Complementary and Alternative Medicine as Adjunct Therapy for the Ovarian Cancer Patients

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ABSTRACT

It is increasingly becoming clear that alternative approaches help significantly in treating cancer patients. Strong evidences suggest the importance of Complementary and Alternative Medicine (CAM) in providing quality life to cancer patients. However, there is a need to study the interaction between the chemotherapeutic agents and the natural extracts for their complementary and synergistic effects and a better therapeutic outcome. Further, in depth investigations are required for improving the efficacy of CAM and reducing the toxicity of chemotherapy.

Key words: Chemotherapy; Cisplatin; Complementary and Alternative Medicine; Ovarian cancer

Abbreviations: CA: Cancer antigen; CAM: Complementary and Alternative Medicine; DACH: Diaminocyclohexyl; EMT: Epithelial mesenchymal transition; EOC: Epithelial ovarian cancer; ROS: Reactive oxygen species; YK: Yukyung Karne
INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer-related death in women and the leading cause of death from gynecological cancer [1]. Ovarian cancer kills ~125,000 women worldwide every year [2]. Early stage detection has a survival rate of over 90% but nearly 70% of the cases reported are diagnosed in the advanced stages [3] and the five years survival rate is approximately 11% when detected in the late stages (stage III/IV). One major hurdle in the early detection is the lack of early biomarkers. Besides, the morbidity rate is high in the ovarian cancer patients since the cancer cells metastasize into the peritoneal cavity and neighboring tissues. Despite significant advances made in the treatment options not much improvement in the survival rate of the ovarian cancer patients has been observed.

With new advancements made in the field of cancer, it is now projected as a preventable disease. Studies have linked environmental factors, diet, radiation, hormones and inherited mutations as the causative agent of cancer [4]. The current chemotherapy for ovarian cancer is the combination of platinum based analogs (carboplatin or cisplatin) and taxanes (Paclitaxel or docetaxel) to treat the advanced ovarian cancer patients but the adverse effects of these drugs and their low success rate has led the researcher and patients to look for a miracle cure in alternative medicine. Recent attention has been drawn towards use of phytochemicals as an alternative approach. It has been reported that 44-53% of women with ovarian cancer seek complementary alternative medicine (CAM) for treatment [5]. Natural dietary compounds have been widely and safely consumed for ages and preclinical studies have suggested their potential in pharmacology of cancer therapy. Lately, many women now opt for CAM as a breakthrough intervention in their routine chemotherapeutic regimen.

CLASSIFICATION OF OVARIAN CANCER

The ovarian cancer is broadly categorized into 3 types based on the origin of cell types- namely epithelial, germ and stromal cells.

Epithelial Ovarian Cancers (EOC)

EOCs are cancers originating from the epithelial cells that cover the surface of the ovary. Most ovarian tumors are benign and do not metastasize or cause serious illness. EOC accounts for nearly 90% of all ovarian malignancies and is primarily a disease of post-menopausal women [6].

Germ Cell Cancers

These are cancerous growth originating from the ova or eggs. Most cases are benign and less than 2% cases develop germ cell cancers.

Stromal Cancers

Stromal cancer arises from structural tissue cells that hold ovary together and produce female reproductive hormones- estrogen and progesterone. Incidences of such cancers are very low (1%) and mostly found in women above 50 years and just 5% occurrence in young girls.
SCREENING OF OVARIAN CANCER

Ovarian cancer is often referred as a silent killer due to the vague or asymptomatic nature of early stages of ovarian cancer. More often the screening programs are not effective in identifying the early stages of ovarian cancer in asymptomatic women. Three major tests in the screening program include bimanual pelvic examination, cancer antigen (CA) 125 and trans vaginal ultrasound. Physical examination detects 1 in 10,000 women whereas immunoassay for CA125 shows elevated level in nearly 80% of ovarian cancer. However, CA 125 levels may also be elevated in women with benign ovarian disease as well as in healthy women which limits its specificity. Likewise, ultrasound screening too shows shortcoming in detection at early stage of EOC. Hence with no definitive screening for average risk, women at high risk are recommended to undergo all the three tests annually.

