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NANO DELIVERY: A SMART CARRIER FOR TREATMENT OF OVARIAN CANCER

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ABSTRACT

Ovarian cancer ranks fifth globally among the causes of death for women and is the most lethal gynecologic cancer due to its high recurrence rate even though it is one of the most sensitive tumors, even at advanced stage. Despite improvements in the field of medicine, the reason for high mortality in ovarian cancer is late diagnosis because of nonspecific symptoms. The most significant reason for the recurrence of ovarian cancer is resistance by reducing cellular uptake, increasing elimination, inactivation/detoxification of drugs. Many efforts have been devoted to develop new treatment options due to the frequency of resistance. To overcome such problems various drug delivery and administration approaches have been developed. Numerous researches indicated that, nanotechnology was found to have advantages for molecular imaging, drug delivery, treatment and tumor targeting. Particulate drug nanocarriers such as liposomes, niosomes, polymeric micelles, solid lipid nanoparticles and polymeric nanoparticles have unique features for interacting with tumor microenvironments and tumor targeting as their submicron size. Nanotechnology-based drug delivery systems can be beneficial for the controlled delivery of chemotherapeutics by means of location and duration without undesirable side effects by overcoming several drug delivery barriers through passive or active targeting strategies.

KEYWORDS: Ovarian cancer, Polymeric nanoparticles, Bioavailability, Drug resistance, Targeting.

INTRODUCTION

Ovarian cancer (OC) is the second most common gynecological cancer, and the leading cause of death from gynecological malignancies[1]with epithelial carcinoma being the most frequent variety.[2] It is the eighth most common cancer in women and the seventh leading cause of cancer death among women, responsible for approximately 140,000 deaths each year.[3] It has been suggested that the majority of assumed ovarian cancers originate from the Fallopian tube epithelium rather than from the ovary itself. In the advanced stages, it is difficult to distinguish tumours that started in the ovary, Fallopian tube or the peritoneal surface. The differential diagnosis is based on agreed morphological criteria. Although there may be behavioural and prognostic differences, therapeutic approach has been similar historically.[4]

TYPES

Different types of ovarian cancer are classified according to the type of cell from which they start.

- Epithelial tumors
- Germ cell carcinoma tumors
- Stromal carcinoma tumors
- Small cell carcinoma of the ovary

Epithelial tumors

About 90 percent of ovarian cancers develop in the epithelium, the thin layer of tissue that covers the ovaries. This form of ovarian cancer generally occurs in postmenopausal women.

Germ cell carcinoma tumors

About five percent of ovarian cancer cases, this type begins in the cells that form eggs. While germ cell carcinoma can occur in women of any age, it tends to be found most often in women in their early 20s. Six main kinds of germ cell carcinoma exist, but the three most common types are: teratomas, dysgerminomas and endodermal sinus tumors.

Stromal carcinoma tumors

Ovarian stromal carcinoma accounts for about five percent of ovarian cancer cases. It develops in the connective tissue cells that hold the ovary together and those that produce the female hormones estrogen and progesterone. The two most common types are granulosa cell tumors and sertoli-leydig cell tumors. Unlike epithelial ovarian carcinoma, 70 percent of stromal carcinoma cases are diagnosed in Stage I.

Small cell carcinoma of the ovary

Small cell carcinoma of the ovary (SCCO) is a rare, highly malignant tumor that affects mainly young women, with a median age at diagnosis of 24 years old. The subtypes of SCCO include pulmonary, neuro-endocrine and hypercalcemic. SCCO accounts for 0.1 percent of ovarian cancer cases. Approximately two-thirds of patients with SCCO have hypercalcemia. The symptoms are the same as other types of ovarian cancer.[8]

