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Ovarian Cancer - The Silent Killer

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Abstract

Ovarian cancer is heterogeneous, multigenetic and epigenetic abnormalities and lethal among all other gynecological women malignancies amongst women. Moreover, ovarian cancer has a distinct biology and behavior at cellular and molecular level. According to National Cancer Institute's Surveillance, Epidemiology and End Result Program Report in 2017 the new case of ovarian cancer exacerbated to 22.4% from 11.7% in 2014. The Therapeutics use of cancer therapies has been restricted due to its nonspecific and dose limiting cellular toxicity and development of multidrug resistance. To overcome the restriction various biotechnological therapies and drug delivery system have been described in this review.

Keywords: Ovarian cancer; Angiogenesis; Polymer drug conjugates

Introduction

Ovarian cancer is the most lethal among all other gynecological malignancy amongst the women. 2,50,000 diagnosed with ovarian cancer globally each year with more than 1,40,000 cancer specific death [1]. Only 20% of the ovarian cancer is diagnosed at first stage when the disease is limited to the ovary, 90% of the patient responds well with existing therapy, Metastasized staged divided in to 3 more categories, i.e., (Stage 2). When the disease metastasized to the pelvic region, after the disease has metastasized to the abdomen region (stage 3) or beyond the peritoneal region (Stage 4) cure rate decrease substantially [2]. Ovarian cancer is heterogeneous; multiple genetic and epigenetic abnormalities have been seen in different individuals. Mutation and loss of TP53 function is one of the most frequent genetic abnormalities in ovarian cancer and is observed in 60-80% of both sporadic and familial cases. Inheritance of DNA repair defects contributes to as many as 10-15% of ovarian cancers. Platinum–paclitaxel combination regimen is considered a first-line treatment for advanced ovarian cancer [3]. Although, the result of treatment with combination therapy and surgery have shown marked improved in advance stages, but death result due to drug resistant during or after complete treatment. Most Ovarian cancer is sporadic and occurs in general population. Risk factors such as use of oral contraceptives, hysterectomy and hereditary syndromes are associated with ovarian cancer. Hereditary syndromes account 5-10% of ovarian cancer mutation arising in *BRCA1, BRCA2* and *MMR* gene [3]. On the basis of screening treatment and genetic stability, ovarian cancer is classified under two categories. Type 1 (Tumor confined to the ovary), these tumors are characterized by specific mutations including *KRAS*, *BRAF*, *ERBB2*, *CTNNB1, PTEN* and *PIK3CA* genes but rarely by *TP53* [4]. These tumors are relatively genetically stable. Type-2 (metastasized in the fallopian tube) is genetically unstable and is the one of the most advance stage of ovarian carcinoma which is indicated by high frequency of *TP53* mutation. Maximal surgical cyto-reduction followed by taxene and platinum based chemotherapy is the primary treatment for ovarian cancer [4]. The therapeutic use of cancer chemotherapy has been restricted due to its non-specific or dose limiting cellular toxicity and development of multidrug resistance. To overcome this restriction various drug delivery system are being studied. In the last few decades polymer drug delivery systems have enormous impact in cancer therapy [5]. Multidrug resistance is a major bottleneck limitation in cancer therapy. After introduction of PDCs (Polymer Drug Conjugates) the limitation has been over come to a large extent. Moreover, PDCs improves selectivity and the therapeutics index of anticancer agents by enabling tumor specific targeting and as a result, there is a vast improvement in toxicity profiling. Polymer Delivery System has become a new domain for research of various existing anticancer drugs. Novel polymer drug conjugates can be designed with multifunctional properties which can be potential to overcome all the limitations related to non-specific and dose related cellular toxicity. In general, targeted delivery of Polymer drug conjugates to cancer cell can be achieved by active or passive mechanism [5]. Passive tumor targeting can be achieved either by enhance permeability and retention effect or by hyperthermia effect. Active tumor targeting of polymer conjugates to cancer cell or tumors can be done by covalent conjugation of cell specific ligands to drug which results in cellular internalization via receptor mediated endocytosis mechanism. In last few decades Polymeric nanoparticles have been developed for experimental and clinical delivery of therapeutic agents for improving toxicity profiling and tumor targeting. The idea of novel drug delivery utilizing stimulus responsive polymer is solely based on the fact of certain abnormalities in the tumor microenvironment and its cells such as an acidic pH, altered redox potential or salt concentration, unregulated proteins and hyperthermia and others [6]. These behaviors are utilized for the preparation of so-called smart drug delivery system, which mimics biological response behavior to a certain level [7].