ETIOLOGY OF OVARIAN CANCER

A clear etiologic factor responsible for the development of ovarian cancer has not yet been identified. However, factors associated with ovulation, pregnancies, lactation, oral contraceptives and use of hormone replacement therapies (Table 1) may contribute towards the development of ovarian cancer [6]. Besides, epidemiological studies have revealed a higher incidence of ovarian cancer in industrialized countries than in developing world implicating the environmental factors in the development of ovarian cancer.

Table 1: Risk factors for the development of Ovarian Cancer.

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<thead>
<tr>
<th>INCREASED RISK</th>
<th>DECREASED RISK</th>
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<td>Age</td>
<td>Multiparity</td>
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<td>Nulliparity</td>
<td>Lactation</td>
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<td>Early menarche or late menopause</td>
<td>Hysterectomy</td>
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<td>Menopausal hormone replacement therapy</td>
<td>Tubal ligation</td>
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<td>Endometriosis</td>
<td>Oral contraceptive use</td>
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<td>BRCA1/2 mutation</td>
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<td>Lynch syndrome</td>
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Role of Genetic Mutation

Genetic mutations are responsible for approximately 10% of the EOC. A new dimension has opened up on understanding the role of BRCA genes. BRCA 1 and 2 act as tumor suppressor genes that readily associate with p53 to serve apoptotic function. Inheritance of mutation in one of these BRCA genes is associated with 27 to 44 % lifetime risk of ovarian cancer compared with 1.4% in the general population [7].
**Role of Epigenetics**

Cumulative genetic alterations in oncogenes and tumor suppressor genes such as mutations, deletions and translocation contribute towards the multistep process of carcinogenesis. Besides, histones and DNAs are primary target of epigenetic changes [8]. Abnormalities in epigenetic modifications such as DNA methylation in CpG islands by DNA methyl transferases and modifications at histone residues with the help of histone methyl transferases, histone acetyl transferases and histone deacetylases. Tumor suppressor proteins play a pivotal role in the cell cycle process and their expression are highly deregulated in ovarian cancers. Epigenetic changes in tumor suppressor genes such as p53, pTEN and p27 has been commonly sighted in ovarian malignancy.

**Role of Oxidative Stress**

Reactive oxygen species (**ROS**) are generated during the process of a normal cellular metabolism. The redox steady state gets imbalanced in cancerous cells. The elevated levels of ROS can induce cell proliferation, genetic instability and DNA damage. For this reason, chronic and cumulative oxidative stress leads to initiation and progression of cancer. Elevated ROS levels and a decreased antioxidan status may lead to oxidative stress and cause damage by acting as secondary messenger in the signal transduction pathways. Most ROS are generated at mitochondria electron transport chain site. During endogenous metabolic reactions, aerobic cells produce ROS such as superoxide anion \( \text{O}_2^- \), hydrogen peroxide \( \text{H}_2\text{O}_2 \), hydroxyl radical \( \text{OH}^- \), and organic peroxides as normal products of the biological reduction of molecular oxygen. The ill effects of ROS in cells are negated by antioxidant defense such as superoxide dismutase, glutathione peroxidase and catalase which chelate superoxides. Besides, vitamin E and C have the ability to quench ROS activity [9]. Glutathione tripeptide is a major endogenous antioxidant produced by the cells which protects them from ROS such as free radicals and peroxides [10].

**TREATMENT OF OVARIAN CANCER**

The initial treatment for most stages of ovarian cancer is surgery followed by 3-6 cycles of chemotherapies for early stage cancer and more than 6 cycles for advanced stage cancer. The current chemotherapy for clinical use is the combination of taxane and platinum compounds. However, stage II and III ovarian cancer cases require hysterectomy and bilateral salpingo-oopherectomy. For stage IV, additional 3 cycles of chemotherapies are done before debulking and 3 cycles after surgery. Yet relapse rate is quite high and the side effects are severe.

