EDITORIAL

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Targeting Inflammation in Ovarian Cancer Through Natural Antioxidants, Potential Therapeutic and Preventive Implications

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There is extensive experimental data to support the hypothesis that Reactive oxygen species (ROS) accumulation is one of the major underlying mechanism for carcinogenesis. Many forms of cancer are associated with excessive accumulation of ROS including ovarian cancer. It is now well understood that ROS production should be scavenged by antioxidant defence mechanism/ DNA damage response of the human body to maintain natural homeostasis (Kruk and Aboul-Enein, 2017). Dysregulation of this balance leads to many inflammatory diseases including the high risk of developing cancer. High ROS concentration is associated with accumulation of mutations which over the years leads to development of cancer. Metabolic pathways including aerobic oxidation in mitochondria respiratory are the major source of ROS which in turn effect different signalling pathways (Kruk and Aboul-Enein, 2017).

Ovarian cancer incidence and current therapeutic approaches

In 2018, there will be approximately 22,240 new cases of ovarian cancer diagnosed and 14,070 ovarian cancer deaths in the United States (Siegel et al., 2018). Ovarian cancer accounts for 2.5% of all malignancies among females but 5% of female cancer deaths because of low survival rates, largely driven by late stage diagnoses (Howlader et al., 2017). Although advancing knowledge about ovarian cancer has previously been hindered by substantial disease heterogeneity and uncertainties about tumor tissues of origin, insight has evolved rapidly in recent years, especially for epithelial tumors, which are the most common type. Ovarian malignant tumours have varied clinical and biologic behaviour In India, during the period 2004-2005, proportion of ovarian cancer varied from 1.7% to 8.7% of all female cancers in various population based registries of Indian Council of Medical Research (Murthy et al., 2009).

A woman's lifetime risk of developing OC is 1 in 75, and her chance of dying of the disease is 1 in 1,004. The disease typically presents at late stage when the 5-year relative survival rate is only 29%. Few cases (15%) are diagnosed with localized tumor (stage 1) when the 5-year survival rate is 92% (Howlader et al., 2016). Strikingly, the overall 5-year relative survival rate generally ranges between 30%–40% across the globe and has seen only very modest increases (2%–4%) since 1995 (Allemani et al., 2015). Despite the public health significance, the etiology of this lethal disease is not completely understood.

In developed countries, more than 90% of malignant ovarian tumors are epithelial in origin, 5%–6% of tumors constitute sex cord-stromal tumors (e.g., granulosa cell tumors, thecomas, etc.), and 2%–3% are germ cell tumors (e.g., teratomas, dysgerminomas, etc.) (Sankaranarayanan and Ferlay, 2006). The pathology and classification of ovarian tumors are described in detail by Chen et al., (2003). Most epidemiologic research, including the present review, focuses on epithelial OC. Epithelial OC reflects a heterogeneous disease with histologic subtypes (histotypes) that differ in their cellular origin, pathogenesis, molecular alterations, gene expression, and prognosis. Malignant OC, also known as carcinomas, are comprised of five main histotypes: high-grade serous (HGSOC; 70%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%), and low-grade serous (LGSOC; <5%) (McCluggage, 2011).

Targeted therapies are the important treatment modality in ovarian cancer which comprises of Monoclonal antibodies and small molecules which target different pathways involved in process of carcinogenesis. Most commonly targeted pathways include angiogenesis and metastasis. VEGFR (Vascular endothelial growth factor receptor) inhibitors like sorafenib or humanized antibodies have been tried against VEGF and its related members. Phase 3 clinical trials by Gynecological oncology group (GOG 218) and gynecologic cancer intergroup (ICON7) using bevacizumab showed a significant

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increase in progression free survival as a monotherapy or as bevacizumab and carboplatin-taxane administration however no improvement in overall survival was seen (Perren et al., 2011). These drug combinations are often associated with severe cytotoxicity and reduction in quality of life and candidate for these drug regimes need to be carefully selected.

A new class of drugs based on the presence of BRCA1/2 gene mutation have emerged in ovarian cancer called poly (ADP ribose) polymerase (PARP) enzyme inhibitors. BRCA1/2 protein are the essential part of DNA damage response mechanism in humans and mutation in these render cells more prone to cancer. PARP inhibitors take advantage of these mutation by causing multiple strand break in the cells and resulting synthetic lethality results in cellular killing. mutations, these double strand breaks cannot be efficiently repaired, leading to the death of the cells. Olaparib and Iniparib are the most commonly used PARP inhibitor to treat ovarian cancer and have relatively low toxicity profile however patient develop resistance to these modalities due to development of resistance mutation. In chemoadjuvant settings olaparib resulted in increased bone marrow toxicity (Chen et al., 2013). Nevertheless existing modalities for treatment of ovarian cancer are increasingly associated high a broad spectrum of toxicities which warrants the development of drugs having minimum off target effects.

