IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
July 2016 Vol.:4, Issue:1

Serum Tumour Marker for Diagnosis and Management of Ovarian Malignancies

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

P.S.S Divya Prasanna[1], Dr. P. Uma Rani MD[2] and Rama Rao Malla*[1]

1. Cancer Biology Lab, Department of Biochemistry, GIS, GITAM University, Visakhapatnam, India.

2. Department of the Consultant Pathologist, Good Samaritan Cancer & General Hospital Eluru, India.

Submission: 1 July 2016
Accepted: 7 July 2016
Published: 25 July 2016

Keywords: Ovarian cancer, CA-125, tumour marker, diagnosis

ABSTRACT

Ovarian cancer is a malignant tumour that develops in women's ovaries. It's the fourth leading cause of cancer deaths among women. Ovarian tumours originate from epithelial, germ and structural tissue cells. The vast majority of the ovarian cancers are epithelial ovarian carcinomas. The symptoms of ovarian carcinoma including bloating or pressure in the belly, pain in the abdomen or pelvis, feeling full quickly during meals and more frequent urination. The risk factors of ovarian carcinoma include family history, age and use of hormone therapy in post-menopausal stage and obesity. It is routinely checked by gynaecological examination, blood test for CA-125 and ultra sound of the ovaries. TNM clinical staging is based on physical examination, histological evaluation and node bearing area. Surgery, chemotherapy, and radiation are mainly used to treat ovarian cancer, depending on the disease's stage. A number of tumour markers are currently being used for ovarian cancer including CA-125. In this article, symptoms, risk factors, diagnosis, staging, treatments and biomarkers of ovarian cancer have been discussed.

INTRODUCTION

Ovarian cancer is a malignant tumour that develops in a women's ovaries. It's the fourth leading cause of cancer deaths among women. It most often occurs in women, who are older than 50. According to the survey of American cancer Society, over half of those diagnosed with ovarian cancer are 60 years or above[1]. When diagnosed at early stage, over 90% of ovarian cancer patients will live longer than 5 years. However, early detection of ovarian cancer is major challenge. Many cases are found after cancer has spread to other organs. In these cases, the cancer is much harder to treat and cure[2].

***Types of ovarian cancer*:**

Epithelial tumours start from the cells that cover the outer surface of the ovary. Most ovarian tumours are epithelial cell origin. Germ cell tumours start from the cells that produce the eggs (ova). Stromal tumours start from structural tissue cells that hold the ovary together and produce the female hormones, estrogen and progesterone. The vast majority of the ovarian cancer are epithelial ovarian carcinomas. These are malignant tumours that form from cells on the surface of the ovary. Each of these cells can develop into different types of tumors[3].

Symptoms and risk factors of ovarian cancer:

The symptoms of ovarian carcinoma include bloating or pressure in the belly, pain in the abdomen or pelvis, feeling full quickly during meals and more frequent urination. These symptoms are common for many conditions that are not cancers. The risk factors and causes of ovarian carcinoma include family history. Chances of developing ovarian cancer are higher if a close relative had an incidence of cancer of the ovaries, breast or colon. Research over centuries found that inherited genetic changes accounts for 10% of ovarian cancers. These includes the BRCA1 and BRCA2 gene mutations, which are also linked to breast cancer. Another major risk factor for ovarian cancer is age, over 50 years. It is most likely to develop after women goes through menopause. Use of hormone therapy in postmenopausal stage may increase the risk. The link seems strongest in women who take estrogen without progesterone for at least 5 to 10 years. So, the combination of estrogen and progesterone boosts the risk as well. Obese women have a higher risk of getting ovarian cancer than healthy women and the death rate for ovarian cancers are higher for obese women too, compared with non-obese women. Studies have shown

that women who had children, who breastfeed, or who use birth control pills have less chance to develop this cancer. These factors decrease the number of times a woman ovulates, and reducing the number of eggs produce during a woman's lifetime, which may lower the risk of ovarian cancer.

Screening test for carcinoma ovary:

Screening is a presumptive identification process, in which a person's body is checked for cancer. It can help to find cancer at an early stage. If abnormal tissue or cancer is found early, it can be easier to treat. By the time symptoms appear, cancer may begin to spread. There is no easy and reliable test for ovarian cancer if women have no symptoms. However, there are two ways to screen for ovarian cancer during a routine gynaecological examination. Blood test to evaluate levels of a protein called CA-125. The other one is the ultrasound of the ovaries[4].

Diagnosis:

Ultrasound or CT scan can reveal an ovarian mass. But these scans can't determine whether the abnormality is cancer. If cancer is suspected, the next step is usually surgery to remove suspicious tissue. A sample is then sent to the lab for biopsy examination.