An alternative strategy of replacing the ligands of platinum with polymer that targets platinum to the tumor for specificity and lessen the adverse effect of platinum. Platinum has +2 oxidation states and is bound to four ligands. Two of these ligands are ammonia molecule. One of the ammonia ligands have been replaced by DACH (diaminocyclohexyl) to oxaliplatin. The hydroxypropylmethacrylamide polymer is used to deliver DACH platinum moiety to tumors. The
release of platinum from the compound is efficient in a low pH environment as generally found in hypoxic tumors. One such compound named AP5346 has entered phase II trial for evaluation of antitumor activity in advanced ovarian cancer. As per outcome of phase I and II, AP5346 has demonstrated both efficacy and safety [11].

Angiogenesis is another key factor for tumor progression. Therapies targeted at angiogenesis has been tested for more efficient drug delivery. Bevacizumab (Avastin) is an anti-VEGF monoclonal antibody that prevents the activation of VEGF receptors. Bevacizumab in combination with chemotherapy has entered into phase III which has shown improved progression free survival in women with ovarian cancer [12]. A similar protocol for treating patients with advanced colorectal cancer has been approved in Japan.

More recently, combining intraperitoneal chemotherapy with intravenous chemotherapy improves survival in women with advanced cancer. The intraperitoneal administration of cisplatin shows a significant improvement in women with debulked or tumor size less than 1cm EOC. EOC is majorly confined in peritoneal cavity in the early stage and in relapsed cases hence integration of intraperitoneal/intravenous is preferred in such cases over intravenous chemotherapy [13].

CAM FOR OVARIAN CANCER

CAM can be considered as adjunct therapy in parallel to the ongoing chemotherapy such as carboplatin for CAMs possessing antioxidant property. Prolonged treatment of cisplatin or carboplatin leads to elevated levels of cytoplasmic thiol containing species that confer resistant to the treatment. Glutathione over-expression sensitizes cancer cells to cisplatin treatment by up regulating the human copper transporter (hCtr1) gene [14].

Although multiple targeting therapies are being tested and combinatorial chemotherapies have not yielded expected clinical outcomes due to adverse side effects, many women seek assistance in CAM for better quality of life and improvement in their survival rate. A survey carried out on 192 patients from Canada and United Kingdom showed 44% of women were identified as CAM users. For this reason, CAM has to be studied in greater depth for their mechanisms and then supplemented with chemotherapy in order to reduce the side effect and increase the efficacy of treatment. For instance, the CYP cytochrome P450 3A4 isoform is responsible for metabolizing over 50% of a drug going through liver hence the interaction of CAM with drug leading to activation or inhibition of CYP enzyme can cause drug toxicity or under-treatment. Similarly Agaricus blazei also known as sun mushroom was often consumed with tea for its medicinal properties against cancer, hepatitis, diabetes, artherosclerosis and dermatitis [15]. Similarly Amygdalin has been used in CAM for treatment of cancer. A 68 years old woman suffering from uroepithelial cancer of the bladder consumed 3g of amygdalin and 4800 mg of vitamin C supplement daily. Vitamin C is known to increase the conversion of amygdalin to cyanide can be life-threatening [16].

When patients opt for CAM therapy, scientific evidence based information should be available to ensure the safety of patient from potential toxicity. A number of studies on CAM’s efficacy have
been reported hence a systematic implementation of therapy in consultation with oncologist will
soon be a model of integrative therapy for cancer patient. Vitamins A, C, and E, beta-carotene
and grape seed extract are few rich sources of antioxidant. Therefore, women undergoing
paclitaxel treatment should consider CAM with different mode of action as some may reduce the
effectiveness of chemotherapy.

Curcumin is a yellow pigment found in rhizome of turmeric (*Curcuma longa*). Pretreatment of
chemo- or radio-resistant cisplatin cells with curcumin improved its sensitivity and effectiveness
of chemo and radiotherapies. Triptolide, a compound extracted from Traditional Chinese medicine
preparation of *Tripterygium wilfordii* exhibits anticancer activity and is effective against a variety
of cancers such as colon, breast, renal, cervical and ovarian cancers. Triptolide can significantly
inhibit the major steps of metastasis such as adhesion, migration, invasion and angiogenesis that
makes the cancer life threatening [17]. The combination of Curcumin and Triptolide displays a
synergistic effect towards inhibiting ovarian cancer cell growth [18].