Ovarian Cancer - Statistics at a Glance

Ovarian cancer has a distinctive biology and behavior at cellular and molecular level. Over the past two decades, treatment with empirical optimized combination of cytotoxic drugs and surgery has substantially improved the 5 years survival rates of ovarian cancer patients. According to National Cancer Institute's Surveillance, Epidemiology and End Result Program Report (SEER) [8] the number of cases of ovarian cancer is 11.7 per 100,000 women per year during the period from 2010 to 2014. Approx. 1.3% women were diagnosed with ovarian cancer at some point during their lifetime, based on 2012-2014 report. There was an estimation of 2,22,060 women living with

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ovarian cancer in United States in 2014. In 2017, estimated new cases of ovarian cancer exacerbated to 22.4% from 11.7% in 2014 (Table 1). Estimated death cases in 2017 due to ovarian cancer are 14,080.

Survival Statistics

Survival Statistics are based on large group of people; these cannot be used to predict what will happen on individual patient as because no two patients are entirely alike and treatment and response to treatment can vary greatly (Figure 1). Diagnosis of stages of cancer, indicate the extent of cancer in the body which determine treatment option and length of survival (Figures 2-4). According to the SEER percentage surviving in 5 years (2007-2013) is 46.5 (Table 1). In general, cancer is categorized under four different stages based on their localization and metastases. Early diagnosis of ovarian cancer has better chance for survival up to 92.5%. Ovarian cancer the percentage of diagnosed cases by stage is depicted in Figure 2.

Estimated new ovarian cancer cases in 2017	% of All new cancer cases	Estimated Death of ovarian cancer patients in 2017	% of Death of all Cancer	% of Survival in 5 years (2007-2013)
22,440	1.3%	14,080	2.3%	46.5%

Table 1: SEER report of data based on ovarian cancer.

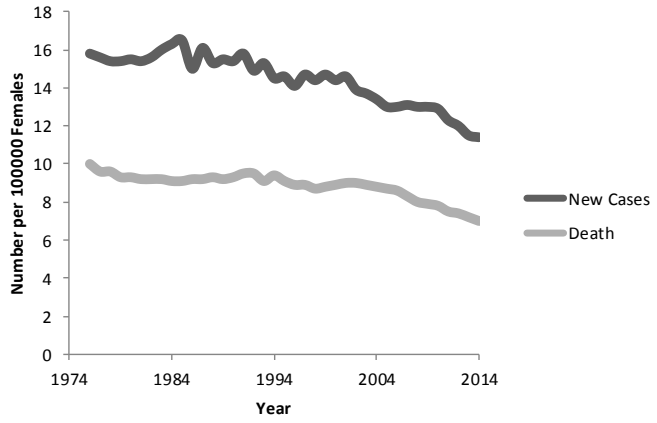

Figure 1: Number of new cases and death per 100,000 people (All races, females, age adjusted).

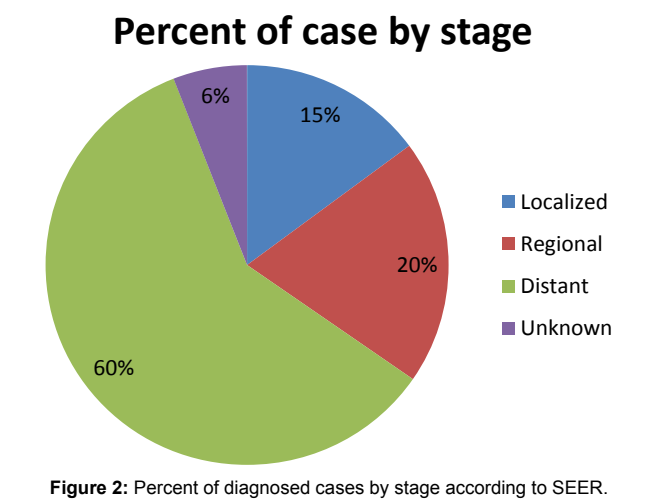

Figure 2: Percent of diagnosed cases by stage according to SEER.