Ovarian cancer and inflammation

Ovarian cancer is the leading cause of cancer death in females, What makes ovarian cancer deadly is the lack of symptoms in early stages so majority of patients are diagnosed at stage 3-4 when the cancer has spread extensively. The existing epidemiological indicate the association of pregnancy and oral contraceptives use to reduction in risk of ovarian cancer. The hypothesis is that repeated ovulation leads to ovarian cancer chances by damage to ovarian surface epithelium which is associated with repeated cycle of wear and tear (Hunn and Rodriguez, 2012). The ovulation is a proinflammatory process and increase in level of luteinizing hormones (LH) as cycle progresses leads to increase in ROS leading to excessive inflammation induced signalling pathways associated with apoptosis and adjacent cells being exposed to inflammation and ROS (Agarwal et al., 2012). Follicular fluid has high level of ROS which results in increased expression of inflammatory genes which if not checked leads to development of ovarian cancer precancerous lesions. There is ample in vitro data which indicate that Ovarian surface epithelium (OSE) cells in primary culture have expression of oxidative stress related genes which further develop in to aneuploidies leading to cellular transformation. In addition in ovarian stroma oocytes are also exposed to oxidative stress as part of their natural developmental process therefore its very important to maintain redox balance in ovary microenvironment which is decided by interplay between ROS and antioxidant enzymes.

Antioxidants in cancer therapy

It is an established fact that oxidative stress (OS) plays an important role in carcinogenesis of ovarian cancer. Therapeutic agents targeting oxidative stress will be valuable not only in reducing toxicity but also altering the tumor microenvironment. The consumption of diet rich in plant derived polyphenolics has been proven to reduce risk of inflammatory diseases including cancer. Dietary antioxidants offers an attractive option to reduced OS due to their well established safety profile and as of today there is sufficient evidence that dietary anti oxidants can reduce the incidence of many diseases related to inflammation. Phytochemicals offers an attractive avenue for development of cancer therapeutics as they have been shown to induce apoptosis and reduce inflammation in many cancers. Among the different antioxidants studies till date curcumin is the most widely studied in different cancers which is attributed to selective killing of cancer cells with simultaneous targeting of apoptotic and inflammatory pathways thereby altering the tumor microenvironment.

Efficacy of Curcumin in Ovarian cancer

Turmeric (Curcuma longa) belongs to family Zingiberaceae is a perennial herb native to hot subtropical climate of southeast asia. Turmeric is the yellow powder which is obtained from rhizome and has a long history of being used in south east asia as a spice and healing aid. As such the turmeric powder contains 70% starch, volatile oil and up to 5% curcumin and its derivatives (Esatbeyoglu et al., 2012). The healing effect of turmeric is attributed to curcumin which have been shown to have anti inflammatory, anti bacterial, anti-oxidant and analgesic properties. In the last two decades curcumin has drawn the attention of cancer researchers throughout the world as it inhibits different hallmarks of cancers like angiogenesis, Metastasis and induces apoptosis in different cancers. Joint FAO/WHO committee on food additives (JECFA) has established the Adequate daily intake (ADI) of curcumin to 0-3 mg/kg bw/day however many studies in humans support that curcumin is not toxic at doses which are much higher then established by JECFA (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010). The toxicity associated with very high dose of curcumin are diarrhea, headache and discolouration of faeces which are first degree toxicity according to gradation of national cancer institute. Collectively the data in human shows that curcumin is relatively safe regime in humans.

There is extensive in vitro data available which describes different mechanism of action of curcumin. Curcumin inhibited proliferation and induces apoptosis in primary cultures of porcine ovarian granulosa cells (Kádasi et al., 2017) and reduces the cellular markers of proliferation (Qin et al., 2015). In mouse follicular cells curcumin induced proliferation and was able to counteract the apoptotic effect of Ionizing radiation. Curcumin have been shown to inhibit growth of different ovarian cancer cell lines like SKOV3, HO-8910, A2780, OVCA420, OVCA429 while simultaneously increasing apoptosis and scavenging ROS (Shi et al., 2006). In orthotopic murine Ovarian cancer model curcumin was able to inhibit NFkB transcription factor leading to suppression of angiogenesis

and growth of tumor cells (Lin et al., 2007). Overall the in vitro point that curcumin can be a promising drug in ovarian cancer therapeutic as well as prevention. It is well understood that tumor microenvironment has elevated ROS which in turn is a contributing factor in promoting process of carcinogenesis. The in vitro data regarding effect of curcumin in ovarian cancer cells point to potent ROS scavenging properties of curcumin thus altering tumor microenvironment.