***Stages of ovarian cancer*:**

The initial surgery for ovarian cancer also helps to determine the level of cancer metastasis. Typical TNM clinical staging is used for staging of ovarian cancer. The following characters are used in TNM system. Physical examination and results of hysterectomy with salpingo-opherectomy. The extent of the disease by histological evaluation of hysterectomy with the salpingo-opherectomy specimen. Evaluation of specimens from a defined node bearing area such as retroperitoneal or periaortic is used. In other words, there must be a lymph tumour markers is required for stage grouping. Stage 1-confined to one or both ovaries, stage 2 - spread to the uterus or other nearby organs, stage 3 -spread to the lymph nodes or abdominal lining and stage 4 -spread to distant organs such as lungs or liver[5].

Treatments of ovarian cancer: Surgery, chemotherapy, and radiation are mainly used to treat ovarian cancer, depending on the disease's stage[6].

Surgery

Surgery is usually preferred to treat ovarian cancer at the 1st phase of treatment. The main objective or the goal is to remove as much of the cancer as possible. This may include a single ovary and nearby tissue in stage 1. In more advanced stages, it is necessary to remove both ovaries, along with the uterus and surrounding tissues.

***Chemotherapy*:**

In all stages of ovarian cancer, chemotherapy is usually given after surgery. This phase of treatment uses drugs to target and kill any remaining cancer in the body. The drugs may be given either orally or through intravenously or intraperitoneally. Women with ovarian tumours usually don't need chemotherapy unless the tumours recur after surgery.

Targeted therapy:

In targeted therapy, angiogenic mechanism of ovarian cancer is targeted. Angiogenesis involves the formation of new blood vessels to feed tumours. A drug called Avastin blocks this process causing tumours to shrink or stop growing. Avastin is approved for the other cancers. But ovarian cancer researchers are still using this therapy.

Radiation therapy:

Radiation therapy is rarely used to treat ovarian cancer. It helps to destroy any cancer cells that are left in the pelvic area. It is also used if the ovarian cancer has recurrence. In most cases, the main goal of radiation therapy is to control symptoms such as pain, not to treat cancer. Radiation therapy uses high energy radiation to shrink tumours and kill cancer cells. X-rays, gamma rays and charged particles are used for cancer treatment. The radiation is delivered from a machine outside the body, external-beam radiation therapy or radioactive material placed in the body near cancer tissue, international radiation therapy also called brachytherapy. Systemic radiation therapy uses radioactive substances, radioactive iodine. Radiation therapy kills cancer cells, whose DNA is damaged beyond the repair. Then the damaged cells are broken down and eliminated by the body's natural process. Many types of external-beam radiation therapy are delivered using a machine called a linear accelerator, also called a LINAC. LINAC uses

electricity to form a stream of fast–moving subatomic particles. This creates high-energy radiation that may be used to treat cancer.

Tumour markers of carcinoma ovary:

Tumour markers or biomarkers are substances that are produced by the cancer cell, or by other cells of the body in response to cancer development. Tumour markers for ovarian cancer are found in the blood, whose levels are measured using a blood test. High level of tumour markers suggests that cancer may be present in the body. However, a high tumour marker level itself is not enough to make a diagnosis. Tumour markers are used in conjunction with other tests such as scans, biopsies, etc. to diagnose a patient who has suspicious symptoms of cancer, to predict prognosis after diagnosis, and to assist in making treatment decisions. Tumour markers are most often used to evaluate the patient's response to cancer treatment or to monitor the recurrence. A number of tumour markers are currently being used for ovarian cancer including Alpha – fetoprotein (AFP), CA-125, HE4, Inhibin A & B, Immunoglobulins , BRCA1 and BRCA2 gene mutations and CEA (carcinoembriyogenic antigen)[6][Ferraro *et al*., 2013].

Tumour marker CA-125:

CA-125 is a membrane associated glycoprotein with a single transmembrane domain. It is highly expressed in tumour cells compared to normal cells in the body. It is first identified in the early 1980s and is frequently used for diagnosis, assessment of response to treatment, and monitoring recurrence of ovarian cancer.

Structure and Functions of CA-125:

It is a single-pass type I membrane protein, normally localize in the cell membrane. Composed of three domains, a Ser-, Thr-rich N-terminal domain, a repeated domain containing more than 60 partially conserved tandem repeats of 156 amino acids each and a C-terminal transmembrane contain a domain with a short cytoplasmic tail. It contains numerous disulfide bridges. Association of several molecules of the secreted form may occur through interchain disulfide bridges providing an extraordinarily large gel-like matrix in the extracellular space or in the lumen of secretory ducts. It is also secreted into extracellular space following the phosphorylation of the intracellular C-terminus, which induces the proteolytic cleavage and

liberation of the extracellular domain. It is thought to provide a protective, lubricating barrier against particles and infectious agents at mucosal surfaces. It binds to MSLN. Binding to MSLN mediates heterotypic cell adhesion. This may contribute to the metastasis of ovarian cancer to the peritoneum by initiating cell attachment to the mesothelial epithelium via binding to MSLN.