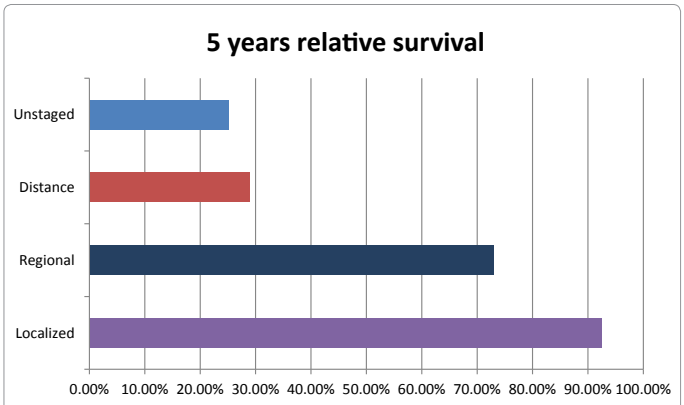

Figure 3: Percent of cases and 5 year relative survival by stage at diagnosis: Ovarian cancer.

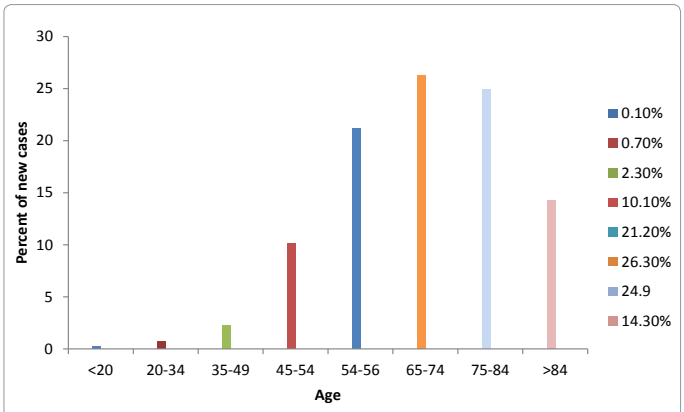

Figure 4: Percent of death by age group of ovarian cancer patient.

Biotechnological Therapies in Ovarian Cancer

There is enormous research going on for identification and development of targeted therapies to disrupt various cancer signaling pathways. Mostly the traditional anticancer drugs have been found to interfere with mitosis, DNA synthesis and the DNA repair system. The new class of agents acts by catastasis (tumor growth retardation) and apoptosis by exploiting the tumor vasculature and cell signaling mechanism [9]. Role of monoclonal antibodies, small molecular protein kinase inhibitor and epidermal growth factor receptor have been explored extensively in the management of ovarian cancer. The major target of these agents includes angiogenesis, epigenetic modulators, ripamycin signaling pathway, ubiquitin proteasome pathways, human epidermal growth factor receptor family and poly (ADP-ribose) polymerase (PARP). Bevacizumab sold under the trade name of Avastin, considered as the most effective anti-angiogenic agent in management of advance ovarian cancer [10]. PARP inhibitor was approved by FDA in 2016 for the management of patience with BRCA positive advance ovarian cancer, rucaparib was the second PARP inhibitor approved in the field. MTORserine/threonine kinase plays a key role in cell growth and proliferation. Preclinical investigation have suggested mTOR complex 1 (mTORC1) and mTORC2 are frequently activated in epithelial ovarian cancer [11]. mTOR inhibitors are also attractive treatment strategies, either alone or combination with chemotherapy, for ovarian cancer.

Targeting angiogenesis

Angiogenesis describe the formation of new blood vessels

(neovascularization) from existing vasculature that is vital for normal physiological function. Angiogenesis is the normal and vital process in growth and wound healing as well as formation of granulation tissue. One of the major pathways involved in tumor angiogenesis is VEGF (Vascular endothelial growth factor) family and its receptor. Over expression of VEGF is often observed in many solid tumors and have been found to be associated in varieties of malignancies including ovarian cancer [12-14]. Moreover, expression of VEGF and VEGFR2 has been recently been found in both ovarian cancer cell [15].

VEGF inhibitors:

Bevacizumab: It is a recombinant humanized monoclonal antibody. Immunoglobin- G (IgG1) antibody targets VEGF-A and is considered as the most effective antiangiogenic drug against advance management of ovarian cancer. Avastin suppress the tumor growth and metastatic disease by binding and neutralizing all biological active forms of VEGF-A receptors [16,17].

Cediranib: It is a highly potent oral tyrosine kinase inhibitor of VEGFR1, VEGFR2 and VEGFR3 effective in preventing tumor progression not only by inhibiting VEGFR3 activity but also by inhibiting VEGFR 2 activity [18].

