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Review Article

Challenges and future Research in ovarian cancer therapy: A brief Insight

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ABSTRACT

Being the top most cause of death, ovarian cancer is the leading cancer in women worldwide. Current diagnostic procedures and treatment options such as chemotherapy, radiotherapy and surgery have shown potential applications. However, non-specific biodistribution, drug resistance and relapse are limiting factors of current therapy. Moreover, lack of effective drug carrier pauses a limit towards efficacy of chemotherapeutic drug. Thus there is an unmet need for developing an effective drug delivery system which not only can eradicate cancer cells but also should not harm the normal cells of the body. Novel drug delivery systems such as liposomes, nanoparticles, dendrimers and micelles have been explored widely to deliver an anti-cancer drug to the site of action effectively. Additionally, surface decorated nano formulations have shown beneficial effects in ovarian cancer therapy in pre-clinical as well as clinical trials. In this brief review, challenges and advances in development of novel drug delivery systems have been discussed as a promising alternative tool for ovarian cancer therapy.

Keywords: Ovarian cancer, target based therapy, active targeting

Introduction and importance of Target based therapy for Ovarian Cancer:

Ovarian cancer is the fifth leading cause of death from cancer in women and the leading cause of death from gynecological cancer, resulting in approximately 21,880 estimated new cases in 2012 with an estimated 13,850 deaths in 2010 in the USA.(1), (2) In 2008, more than 224,000 new diagnoses, and 140,000 deaths occurred from this neoplasm in the world(3).

Epithelial ovarian cancer, arising from the ovarian surface epithelium (OSE), account for ~90% of ovarian malignancies. Currently, there is no effective method of screening for early stage ovarian cancer in the general population. Moreover, typical symptoms in affected women are

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nonspecific and of a gastrointestinal or abdominopelvic nature, which commonly delays a confirmed diagnosis(4). As a result, most women (70% to 75%) have advanced-stage (III-IV) disease at the time of presentation(5), (6).

Treatment usually involves chemotherapy and surgery, and sometimes radiotherapy and biologicals based therapy. The standard initial management of advanced stages is a cytoreductive surgery. At present, this treatment is followed by a current standard chemotherapy of carboplatin-paclitaxel given intravenously every 21 days for six cycles. Intravenous docetaxel plus carboplatin or paclitaxel plus cisplatin are options in case of paclitaxel reaction. The carboplatin/paclitaxel combination is regarded as a valid option for challenge in patients with platinum-sensitive recurrent ovarian cancer. However, this approach has been limited by the risk of cumulative peripheral neuropathy (7), (8), (9) . Despite a high initial response, the patients often relapse within a median time of less than 2 years(10), (11), (12). The current chemotherapy is associated with serious side effects such as neutropenia and neurotoxicity due to the non-specific bio distributionand low therapeutic index of anticancer agents(13).

The major drawback of standard treatment of ovarian cancer is that anticancer agents used are low-molecular-weight drugs presenting a low bioavailability, and a non-specific body distribution. Thus, use of high dose of these molecules results in severe systemic toxicity and poor patient compliance. These results point the need for significant improvements by different ways like other therapeutic strategy administration and new targeted agents. New drug formulations and targeting approaches have been developed to better control the bio distribution of drugs, to improve the therapeutic efficacy and reduce the side effects at the same time(14), (15). The existing therapeutics may be used more effectively with less generalized side effects with the use of smart delivery systems like antibody conjugated nanocarriers.

Challenges and future Research Development

The concept of **site specific** drug delivery for treatment of localized disease in the body to improve therapeutic index of the drug is considered as perennial challenge to the formulator in modern formulation design. Constant efforts have been pursued in designing such an ideal drug delivery system which can effectively overcome dose related toxicity and adverse side effects and thus improve patient compliance(16). One such area which has attracted ever growing attention of pharmaceutical scientist and has shown tremendous potential and promise is colloidal drug carrier system(17).

