kidney or liver disease, etc.) which may increase the risk of complications during or following the operation. The type of anesthesia used depends on the type of surgery being considered, but also on her medical history. General anesthesia is most often offered. In addition, in order to limit postoperative pain, the patient may benefit from an epidural which will be installed before the operation, unless contraindicated. The patient will be prescribed compression stockings that she must wear on the day of the operation and throughout her hospital stay to avoid the risk of phlebitis. (**Brand, 2017**)

c) *Surgical intervention:* The duration of the procedure depends on the type of surgery performed. Most often surgery is performed in two stages: The first step is usually laparoscopic. This surgery under general anesthesia allows, through small incisions on the stomach, to introduce a camera to assess the cancer and take the tumor required for the final diagnosis by the pathologist. The second step is that which allows the completion of the surgical assessment of the tumor extension (for example, the removal of the lymph nodes) and the complete excision of the cancer if possible. The laparoscopic route may be sufficient to treat localized stages (or stage I). In a young woman of childbearing age, the goal will be to keep the unaffected ovary and uterus, for possible pregnancy, if this is possible without compromising her chances of recovery. (**Bharathan, 2018**) In all other cases, a median xypho-pubic laparotomy will be performed in order to allow the most complete possible surgery. The surgeon seeks to obtain a complete resection of the tumor to avoid as much as possible the risk of recurrence. When complete resection cannot technically be obtained, neo-adjuvant chemotherapy is offered for 3 or 4 cycles to reduce the tumor and facilitate the surgical procedure with less risk of complications for the patient. The patient file will be seen in a multidisciplinary consultation meeting (RCP) by the doctors (in general the surgeon, the oncologist, the radiologist and the pathologist) who will decide on the continuation of her treatment according to the analysis of the tumor that will have been made. At this stage of the treatment process, the attending physician will need to apply for ALD (Long Term Affection) to the patient social security in order to obtain 100% coverage of all care relating to her illness. (**Amanda, 2007**)

d) *Immediate follow-up:* At the end of the procedure the patient will be placed in the recovery room to control her breathing, pulse and blood pressure until the patient wakes up completely. One or more drains (plastic or rubber tubes) can be put in place to drain the blood and lymph, which are collected in a bag whose level is checked by medical personnel. When the amount of fluid drained daily decreases below approximately 30 cm3, the drain is removed. A urinary catheter placed during the procedure will be removed after a few hours. (**Stratton, 2001**) The epidural will be removed as soon as the patient no longer needs it. Quite quickly, the doctors ask the patients to stand up to avoid phlebitis. The onset of these will also be prevented by injecting anticoagulant medication and wearing compression stockings until the patient is able to walk regularly. It is on average a week but can be longer. The patient discharge from the hospital depends in particular on the absence of complications and the resumption of intestinal transit. A home nurse will provide the necessary care on medical prescription (scar care, anticoagulant injections, etc.). It will be necessary

to avoid any effort on the scar (no abdominals postoperatively, do not carry loads) but walking is recommended and will be adapted according to the patient state of fatigue. (**Lucas, 2012**)

e) *The "advertisement consultation":* This consultation is organized at the end of the surgery and examinations of the patient tumor, after the multidisciplinary consultation meeting in the presence of the oncologist who will now follow the patient, the announcement nurse. It is advisable to go there with a trusted person who will help the patient write down any explanations the oncologist gives. During this consultation, the oncologist will explain to the patient the possible continuation of the treatment, and if she must have chemotherapy, he will explain the protocol that will be applied to her, with the schedule of the sessions, the products used and their main side effects as well as treatment monitoring. This is called the *personalized program of care*. (**Bharathan, 2018**) The announcement nurse will reformulate the doctor's words, explain the course of treatment and can direct the patient to other professionals such as psychologist, social worker, dietitian, physiotherapist, socio-esthetician, etc. (**Stratton, 2001**)

f) *Complications and side effects:* During hospitalization, the patient will be monitored by the medical team who will take any measures that her condition requires. In particular, the patient may experience: Pain in the scar, which is usually moderate and transient, and generally fairly well controlled by painkillers. If this pain persists or gets worse, it may be a sign of infection or bruising, report it. She may have fatigue, due to the procedure and anesthesia. Pain in one leg, which should be mentioned because it may be a phlebitis (normally prevented by treatment and wearing compression stockings). She may have pain in the stomach and/or difficulty urinating. (**John, 2011**)

g) *Other complications are possible*: Persistent fatigue which may be due to anemia, a consequence of the surgery, Intestinal or urinary disorders, A lump or gap at the scar, which may be a sign of a healing defect in the abdominal wall (under the skin), Sexual problems due to the lack of lubrication of the vagina, Lymphedema due to the removal of the pelvic lymph nodes which may require treatment with physiotherapy and wearing of compression stockings or tights, Lymphocele (lymph pocket) secondary to lymph node removal, which may disappear spontaneously or require a needle puncture, and lastly the effects of menopause in young women who have undergone major surgery, with hot flashes, night sweats, etc. (**Olaitan, 2011**)