VEGF Trap: Aflibercept binds to VGEFs acts by inhibiting the activity of vascular endothelial growth factor subtypes VEGFA, VEGFB and placental growth factor (PGF), which inhibits the growth of new blood vessel in tumor [19].

PDGF inhibitors: Platelet derived growth factor (PDGF) and PDGF receptor stimulates growth, survival and mortality of mesenchymal cells and certain other cell types [20]. Over activity of PDGF receptor signaling may drive tumor cell growth. PDGF receptors modulate angiogenesis by regulating endothelial cell survival and vascular smooth muscle recruitment [21]. Moreover, PDG receptors enhance the proliferation of human ovarian surface epithelial cells and ovarian cancer cells. Expression of PDGF was found in malignant ovarian tumor but not in normal ovaries or benign tumors [22] (Table 2).

Targeting signaling

Numerous studies have shown that targeting specific signaling pathways could be promising in cancer therapy in terms of inhibition of cell migrations, invasion and tumor growth [23-25]. It is well known now that ovarian cancer is genetically complex malignancy in which numerous genes are altered or mutated which give rise to tumor genesis. In this review an attempt is made to discuss the most important signaling pathways involved in ovarian cancer along the specific therapeutic agent targeting the signaling pathways [26,27].

Notch signaling pathway: Notch signaling pathways functions through cell to cell interaction and involved in regulation, proliferation and cell apoptosis. There are four different Notch cellular membrane receptors called Notch1-4 and five ligands found in mammals. Three of these ligands belong to Delta-like family (DII 1, 2 and 3) and two ligands are Jagged1 and Jagged2 are serrate like [28]. Delta like 1, 3 and 4 and Jagged 1 and 2 are the main ligands in human [29]. Notch 3 receptor is found to be up regulated in ovarian cancer. Notch 3 proteins play a significant role in development and survival of the tumor [30]. It was found the interaction between Notch 3 and Jagged 1 proteins promotes cell proliferation [31]. Gamma-secretase inhibitors (GSIs) are the most widely studied Notch pathway targeting agents. GSIs have shown reduction and induction of apoptosis in A2780 and OVCR3 ovarian cancer cell line. In case of Platinum resistant tumor, combination therapy of GSIs with Paclitxel led to a great reduction of tumor size [32].

Wnt/β-catenin pathway: Wnt signaling plays a significant role in cellular communication such as differentiation, proliferation regulation of cell cycle and cellular adhesion. The Wnt/β-catenin pathway is one of the major signaling pathways thought to be involved in epithelial-to-mesenchymal transition [33]. Abnormal activation of Wnt/β-catenin signaling Pathways led to the development of multiple diseases like congenital malformation and Cancer. In Ovarian carcinomas especially β-catenin mutation along with over expression of Wnt target genes, Auxin 2 and Fibroblast growth factor 9 is reported [34]. Sinomenine (SIN), an isoquinoline extracted from the Chinese medicinal plant *Sinomenium acutum, Qingfengteng* (*Caulis Sinomenii*), is well known for anti-rheumatic and anti-arthritic disease [35]. SIN gradually reduced the growth capacity of tumor in dose dependent manner and might play anti proliferation and anti-metastasis function via regulating MCM2 gene thereby regulating or controlling Wnt/β-catenin signaling pathway.

PTEN/PI3K/AKT/mTOR pathway: PI3K pathway is a complex signaling network composed of a p110 catalytic and p85 regulatory subunit, p110 subunit phosphorylates PPI2 to active secondary messenger to PIP3, after phosphorylation PIP3 recruits AKT [36]. AKT is a serine threonine which phosphorylates proteins involved in cell cycle regulation and apoptosis thus controlling cell cycle progression and survival. Phosphate and Tensin homology (PTEN) encoded by PTEN gene, have both protein and lipid phosphate activity, plays a key role in cell cycle arrest, apoptosis and cell migration. Mammalian target of rapamycin (mTOR) is a component of the phosphatidylinositol 3-kinase (PI3K) cell survival pathway, composed of two components, the mTORC1-Raptor complex (coordinator of translation control) and the mTORC2-Rictor complex (regulates late cell proliferation and survival). mTORC1 is sensitive to rapamycin whereas mTORC2 is not sensitive to ripamycin [37] (Figure 3 and Table 3).