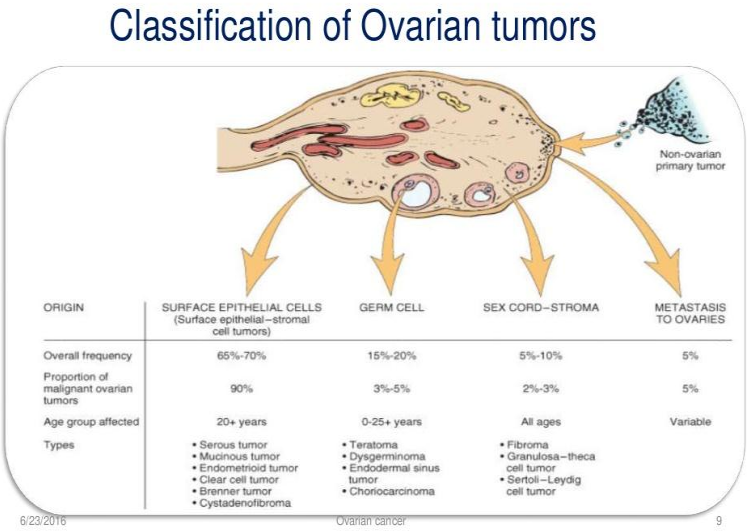

Fig. no.1: classification of ovarian cancer.

Signs and Symptoms of Ovarian Cancer

The most common symptoms include:

- Bloating
- Pelvic or abdominal pain

● Trouble eating or feeling full quickly Urinary symptoms such as urgency (always feeling like you have to go) or frequency (having to go often).

Others symptoms of ovarian cancer can include

● Fatigue
● Upset stomach
● Back pain
● Pain during sex
● Constipation
● Menstrual changes

● Abdominal swelling with weight loss However, these symptoms are more likely to be caused by other conditions, and most of them occur just about as often in women who don't have ovarian cancer.[5]

PATHOPHYSIOLOG

The PI3K/Akt/mTOR signaling pathway

The phophatidylinositol 3 Kinase (PI3K) pathway is a complex signaling network coordinating a number of direct upstream inputs from growth factors (EGF, heregulin, TGF, and others), tyrosine kinase receptors (IGF1R, EGFR, HER2…) or other membrane receptors such as Met as well as cross-talk with the Ras-Raf-Mek-Erk pathway via indirect input from Ras.PI3K is composed of a p110 catalytic subunit and a p85 regulatory subunit. The p110 subunit of PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to the active second messenger, PIP3 which recruits Akt to the plasma membrane, and results in a conformational change and activation of PDK1 and Akt proteins. Akt is a serine threonine kinase that regulates a huge number of downstream targets, while the phosphatase and tensin (PTEN) analog protein acts as an endogenous pathway repressor by de-phosphorylating PIP3 back to PIP2. Akt controls critical cellular survival and metabolic processes by influencing some of the following:

1. Via downstream regulation of p53, NFκB (nuclear factor κB) or CREB (cAMP response element-binding protein), Akt promotes the transcription of genes involved in anti-apoptotic and proliferative responses such as XIAP (X-linked inhibitor of apoptosis protein), the apoptosis regulating protein Bcl-2, survivin and others.
2. Akt also phosphorylates proteins involved in cell cycle regulation and apoptosis thus promoting cell cycle progression and survival:

a. Phosphorylation of GSK3 inhibits proteosomic degradation of cyclin D1,
b. Phosphorylation of the cyclin-dependent kinase (CDK) inhibitors p21 and p27 commits them to nuclear export and removes their inhibitory effect on cyclin D and cyclin E,
c. Downregulation of the apoptotic effector, caspase.

1. In addition downstream signaling via mammalian target of rapamycin (mTOR) activates two key substrates 4EBP1 and p70S6K resulting in increased translation of target genes involved in angiogenesis (VEGF), or cell cycle progression (cyclin D1, c-Myc).

In addition to activation via upstream input, the PI3K pathway can be 'intrinsically' activated due to i) gain of function mutations or amplifications in the p110 subunit of PI3K (*PIK3CA*),

ii) mutations in the p85 subunit (*PIK3R*), iii) mutations or amplifications in one of the Akt isoforms (*AKT1, AKT2, AKT3*), or iv) due to loss of its negative regulator, *PTEN* via inactivating mutations, copy number loss or homozygous deletions.

While mTOR is probably the best described direct target of Akt, the mTOR complex is actually composed of two components, the mTORC1-Raptor complex primary coordinator of translational control via 4EBP1 and p70S6K; and the mTORC2-Rictor complex whose function is less well described but likely regulates cell proliferation and survival in part by Akt activation via phosphorylation at Serine 473.Importantly mTORC1 is sensitive to inhibition by rapamycin, while mTORC2 is not. In the presence of selective mTORC1 inhibition, mTORC2 can exert a positive feedback on Akt.As discussed later, this positive feedback loop may have important implications regarding the emergence of resistance to first generation mTOR inhibitors (rapalogs) that exclusively target mTORC1, with no effect on mTORC2.