Corilagin, a compound isolated from the medicinal plant *Phyllanthus niruri* L, is shown to be
effective in retarding the growth of hepatocarcinoma cells. Recently Corilagin was found to be
effective against ovarian cancer cells both *in vitro* and *in vivo*. Apparently, Corilagin suppresses
TGF-ß secretion and blocks the activation of ERK/AKT signaling pathways. Hence Corilagin can
be an effective therapeutic agent against ovarian cancer [19].

Silibinin also known as Silymarin extracted from milk thistle (*Silybum marianum* L.) has shown
promising results as hepatoprotective agent and lately as anti-cancer therapy against breast,
prostate, skin, lung, colon, bladder and ovarian cancer. Particularly, silibinin can enhance the
sensitivity of human ovarian cancer cell A2780/taxol to paclitaxel thereby induce apoptosis and
cell cycle arrest at G2/M phase. Combination of Silibinin with paclitaxel can inhibit the invasion
by suppression of MMP2 and 9 expressions [20].

Sulfur containing compound S-allylcysteine found in garlic exhibited anti-cancer activity
against neuroblastoma, human prostate, breast, colon, gastric and ovarian cancer cells with no
adverse effect when administered in nude mice [21]. Ginger (*Zingiber officinale*), a natural dietary
component is reported to inhibit growth of ovarian cancer cells by suppression of angiogenic
factor-VEGF [22]. Thus, the use of dietary agents such as garlic, ginger and curcumin may have
potential in the treatment and prevention of ovarian cancer.

CAM therapy should be followed under supervision of oncologist. Recent studies have shown
oral ß-carotene (4.8mg), vitamin C (200UI), vitamin E (200UI) and selenium (15mg) given
concurrently with chemotherapy -Cisplatin (40mg/m² SC) and radiotherapy (50Gy) was able
to reduce oxidative stress and maintain hemoglobin level that allows better quality of life in
randomized cervical cancer patients of stage IB2, IIA, IIB, IIIA and IIIB [23].

A recent study from our laboratory has shown that the Traditional Tibetan medicine-Yukyung
Karne (YK) exhibits potent anticancer (Figure.1) and anti-metastatic activities in ovarian cancer
cells [24]. Most crucial challenge faced in the field of chemotherapy is the adverse effect on healthy cells. MTT assay using different cell lines treated with YK showed its specificity towards cancerous cells than normal cells and thus, overcoming the limitations of current chemotherapeutics to differentiate between cancer and normal cells. YK treatment of ovarian cancer cells led to up regulation of p21, a potent inhibitor of cell proliferation and pTEN, a potent tumor suppressor. It also induced the release of cytochrome c from mitochondria into the cytosol for formation of apoptosome that precedes cell death. Morbidity in ovarian cancer is mostly due to its metastasis to the neighbouring organs. YK effectively countered a range of anti-metastatic properties in ovarian cancer cells such as adhesion, invasion, migration, suppression of angiogenesis. Besides, EMT is considered to aid in invasion of primary tumor cells to secondary sites and loss of the adhesion molecule E-cadherin. E-cadherin negative tumor is a predictor of poor overall survival [25]. YK treatment showed loss of mesenchymal marker (Vimentin and N-cadherin) and gain of epithelial marker (E-cadherin) hence reduce the tumorogenicity of ovarian cancer. Separation of extracellular matrix components by proteases enables cancer cells to migrate leading to metastasis. MMP2 and MMP9 are two crucial enzymes for initiation of metastasis and its activities are found significantly high in ovarian cancer. When ovarian cancer cell SKOV6 was treated with YK, a marked inhibition was seen in MMP2 /9 activities thus scientifically validating the properties and it proved to be an ideal candidate for management of ovarian cancer metastasis [26].

**Figure 1:** Anti-cancer activity of the Traditional Tibetan medicine-Yukyung Karne (YK).
To summarize, CAM appears to be of immense pharmacological significance in the management of ovarian cancer cases. CAMs appear to complement the action of anticancer drugs by improving their efficacy and reducing their side effects. These may be used along with other standard anticancer therapeutics to treat ovarian cancer patients.

References