Curcumin bioavailability a major hurdle in its transition from bench side to bed side

Despite very encouraging invitro data the transition of curcumin from bench side to bedside to treat ovarian cancer is still an unrealised dream. The main issue that has plagued this is its poor bioavailability. Curcumin is hydrophobic in nature and it is converted in to more hydrophilic form as a result the net concentration is small is less due to its conjugation with glucuronic and sulfate which is catalyzed by cytochrome P450 enzymes in liver and gut (Vareed et al., 2008). In advance colorectal cancer patients who were put on a dose of 3.6 g of curcuminoid per day for 3 months the mean plasma concentration of curcumin after 1 hr was found to be 8.9 and 15.8 nmol/L for curcumin sulfate and curcumin glucuronides with urine showing the mean concentration of curcumin, curcumin sulfate and curcumin glucuronides being 0.1-1.3 micromole, 19-45 nmol/L and 210-510 nmol/L respectively (Sharma et al., 2004). These presence of low curcumin in blood and its conjugate derivatives in secretion indicates low bioavailability at site of tumor. Subsequently many attempts have been made to increase bioavailability of curcumin by synthesizing different derivatives of curcumin which include array of unconjugated curcumin or curcumin conjugated to antibody or ligands which allows targeted delivery of curcumin to tumor sites.

Analogues of curcumin as therapeutic agent in ovarian cancer

Analogues of curcumin have drawn significant attention in recent years like Nano capsulated curcumin (Nano-CUR) (Selvendiran et al., 2011) which comprises of curcumin conjugated to monoclonal antibody which is specific for ovarian cancer cells (anti TAG 72 mAb, CC49) which was encapsulated in PLGA poly (lactic-coglycolic-acid) which enhances its bioavailability. Nano-CUR application substantially decreased proliferation of cisplatin resistance cells thus can be used effectively to reduce dosage of cisplatin and IR. Polycurcumin (PCurc8) which is synthesized by polycondensation with polyethylene glycol 200 and divinyl ether was found to be cytotoxic to SKOV3 and OVCAR-3 cancer cells (Tang et al., 2010). The IC50 values for PCurc8 were much lower as compare to curcumin indicating its potent anticancer activity. In the murine model at the dose of 100mg/kg PCurc8 a significant loss in tumor weight was seen in treated mice as compared to control mice.

Another potent analogue that has been extensively in treatment of ovarian cancer is diarylidenyl piperidones (DAPs) which is synthesized by shortening and incorporation of a piperidone ring within the β diketone backbone of curcumin and fluorination of the phenyl group (Rath et al., 2013). Many DAPs have been designed to evaluate anticancer properties in different cancers. These derivatives have been found to be more toxic to ovarian and colon cancer cells as compared to lung and prostate cancer cells. One of the DAP HO-3867 has been found to be potent apoptosis inducer in different ovarian cancer cell lines and xenograft models (Dayton et al., 2010) while being much less toxic to non transformed cells.

Curcumin and its derivatives in clinical trial

Curcumin and its derivative are being assessed in different cancers as part of ongoing clinical trial. In advanced and metastatic breast cancer on administration of 8g/day of curcumin with docetaxel (100 mg/m^2) for seven for 3 weeks resulted in significant downregulation of metastatic markers like VEGF (Bayet-Robert et al., 2010) however level of CA15.3 was not altered but carcinoembryonic antigen (CEA) was downregulated. In patients with advanced pancreatic cancer in phase 2d clinical trial in which 25 patients were enrolled and received 8g/day curcumin for 8 weeks downregulation of inflammatory markers like NF Kb and COX 2 was seen in peripheral blood cell of the patients (Dhillon et al., 2008). The data from these and several other studies indicate that curcumin is well tolerated with a very good safety profile and warrants its development as a drug to treat ovarian cancer. Curcumin has been found to have multiple targets at cellular level in cancerous cells and this adds to its safe and effective use in cancer therapy. Its multiple targets include inhibition of enzymes generating ROS like COX, iNOS and inhibition of inflammatory transcription factors like NFkB, STAT3 with the simultaneous upregulation of anti oxidant pathways. A search at cancertrial.gov show that It is being evaluated for treatment of different cancers like Prostate, Breast, colorectal and endometrial cancers just to name a few but uptill now no trial has been initiated in ovarian cancer even with a lot of preclinical data. Since ovarian cancer is a disease related to inflammation it would make sense to test curcumin alone or as a chemoadjuvant in ovarian cancer.

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