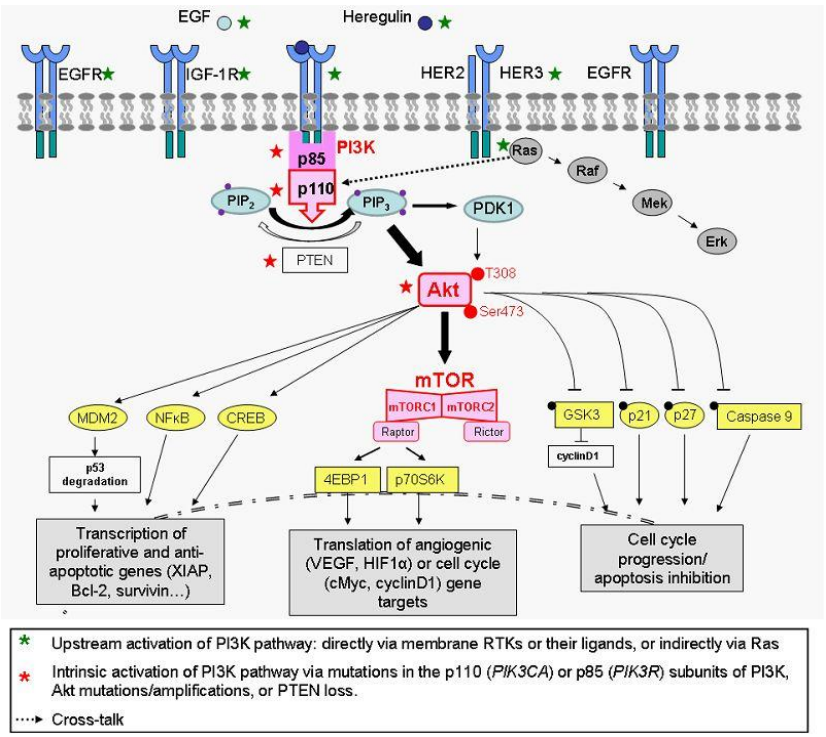

Fig. No.2: The PI3K/Akt/mTOR signaling pathway.

2. Relevance of PI3K/Akt/mTOR signaling in ovarian cancer

The PI3K/Akt/mTOR pathway is frequently deregulated in ovarian cancer. Array Comparative Genomic Hybridization (aCGH) studies on 93 ovarian tumors have identified this pathway as the most frequently altered in ovarian cancer. Copy gains in the genes

encoding both the p110α (*PIK3CA*) and p110β (*PIK3CB*) subunits of PI3K were associated with a poor prognosis in patients with ovarian cancer. Expression levels of both p110α and pAkt were analyzed in over 500 ovarian cancer tumors and associated with decreased survival. Activation of the pathway as measured by Akt or mTOR phosphorylation levels is almost ubiquitous in ovarian cancer and an independent negative prognostic marker.

Interestingly, the type of PI3K/Akt/mTOR molecular alteration appears to be histological subtype specific. There is mounting evidence that ovarian cancer is a highly heterogeneous disease with marked differences in molecular profile, histology, prognosis and chemosensitivity depending on the subtype.The most common subtype (70%) high grade serous ovarian cancer (HGSOC) is characterized by almost universal p53 mutations (95-97% of cases) and marked genomic instability resulting in frequent somatic copy number alterations (amplifications or deletions)[13]. In HGSOC, oncogenic mutations are rare, but amplifications of the p110 subunit of PI3K (*PIK3CA)* have been described in 20% of cases, amplifications of one of the *AKT* isoforms (*AKT 1, AKT2* or *AKT3*) occur in 15% to 20%, while *PTEN* deletions have been described in 5%. Finally*RICTOR* or *RAPTOR* amplifications have also been reported. Rare but potentially relevant mutations in HGSOC include activating *PIK3CA* mutations (3%), or loss of function *PTEN* mutations (1%).Mutations have also been described in the p85α subunit of PI3K (*PIK3R1*, 4%), resulting in loss of its negative regulation on the p110 subunit and constitutive kinase activity.In summary, 40 to 50% of HGSOC may have constitutive PI3K signaling. In a significant proportion of HGSOC, hyperactive PI3K/Akt/mTOR pathway may also be attributable to upstream deregulations in receptor tyrosine kinases (RTKs) or cross-talk with the Ras/Mek/Mek/Erk pathway. Indeed, amplifications or mutations in RTKs such as *ERBB3*, *ERBB2*, *EGFR* or *IGF1R* have been described with frequencies of 1% to 9% Similarly, the ras pathway is often altered in HGSOC by amplifications in *KRAS*(11%), *MAPK* (20%), loss of the tumor suppressor *NF1* (8%), or less frequent mutations in *KRAS*,*NRAS*, or *BRAF*.