Measurement of CA-125:

CA-125 is usually measured in a venous blood sample using ELISA based immune assay. This test is based on the use of an antibody that is directed against the CA-125 protein. It utilizes a CA125 monoclonal antibody immobilized on the microtiter wells. A rabbit anti-CA125 antibody conjugated to horseradish peroxidase (HRP) is in the antibody-enzyme conjugate solution. The test sample is allowed to react simultaneously with the two antibodies, resulting in the CA125 molecules being sandwiched between the solid phase and enzyme-linked antibodies. After incubation at 37°C for 90 mins, the wells are washed with wash buffer to remove unbound-labeled antibodies. A solution of TMB substrate is added and incubated for 20 min resulting in the development of a blue colour. The colour development is stopped with the addition of stop solution. Absorbance is measured spectrophotometrically at 450 nm. The concentration of CA125 is directly proportional to the colour intensity of the test sample. The normal values of CA-125 are 0 to 35 units/ml.

***Significance of elevated CA-125 level*:**

It is not possible to interpret the abnormally high CA-125 levels without additional information about the particular patient. It is used most oftenly to monitor patients with a known cancer malignancy. The limitations of using CA-125 as a marker of ovarian cancer are a lack of sensitivity in stage 1 disease, poor specificity, elevated in benign and other malignant conditions.

Early detection of ovarian cancer:

Early detection of ovarian cancer through the measurement of CA-125, usually in combination with other modalities such as bimanual pelvic examination and transvaginal ultrasonography, is the most promising application of this tumour marker, permitting effective triage of patients for primary surgery. An algorithm has been developed that estimates the risk of ovarian cancer based on the level and trend of CA-125 values. In addition, several trials are ongoing to

determine the potential of CA-125 in combination with other markers to increase earlier detection of ovarian cancer.

CONCLUSION

The ovarian cancer is the leading cause of death among gynecological cancers. Recently, it has been noticed that there is an increase in the incidence of the ovarian carcinomas. Ovarian cancer accounts for approximately 3 percent of cancers in women. There higher prevalence in the age group of 45 to 60yrs. Serum tumour markers are very much useful in early detection of ovarian malignancies. Tumour markers are used to diagnose, predict prognosis and evaluate the treatment for ovarian cancer. A number of tumour markers are currently being used for ovarian cancer including Alpha – fetoprotein (AFP), CA-125, HE4, Inhibin A & B, Immunoglobulins, BRCA1 and BRCA2 gene mutations and CEA (carcinoembriyogenic antigen). However, CA-125 is first identified in the early 1980s and is frequently used for the diagnosis, assessment of response to treatment, and monitoring recurrence of ovarian cancer.

ACKNOWLEDGEMENT

Authors thanks the DST-SERB, New Delhi, Good Samaritan Cancer & General Hospital, Eluru and GITAM University, Visakhapatnam for supporting this work.

REFERENCES

1. Noel S. Weiss, Taniahomonchuk, and John L. Young. Gynecologic Oncology 1977; 5:161-167.
2. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer 2015; 136(5):E359-86.
3. Moyer VA. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2012; 157(12):900-904.
4. Bernard W. Stewart and Christopher P. Wild. *World Cancer Report 2014*. World Health Organization 2014; Chapter 5; pg.12.
5. Alfred B. Kurtz, John V. Tsimikas, Clare M. C. Tempany, Ulrike M. Hamper, Peter H. Arger, Robert L. Bree, Richard J. Wechsler, Isaac R. Francis, Janet E. Kuhlman, Evan S. Siegelman, Donald G. Mitchell, Stuart G. Silverman, Douglas L. Brown, Sheila Sheth, Beverly G. Coleman, James H. Ellis, Robert J. Kurman, Daryl J. Caudry and Barbara J. McNeil. Diagnosis and Staging of Ovarian Cancer: Comparative Values of Doppler and Conventional US, CT, and MR Imaging Correlated with Surgery and Histopathologic Analysis—Report of the Radiology Diagnostic Oncology Group. Radiology 2012; 212:19-27.
6. Jayson GC, Kohn EC, Kitchener HC and Ledermann JA. Ovarian cancer. Lancet 2014; 384: 1376-1388.

7. Ferraro S, Braga F, Lanzoni M, Boracchi P, Biganzoli EM, Panteghini M. Serum human epididymis protein 4 vs carbohydrate antigen 125 for ovarian cancer diagnosis: A systematic review. Journal of clinical pathology 2013; 66(4):273-81.