Receptor mediated targeting

Agent targeting EGFR family: Some of the EGFR inhibitors on which clinical studies are going on is tabulated in Table 3. The epidermal growth factor receptor (EGFR) family is the key factor in epithelial malignancies, plays essential roles in regulating cell proliferations, survival, differentiation and migration [38,39]. EGFR is a member of ErbB family of tyrosine kinase receptors, transmit signal which promote cell growth [40,41]. The epidermal growth factor consists of four members: ErbB1 (HER1), ErbB2 (HER2) and ErbB3 (HER3) and ErbB4 (HER4) [42]. In normal cell EGFR ligands (TGFα) maintain the cell proliferation according to the tissue requirement for homeostasis. However, in cancerous cell it is abnormally stimulated in tumor microenvironment due to mutation and as a result there is a continual activation of the receptor [43].

Drug Name	Class	Brand Name	Clinical Trials	Uses	References
Bevacizumab	VEGF Inhibitor	Avastin	Phase II/III	Ovarian cancer, primary peritoneal cancer and Fallopian tube cancer.	[23,24]
Cediranib	VEGF Inhibitor	Recentin	Phase II/III	Used orally in recurrent ovarian cancer in Phase II clinical trials.	[25]
VEGF Trap	VEGF Inhibitor	Aflibercept	Randomized Phase II	Ovarian cancer, primary peritoneal cancer and Fallopian tube cancer.	[26]
Imatinibmesy-late	PDGF inhibitor	Gleevec	Phase II	Platinum resistant ovarian cancer	[27]

Table 2: List of antiangiogesis inhibitors used in ovarian cancer.

Drug Name	Class	Target	Cell Line/Uses	Clinical trials	Reference
DAPT	γ-Secretase Inhibitor	Notch Signaling Pathways	Ovarian cancer Cells (A2780 and OV2008)	Preclinical Studies	[38]
Sinomenine	*Anti-proliferation and Anti Metastasis*	*MCM2 gene/Wnt*/β-catenin signaling	Ovarian Cancer Cells (IGROV1, HeyA8 and SKVO3 cells)	Preclinical Studies	[35]
XL147	Induce Apoptosis in tumor cells	Inhibits PI3 Kinase	Non-Small Cell Lung Cancer Endometrial Carcinoma Ovarian Carcinoma	Phase 1	[39]
Perifosine	*Anti-proliferation*	AKT inhibitor	OVCA cells	Preclinical Studies	[40]
Temsirolimus	Arrest cell cycle, Antiangiogenic	mTOR inhibitor	Epithelial ovarian and primary peritoneal malignancies	Phase II	[41]

DAPT=(N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester)

Table 3: List of ongoing clinical studies and Pre clinical studies of cell signaling specific agents.

Drug Name	Class	Brand Name	Clinical Trials	Uses	References
Gefitinib	EGFR Inhibitors	**Iressa**	Phase II	Relapsed/Persistent ovarian carcinoma	[45]
Erlotinib	EGFR Inhibitors	Tarceva	Phase II	Ovarian, fallopian tube and primary peritoneal cancer	[46]
Cetuximab	EGFR Inhibitors	Erbitux	Phase II/III/IV	Recurrent ovarian cancer	[47]
Trastuzumab	EGFR Inhibitors	Herceptin	Phase II	Recurrent ovarian carcinoma	[48]
Pertuzumab	EGFR Inhibitors	Omnitarg	Phase II	Platinum resistance ovarian carcinoma	[49]

Table 4: List of ongoing clinical studies of EGFR inhibitors.

Trastuzumab/herceptin is approved for the treatment of early stage breast cancer in both the cases where the Human Epidermal Growth factor Receptor 2 positive (HER 2+) which spread in to the lymph nodes, and also which is not spread in to the lymph node. Herceptin, a recombinant humanized monoclonal antibody binds to the extracellular domain of the HER 2 receptor and block activation of intracellular signal transduction pathways [44] (Table 4).

Targeted polymeric drug delivery system

Multi drug resistance and toxicity of the anticancer drugs have made the idea of novel drug delivery system in to existence [45-49]. The novel drug delivery has been linked to three major categories:

1. Lipids based drug delivery system

2. Nano based drug delivery system

3. Polymeric drug delivery system

Advance in polymer drug delivery have resulted in the synthesis and design of polymers with unique properties. To optimize the novel drug delivery system as successful drug carrier, they should be bio-compatible, non-immunogenic and bio-degradable. They should maintain low variability in particle size distribution to ensure the homogeneity of polymer drug conjugates [50]. Polymer Drug conjugates improves the cell specificity of low molecular weight drugs [51].