Whereas individual mutations remain an infrequent event in HGSOC, they are much more prevalent in the rarer subtypes such as low grade serous, mucinous, endometrioid or clear cell ovarian cancer. For example, 20% of endometrioid and 35% of clear cell ovarian tumors display *PIK3CA* mutation. In addition, while *PTEN* loss of function mutations are rare in ovarian cancer in general, they are well documented in up to 20% of endometrioid tumors

and *PTEN* deletion occurs in 20% of endometrioid and clear cell ovarian cancers.. Low grade mucinous and serous subtypes do not tend to demonstrate intrinsic activation of PI3K effectors, however they frequently exhibit *KRAS* mutations, or amplifications/mutations in *ERBB2*.

Importantly intrinsic activation of the pathway (via *PIK3CA* mutations and *PTEN* loss) has been shown to initiate ovarian tumors in mice and inhibition of PI3K/mTOR in these models delayed tumor growth and prolonged survival, thus providing critical proof of concept for the pathologic relevance of this pathway in OC and its potential as a therapeutic target.Whether amplifications of pathway members actually activate PI3K signaling and confer comparable sensitivity to pathway inhibitors remains to be established. Similarly, while cross-talk with Ras may result in PI3K activation, it is unlikely that this also results in PI3K pathway dependence, however as discussed later, alterations in KRAS may be relevant with regards to predicting benefit from dual PI3K-Ras inhibition.

High grade serous ovarian cancer is exquisitely chemosensitive, with response rates to first-line platinum-based chemotherapy of 75%, but almost invariably relapses with acquired resistance. The rarer subtypes tend to respond poorly to platinum chemotherapy with response rates of only 15% to 30%. Thus both acquired and de novo chemotherapy resistance remains a significant clinical challenge in ovarian cancer. Increased phosphorylation of mTOR has been described in cell lines with acquired cisplatin resistance, and Akt signaling has been implicated in primary platinum resistance.Inhibitors of Akt or mTOR were shown to restore chemo-sensitivity in vitro and in xenograft models. These data suggest a potential role for inhibitors of the PI3K pathway in modulating chemotherapy sensitivity and justify their use in combination with conventional cytotoxic.

PHARMACOLOGICAL TREATMENT

Chemotherapy is used to shrink ovarian cancer and slow cancer growth. Chemotherapy is recommended for most women after the initial surgery for ovarian cancer. sometimes Chemotherapy is given to shrink the cancer before surgery. The number of cycles of treatment will depend on the stage of disease.

Chemotherapy medicines for ovarian cancer may be taken by mouth, injected into a vein (IV), or given through a thin tube into the body (intraperitoneal, or IP).

Medicine choices

Some of the chemotherapy medicines used for ovarian cancer include:

- Carboplatin.
- Cisplatin.
- Docetaxel.
- Paclitaxel

Other medicines that may be used include:

- Cyclophosphamide.
- Doxorubicin.
- Gemcitabine.
- Oxaliplatin.
- Topotecan.

Treatment of ovarian cancer with chemotherapy can cause nausea and vomiting.