c) Chemotherapy as a treatment of ovarian cancer

Depending on the type of tumor, its grade and degree of extension, surgical treatment may or may not be supplemented by chemotherapy. Chemotherapy is a treatment with drugs given by the intravenous or oral route. These drugs travel through the blood to cancer cells throughout the body. Their particularity is that they are toxic on all cells capable of dividing, for cancer cells but also for others. Chemotherapy is called neo-adjuvant when it is given before surgical treatment to shrink the tumor for surgery. Chemotherapy is said to be adjuvant when given after surgery to prevent recurrence. In everyday language, the first treatment with chemotherapy is said to be 1st line. Chemotherapy is given in several cycles most often spaced three weeks apart, this period of rest allowing normal cells to recover. Within each cycle, chemotherapy drugs can be administered at a variable rate: once a week, or every 2 weeks, or just once during the cycle. (**Sato, 2016**)

a) *Precautions to be taken:* At the time of diagnosis and before starting chemotherapy treatment, tests are necessary. It is best to rule out all sources of infection before starting chemotherapy. The most common source of infection is dental. A blood test will be taken before each cycle of chemotherapy to ensure the proper functioning of organs essential for metabolism and elimination of drugs, such as the liver and kidney. Pregnancy is not recommended during the treatment. Doctor may talk with the patient who needs preserving at least one ovary and if she plans to become pregnant. (**Cristea, 2010**)

b) *Implantable chambers:* If a drug must be administered over several hours and even more over several days, if the duration of chemotherapy is long enough, if the veins in the arm (s) are not sufficient or if the previous injections of chemotherapy have caused inflammation veins, the establishment of a central catheter for the duration of chemotherapy is proposed. With proper follow-

up, these catheters can stay in place for as long as needed, preventing the patient from being pricked in the arm with each chemotherapy session. The catheter and the chamber are implanted in the operating room, under local anesthesia or under short-term general anesthesia. In the 48 hours following the installation, pain at the base of the neck is quite common; the patient will be prescribed medication against pain to relieve it. (**Ignace, 2010**) Thereafter, no dressing will be necessary. The patient will be able to lead a normal life with this device. Only violent sports are to be avoided. A room surveillance log will be given to the patient to note the actions carried out at this level. A room can be kept for several years. Incidents related to the device are rare but should lead to consulting: Pain and redness in the casing should raise concerns about infection, Pain and swelling in the arm may suggest vein obstruction, and Fever. Chemotherapy can be administered in the days following the placement of the implantable chamber. (**Chyke, 2016**)

c) *The current standard protocol:* First-line chemotherapy, whether neo-adjuvant or adjuvant, in most cases combines a platinum salt (most often Carboplatin) and a taxane. One cycle is administered every 21 days. The patient will receive six cycles, sometimes eight, of chemotherapy. In some cases, these products may be given to the patient on a weekly basis, at doses suitable for this rate of administration. The protocol is administered on an outpatient basis over a day and is preceded by premedication to prevent allergic reactions and nausea. At each consultation, the patient should tell her doctor about all the affects her feel, so that the doctor can adjust the doses or treat disabling side effects. (**Sato, 2016**)

d) *Procedure:* The first chemotherapy session takes place under more intensive supervision, in order to check that the patient is tolerating the products administered. She may report any unpleasant effects to the nurse. Standard protocol sessions last around 4-6 hours, so the patient might want to bring something to make the time as pleasant as possible. (**Cristea, 2010**)

e) *Side effects:* Products used to treat cancer can cause side effects, but these are not always the case and some patients tolerate chemotherapy very well. Some effects are more frequent than others, more bearable than others; they can be prevented or reduced by following doctor's recommendations. It can be dangerous to take medicines other than those prescribed by the doctor, as these may be incompatible with chemotherapy products and cause serious side effects. (**Ignace, 2010**) If in doubt, speak to the oncologist.

- Nausea, vomiting: There are effective preventive treatments available today. In addition to preventive treatments, the patient can limit the risk of nausea by favoring cold, light and divided meals, preferably by drinking without meals and sufficiently. Some patients are particularly relieved by Coca-Cola. Avoid too fatty or too spicy foods and tobacco. (**Cristea, 2010**)
- Decrease in white or red blood cells or platelets: Before each cycle, a blood test will check the level of blood cells and if this level is found to be too low, the chemotherapy session may be postponed, or the doses of product adapted to the case. (**Chyke, 2016**)
- Oral lesions: The patient may have difficulty swallowing, painful sensations in the mouth or in the esophagus during chemotherapy. This is mucositis, which is an inflammation of the lining of the mouth and esophagus. To limit these effects, the doctor will prescribe mouthwashes (without alcohol) to be performed after each meal. The patient should also wash her teeth with a soft toothbrush, drink a lot (water, herbal teas, crushed ice) and avoid foods that are too spicy or too acidic or that promote the appearance of canker sores (nuts, gruyere, pineapple for example) as well as the consumption of alcohol or tobacco. (**Mahner, 2016**)
- Nervous disorders of the hands and feet (hand / foot syndrome): Taxol in particular can cause sensitivity disorders such as tingling, burning, numbness or tingling, most often affecting the hands and feet. It is very important to report them to the doctor who is undergoing chemotherapy and who will assess their possible progression. (**Sato, 2016**)