The idea of drug carrier with targeted specificity has fascinated scientists for number of years and in the last decade successful efforts have been made to achieve this goal(18). The ultimate form of targeted drug delivery system should be realization of Paul Ehrlichs “magic bullet concept” (19)which documents the delivery of drug exclusively to a preselected targeted cell type.

Different types of nano-sized carriers, such as polymeric nanoparticles, solid lipid nanoparticles, ceramic nanoparticles, magnetic nanoparticles, polymeric micelles, polymer-drug conjugates, nanotubes, liposomes, nanocages and dendrimers, etc., are being developed for various drug-delivery applications to the target site.

Amongst all targeted drug delivery systems, Liposomes are recently gaining popularity because of their biological inert nature, freedom from antigenic, pyrogenic or allergic reaction and their enhanced stability(20).Liposomes are micro-particulate or colloidal carriers which form spontaneously when certain lipids are hydrated in aqueous media (21). Liposomes are composed of relatively biocompatible and biodegradable material and they consists of aqueous volume trapped by one or more bilayers of natural or synthetic lipids. Highly lipophilic drugs, with partition coefficient greater than 5 are entrapped almost completely in the lipid bilayer of liposomes. Cancer chemotherapy is generally accompanied by side effects and severe toxicities such as bone marrow depression results in granulocytopenia, agranulocytosis, throbocytopenia, and aplastic anaemia, lymphocytopenia and inhibition of lymphocyte function results in suppression of host immunity and etc(22). If an anticancer drug could deliver only the right site in the right concentration at the right time, cancer could be cured without side effects. For such delivering system, liposomal formulation is thought to be useful since liposomes are essentially non-toxic and biodegradable, their size, components, and modifications with various molecules are easily controlled, and they could deliver the large amount of either hydrophilic or hydrophobic agents(23).

The delivery of liposomes at the appropriate site, however, is still not achieved. For this purpose, both active targeting and passive targeting are considered. Conventional liposomes, however, tend to be trapped by the reticuloendothelial system (RES) such as liver and spleen before encountering the target. On the contrary, passive targeting, especially targeting to tumor tissues, could be achieved by reducing the RES trapping, since the

vasculature in the tumor tissues is leaky enough to extravasate liposomes and circulating liposomes may accumulate passively in tumor tissues(24). The development of liposomes containing lipid derivatives of PEG or saturated phospholipids such as DSPC with cholesterol has made targeted liposomal therapy more feasible by reducing the uptake by the RES system and there by prolonging the circulation time.

Particularly, PEG is useful because of its ease of preparation, relatively low cost, controllability of molecular weight and link ability to lipids or protein including the antibody by a variety of methods(25). The presence of PEG reduces binding of serum protein, i.e. opsonization marking the liposome for clearance by macrophages. We proposed that antibodies should be attached to the distal end of PEG chains which are already bound to the liposome membrane(26).In the proposed research, we have selected several functionalized PEG derivatives such as DPPE-PEG-Mal, and DSPE-PEG in order to prepare pegylated liposomes(27).

Active targeting of liposomes to tumor cells is generally attempted by conjugating ligands to the liposomal surface which allow a specific interaction with the tumor cells(28). Several types of ligands have been used for this purpose, including antibodies or antibody fragments, vitamins, glycoproteins, peptides (RGD-sequences), and oligonucleotide aptamers(29). Among the different approaches of active targeting, immunoliposome using antibody or antibody fragment as a targeting ligand and a lipid vesicle as a carrier for both hydrophilic and hydrophobic drugs, is a fascinating prospect in cancer therapy. The process of targeted drug delivery with immunoliposomes can be roughly divided into two phases: the transport phase, in which the immunoliposomes travel from the site of administration (often i.v. administration) to the target cells, and the effector phase that includes the specific binding of immunoliposomes to the target cells and the subsequent delivery of entrapped drugs(30).