Synthetic polymers are widely used over the natural polymers for Drug delivery. Natural polymers include polysaccharides such as polypeptide, polynucleotide, dextran and chitosan [52]. Most synthetic polymers are widely used in cell culture and preclinical trials. Synthetic polymer includes HMPA copolymer Poly (ethylene glycol), Poly (L-glutamic acid) Poly (L-lysine) Poly (vinyl pyrrolidon), etc. Among them, some synthetic polymers such as HMPA copolymer and PEG contain multifunctional group which have been used successfully used in the field of polymer drug conjugates [53,54]. In Addition to low molecular weight chemotherapy regimens, Polymer Drug Delivery system can deliver several drugs simultaneously, e.g. N-(2-hydroxypropyl) methacrylamide (HPMA) co polymer conjugates containing both doxorubicin and Mesochlorin c6 (Photoactivable compound) showed better cytotoxicity activity than HMPA Doxorubicin used alone. This concept provides new opportunity in multiple drug resistant carcinomas. Although cancer chemotherapeutics have strong potential on tumor inhibition; they are associated with serious toxicity and adverse effect. This is the area where polymer drug delivery excel, by direct the maximum concentration of drug to the tumor, without exploiting the surrounding environment, as a result it decrease the systemic toxicity. Nevertheless the progress of polymer therapeutics is almost unseen. There are still enormous challenges to overcome to ensure the safety and rapid translation/metabolism of polymer therapeutics in to routine clinical use.

HMPA copolymer for designing of anticancer conjugates: HMPA copolymer conjugates have been investigated with several anticancer agents such as DOX (Doxorubicin) Conjugates, Camptothecin conjugates and Paclitaxel conjugates, entered in the Phase I/II clinical trials [55-57]. Doxorubicin covalently conjugated to HMPA co polymer via hydrolytically labile pH sensitive hydrazine bond which increase the stability and release rate at pH 7.4 and pH 5 respectively. HPMA copolymer-bound doxorubicin has showed greater potency than free doxorubicin in the treatment of ovarian cancer. HMPA bound doxorubicin induce apoptosis in ovarian cancer by simultaneously activation of both the caspase dependent and caspase independent pathways of DNA damage.

PEGylation to improve anticancer drug delivery: PEGylation involve the direct conjugation of one or more PEG molecules to various therapeutics including drug or protein. The Biomedical application of PEG polymer has been increased due to its nontoxicity, non-immunogenicity, non-antigenicity biodegradability and biocompatibility. PEG drug conjugates are used to enhance passive tumor accumulation of therapeutic in combination with EPR effect (Table 5).

Conjugates	Cell-line	References
Folic acid CHP conjugates	Ovarian cancer cell line A2780	[58]
Polycurcumin	Human ovarian cancer cells C-13, SKOV-3, OVCAR-3 ovarian cancers, MCF-7 breast cancer cell line	[59]
HA paclitaxel conjugates	Breast, colon and ovarian cancer cells and CD44 (+) human ovarian carcinoma cell lines such as SKOV-3ip	[60]

Table 5: Example of pre -clinically developed polymer-anticancer drug conjugates.

Conclusion

The therapeutic use of cancer chemotherapy has been restricted due to its non-specific or dose limiting cellular toxicity and development of multidrug resistance. To overcome this restriction various drug delivery system are being studied. In last few decades polymer drug delivery system have an enormous impact in cancer therapy, multidrug resistance is a major bottleneck limitation in cancer therapy, after introduction of PDCs limitation has been over come to a large extent? Moreover PDCs improves selectivity and the therapeutics index of anticancer agents by enabling tumor specific targeting as a result there is a vast improvement in toxicity profiling. Polymer Delivery System has become a new domain for research of various existing anticancer drugs. Novel polymer drug conjugates can be designed with multifunctional properties which can be potential to overcome all the limitations related to non-specific and dose related cellular toxicity**.** Nevertheless the progress of polymer therapeutics is almost unseen. There are still enormous challenges to overcome to ensure the safety and rapid translation/metabolism of polymer therapeutics in to routine clinical use.

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