- Loss of hair and body hair: Hair loss is often badly experienced psychologically, as it is the most visible part of the disease. About 2 or 3 weeks after starting chemotherapy (Taxol) hair falls out, as does body hair (legs, armpits, and pubis) and eyelashes and eyebrows. This is temporary and hair will grow back within 6 to 8 weeks after stopping Taxol. The doctor may prescribe the wearing of hair prosthesis and the patient may, if the patient wishes, benefit from certain specific aesthetic care centers. In some protocols, this effect may be limited by wearing a helmet and / or cooling gloves during the chemotherapy session. (**Mahner, 2016**)
- Allergies and skin disorders: Chemotherapy causes severe skin dryness, sometimes with itching or redness. These are most often minor disorders that can be limited by: Avoiding exposure to the sun (in particular Taxol is photosensitizing), Favoring mild soaps that do not dry out the skin, and Applying suitable body lotions. (**Ignace, 2010**)
- Tiring: Fatigue is due to both the disease and its treatments; it can be intense and disabling. The patient should talk about it and the doctor has to assess it with the healthcare team. While it is bearable, moderate but regular physical activity will gradually reduce its effects. (**Lheureux, 2019**)

- **Targeted therapies of ovarian cancer**

A "target" is a biological characteristic of the cancer cell, determined in practice by anatomopathological or molecular analysis of the cells constituting the tumor. Targeted therapy is a treatment that acts on this target with the end result, if this target is important for the existence of the tumor, a destructive action. If the target is only present on tumor cells, then damage is expected which mainly affects these cells. (**Muallem, 2017**) For ovarian cancers, we can cite:

a) *Bevacizumab (Avastin)* in stage III or IV, the patient may be offered a combination of bevacizumab with chemotherapy. This is an antibody that specifically targets VEGF (Vascular Endothelial Growth Factor). It is an essential factor for the growth of small vessels that nourish tumors and provide them with nutrients and oxygen; it is therefore an antiangiogenic treatment. It has been shown to be effective in increasing the activity of chemotherapy. Before prescribing Avastin, the doctor will check the patient blood pressure, as well as her cardiac and renal functions. (**Zhang, 2016**)

b) *Anti PARP (Poly-Adenosyl Ribose Polymerase):* PARPs are enzymes that repair certain single-stranded breaks in the DNA of our cells. If the repair of these single-strand breaks is not carried out, the multiplication of cancer cells is more difficult and particularly compromised when the other repair pathways DNA breaks are found to be deficient. This is particularly the case when there is damage to the BRCA genes, whether it is constitutional (present at birth) or somatic (acquired from the tumor). (**Murthy, 2019**)

- **Hormone therapy of ovarian cancer**

In certain types of malignant ovarian tumors, there are receptors for hormones (estrogen and progesterone). These hormones can be involved in the proliferation of cancer cells. By blocking these receptors, there is an impediment to tumor growth. The most prescribed drugs, mainly in relapse situations, are tamoxifen or anti-aromatases. Many other avenues of interest are being explored in therapeutic trials and seem promising. (**Mørch, 2009**)

d) Immunotherapy as a treatment of ovarian cancer

Immunotherapy represents a new avenue of treatment for ovarian cancer. These molecules (anti-CTLA4, anti-PD1 or anti PDL1) have an original mode of action restoring the functions of T lymphocytes with the ultimate goal of eliminating cancer cells by the patients' own defenses. (**Liu, 2010**) These drugs can be combined with each other or with chemotherapy or antiangiogenic therapy. However, the best way to prescribe them remains to be determined and many trials are underway, both as a primary treatment and as a relapse to determine their place in ovarian cancer. (**Palaia, 2020**)

RECOMMENDATIONS

Two situations should be distinguished when it comes to applying a screening strategy for ovarian cancer, are to be considered separately the subjects at risk and the general population. With regard to people at risk, we know that certain individual factors (precocious

puberty, infertility, late menopause, etc.) are involved, but it is impossible, in practice, to take them into account. Only the concept of family risk can be used**.** A genetic analysis (with an onco-geneticist) is therefore increasingly offered for most patients with ovarian cancer. When the patient gets home, she should tell her doctor immediately of any pain, discomfort, fever. The patient should not hesitate to take a notebook to write down all the affects she feels between chemotherapy sessions in order to talk to your oncologist during the check-ups. In any case, the patient should talk to her doctor about anything that seems abnormal and write down anything she felt since the last chemotherapy session before the consultation; this makes it possible not to forget anything.

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