Immunoliposomes for the treatment of tumor should satisfy a number of requirements aimed at maximum targeting effect of immunoliposome administered systemically in the bloodstream. Antigen binding site of the liposome-conjugated antibody must be accessible for unperturbed interaction with antigen on the surface of target cells(31). The blood clearance of immunoliposomes must be minimized in comparison with rate of extravasation in the tumor. Immunoliposome must allow efficient loading and retention of a selected anticancer drug. And finally, the drug and antibody incorporation must be stable enough to permit liposomal entry into the tumor tissue without the loss of either of this agents.

In the proposed work an attempt is being made to develop pegylated liposomes, by attaching functionalized PEG derivatives over the liposome membrane and immunoliposomes, by attaching suitable monoclonal antibody to the distal end of PEG chain, for site specific delivery of selected anticancer drugs(32).

Immunoliposomes have the following advantages over conventional liposomes.

- Decreased RES uptake and prolonged circulation time
- Selective active targeting to tumor tissues
- Increased efficacy and therapeutic index
- Reduction in toxicity of encapsulated agent

The use of an antibody molecule as a homing device has been especially facilitated by the development of the hybridoma technology, which makes it possible to produce a large quantity of a monoclonal antibody to a wide variety of cell determinants(33). New drugs were developed, and among them, monoclonal antibodies have been designed to specifically target tumor cells, tumor stroma, tumor vasculature, and cellular signaling mechanisms that are aberrant in tumor tissues. Among targeted drugs developed for the treatment of ovarian cancer, some of them were designed to inhibit angiogenesis, the growth of new blood vessels. Besides these approaches, targeted conjugates have been also engineered. To develop drug delivery systems able to actively target cancer ovarian cells, strategies have to be defined concerning the choice of the target. Active drug delivery systems are developed by benefiting from targets like receptors naturally present or overexpressed at the surface of cancer ovarian cells, by targeting biomarkers, or by exploiting process associated with tumor development like neoangiogenesis and increased nutrients intake.

In the present research we have selected the monoclonal antibody targeting FSHR or Tfr or any suitable specifically overexpressed in majority of the ovarian cancer, to study whether immunoliposomes injected intravenously can extravasate into the solid tumor tissue and bind to tumor cells. One of the proteins expressed abundantly and more or less selectively in ovaries is the follicle-stimulating hormone receptor (FSHR) (34). FSHR is a G-protein coupled receptor with seven-transmembrane domains. This receptor is expressed on the ovarian surface epithelium(35), (36) is limited to the reproductive system. The expression of this receptor is maintained and even overexpressed on

ovarian cancer cells. Further, FSH receptor is selectively expressed on the surface of the blood vessels of various carcinogenic tumors. Hence, it presents as an ideal candidate for targeted therapies to ovaries. The transferrin receptor (TfR) is a cell membrane-associated glycoprotein involved in the cellular uptake of iron and in the regulation of cell growth. TfR is over expressed in many solid tumors, ovarian cancer cells in particular (A2780, OVCA429, OVCA432, OVCAR-3, SKOV3 and HEY). Transferrin or the antibodies against the transferrin receptor (for instance, R17217 and OX26 monoclonal antibody) can be used to target TfR(37), (38). Also, in the present research an attempt is being made to use Fab' fragment instead of whole antibody as it eliminates the immunogenic effect of Fc portion and the increased RES clearance through specific recognition by the phagocytic cells carrying Fc receptors. Fab' fragments also allow better way of conjugation to the liposomes containing DPPE-PEG-Mal through unique thiol groups in the hinge region.

CONCLUSION

Ovarian cancer is the leading gynecological cancer globally and current therapy limits its use due to non-specific nature of the drug delivery systems, resistance to currently available drugs and relapse. Formulation scientist worldwide has explored various drug delivery systems to impart site specificity which will come up with an effective and safe carrier to deliver chemotherapeutic drug. The targeted drug delivery systems will be the promising therapeutic tool in the future treatment of ovarian cancer. However, in vivo correlation with in vitro results has to be established in future.

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