DIAGNOSIS

Consultation with a specialist

If the results of your pelvic exam or other tests suggest that you have ovarian cancer, you will need a doctor or surgeon who specializes in treating women with this type of cancer. A*gynecologic oncologist* is an obstetrician/gynecologist who is specially trained in treating cancers of the female reproductive system. Treatment by a gynecologic oncologist helps ensure that you get the best kind of surgery for your cancer. It has also has been shown to help patients with ovarian cancer live longer. Anyone suspected of having ovarian cancer should see this type of specialist before having surgery.

Imaging tests

Imaging tests like computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, and ultrasound studies can confirm whether a pelvic mass is present. These studies cannot confirm that the mass is a cancer, but they may be useful if your doctor is looking to see if ovarian cancer has spread (metastasized) to other tissues and organs.

Ultrasound

Ultrasound (ultrasonography) is the use of sound waves to create an image on a video screen. Sound waves are released from a small probe placed in the woman's vagina or on the surface

of her abdomen. The sound waves create echoes as they enter the ovaries and other organs. The same probe detects the echoes that bounce back, and a computer translates the pattern of echoes into a picture.

Computed tomography (CT) scans

The CT scan is an x-ray test that produces detailed cross-sectional images of your body. Instead of taking one picture, like a conventional x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into an image of a slice of your body. The machine will take pictures of multiple slices of the part of your body that is being studied.

CT scans do not show small ovarian tumors well, but they can see larger tumors, and may be able to see if the tumor is growing into nearby structures. A CT scan may also find enlarged lymph nodes, signs of cancer spread to liver or other organs, or signs that an ovarian tumor is affecting your kidneys or bladder.

Barium enema x-ray

This is a test to see if the cancer has invaded the colon (large intestine) or rectum (it is also used to look for colorectal cancer). After taking laxatives the day before, barium sulfate, a chalky substance, is put into the rectum and colon and x-rays are taken. Because x-rays don't penetrate (go through) barium, the colon and rectum are outlined on the x-rays. This test is rarely used now in women with ovarian cancer. Colonoscopy may be done instead.

Magnetic resonance imaging (MRI) scans

MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of tissue and by certain diseases. A computer translates the pattern of radio waves given off by the tissues into a very detailed image of parts of the body. Not only does this produce cross-sectional slices of the body like a CT scanner, it can also produce slices that are parallel with the length of the body. A contrast material might be injected into a vein (same as with a CT scan). MRI scans are not used often to look for ovarian cancer.

Chest x-ray

This test may be done to determine whether ovarian cancer has spread (metastasized) to the lungs. This spread may cause one or more tumors in the lungs and more often causes fluid to

collect around the lungs. This fluid, called a *pleural effusion*, can be seen with chest x-rays as well as other types of scans.

Other tests

Laparoscopy

Colonoscopy

Biopsy

Blood tests

ADVATANGE OF NANOFORMULATION OVER TRADITIONAL FORMULATION

Taxol

Taxol, a potent anticancer agent, has stimulated an intense research effort in recent years. In humans it has been shown to have activity against a number of leukemias and solid tumors in the breast, ovary, brain, and lung.

- Taxol was isolated from the bark of the Pacific Yew tree in 1971, and is among the first FDA-approved chemotherapy drugs that originated from natural sources. Its brand Cancers name is Paclitaxel. A polymeric drug delivery system for Paclitaxel is, intended to be intravenously administered, capable of improving its therapeutic index, and devoid of the adverse effects of Cremophor.

- incorporation of Paclitaxel in nanoparticles strongly enhances the cytotoxic effect of the drug as compared to Taxol, this effect being more relevant for prolonged incubation times.

HOW NANOPARTICLE TARGET OVARIAN CANCER[7]

A gene which produces the diphtheria toxin, responsible for killing cells by disturbing their ability to manufacture proteins. Bacterium Corynebacterium diphtheria is a toxin which is widely used. Currently the functional DNA has delivered by polymerDNA nanoparticle when subjected near or into the targeted tissue/ organs. Hese nanoparticles as an alternative to viruses have been developed by MIT-Lankenau, which are which are coupled with safety risks. Inspite of treating ovarian cancer.

CONCLUSION

In this paper we focused on the use of nano drug delivery systems for ovarian cancer therapy is gaining more and more importance day by day due to their excellent properties and promising results. There are lots of nano-sized drug delivery systems designed for diagnosis and therapy under preclinical and clinical development and will be marketed a lot more in the near future.[10]

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