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Review Article

Smart Nanoparticles for Targeted Cancer Therapy

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ABSTRACT

Cancer remains one of the major death situations all over the world and more effective and specific therapeutic approaches have to be developed urgently. Although the conventional chemotherapy is effective, it is generally attributed with systemic toxicity and low tumor tissue selectivity. Over the last few years, nanotechnology has emerged with a hope that the above limitations could be overcome through the design and use of Nano carriers as a method to deliver drugs to cancer. Nano carriers Nano-engineered materials that are encapsulated on a Nano scale, have the room to advance the nature of therapeutic agents such as the stability, bio-availability, and delivery efficiency of the therapeutic agents lying within. A major goal of Nanocarrier systems is to prevent premature degradation of drugs in the systemic circulation and to permit accumulation of such drugs at the tumour site in therapeutically effective concentrations. The targeted delivery can reduce the exposure of drugs to the healthy tissues hence, the adverse side effects. Nanoparticle-mediated drug targeting has two major strategies; active and passive targeting. Passive targeting is done using the increased permeability and retention (EPR) effect whereby the abnormal and leaky endothelium in the tumor tissues enables the nanoparticle to selectively accumulate in tumor. Active targeting is the process of functionalization of nanocarriers by use of specific ligand, e.g., antibodies, peptides, or small molecules, which are able to interfere with overexpressed receptor on the surface of cancer cell, improving cellular uptake and tumor specificity. Nanocarriers are designed and manufactured in such a way that determines their success in treating cancer. Major parameters that would have a huge impact are particle size, shape, cell surface charge, and hydrophilicity-/hydrophobicity balance which would have a massive effect on the uptake of these particles into the body and its pharmacokinetics, cellular uptake as well as biocompatibility. As an example, the size of nanoparticle usually is 10-200 nm, which is more or less ideal in terms of tumour penetration and

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retention. The circulation time and immune recognition of the graft can be prolonged by surface changes, e.g. polyethylene glycol (PEG)ylation. The recent trends in Nanocarrier system are the development of nanoparticles with stimuli responsive behaviors, multi-functional hybrid Nanomaterials, and customized nanomedicine. Such intelligent systems have the capability to release drugs when triggered by a given stimulus in a tumor microenvironment e.g. pH, temperature, enzymes or redox gradients which further adds to the therapeutic efficacy and limits the off-target effects. To sum up, nanocarriers are the innovative solution in cancer treatment as they provide better drug delivery, treatment selectivity, and low-toxicity. Further application of both nanomaterial infrastructures and functionalization of Nano materials promises a bright future of cancer treatment, more effective, more personalized and safer.

INTRODUCTION

The disease of cancer is among some of the greatest health issues in the world and is still the major cause of morbidity as well as mortality in the world. As the epidemiological evidence studies and reports the burden of the disease caused by cancer would grow in the next decades, representing the central cause of the death of the population worldwide(1). In spite of the recent noticeable advancements in the development of the tumor histology and the implementation of new treatment plans, conventional forms of cancer therapy, traditionally referred to as surgery, radiotherapy, chemotherapy and immunotherapy, still experience devastating constraints(2). Such strategies have an urge to deliver suboptimal results because of such factors as systemic toxicity, the lack of specificity of the medication against cancerous cells, a severe depletion of the drug, and development of multidrug resistance(3). In this respect, nanotechnology provides an outstanding platform in advancing more effective and selective cancer therapies. Nanocarriers - owing to the potential to enhance anticancer agent pharmacokinetic and pharmacodynamics profiles - have attracted a significant deal of interest in the

field of drug delivery(4). The nanocarriers are capable of encapsulating the therapeutic agents and protecting against any premature degradation, improve their solubility and stability as well as release them at the tumor site in a controlled and prolonged manner(4). These characteristics indicate greatly augmented therapeutic potential of medicines, decreased non-specific effects, and enhanced patient adherence. Another immune-evasion mechanism that is very significant to nanocarriers is the enhanced permeability and retention (EPR) effect that can be exploited to favour the accumulation of these nanoparticles in the tumor tissues following leaky vasculature and hampered lymphatic drainage in the tumor microenvironment(5). The active targeting strategies can also enhance this passive targeting mechanism as nanoparticles are covered or functionalized with ligands which bind to over expressed receptors existing in cancer cells like antibodies, peptides or aptamer. Secondly, the progress made in the design and fabrication of nanomaterial has made it possible to develop multifunctional platforms incorporating therapeutic and diagnostic features, so-called theranostic(6).” The platforms can enable the simultaneous imaging, drug administration and real-time treatment efficacy monitoring, which enables a more personalised management of cancer. The choice of appropriate biomaterial in the preparation of nanocarriers is very important to ascertain safety, biocompatibility and biodegradability(7). Lipids, polymers, dendrimers and inorganic nanoparticles are all materials routinely used as components of Nano systems to achieve a set of desired physico-chemical properties. Surface modification is also very easy to do, and it is possible to design specific nanoparticles using the desired functionality, e.g. pH-sensitive, temperature-sensitive, drug release in response to enzymes(8). Besides, the application of nanotechnology on cancer treatment



does not end in the drug delivery. The research on Nanomaterials is also being developed in the field of early diagnosis and biomarkers, photo thermal or photodynamic therapies and imaging. These inventions altogether bring about the realization of newer and less intrusive methods of treating cancer(9). To summarize, nanotechnology and oncology should become an innovative solution to cancer treatment. This is because by overcoming the drawbacks of conventional treatments and paving the way to the selective, efficient and safer drug delivery, nanomedicine can make a profound difference in the clinical practices and survival of cancer patients(10). This review will give credit to the latest developments in nanoparticle design and increased use of nanotechnology in anti-cancer battle. Nanomedicine Targeting Strategies and Targeting Strategies in Cancer Nanomedicine(11). The use of nanoparticles in drug delivery can be traced back to the 50s when Jatzkewitz first synthesised a conjugate of polymer and a drug. It was later strung with an enormous leap in the 1960s when Bangham et al. introduced liposomes which were spherical vesicles. They had the unsurpassed ability to pack in therapeutic agents(12). Another early example is that of Scheffel and co-authors who in 1972 published about albumin-based Nano-particles that the lead to development of Abraxane, albumin-bound paclitaxel. Other well-known preparations of this type are the polymer-drug conjugates such as PEG-asparaginase and PEG-IF2, and Abelcet (liposomal amphotericin B complex) which was approved to treat systemic fungal infections of immune compromised, cancer patients(13). The next big breakthrough in nanoparticle delivery was in the 1980s when Matsumura and Maeda described the Enhanced Permeability and Retention (EPR) effect. They discovered that because of leaky and irregular architecture of tumor vasculature, nanoparticles selectively accumulate at the tumor site(14). The size of the

fenestrations" on these abnormal vessels varies between 200 and 800 nm, (compared with 510 nm in normal tissues) and this means the nanoparticles can enter the tumor interstitium and be trapped here (passive targeting). But passive targeting may not be adequate as there is inconsistency in tumor vasculature and low EPR effect in some tumor(15). Such has led to the development of active targeting where nanoparticle surfaces are functionalized with specific ligands (e.g. antibodies, peptides) that specifically bind to overexpressed receptors on cancer cells and enhancing drug accumulation and therapeutic outcome(16). The mentioned developments represent a serious breakthrough of nanomedicine and remain to unfold future of goal-oriented cancer treatments(17).

2. ACTIVE TARGETING IN CANCER NANOMEDICINE: MECHANISM AND THERAPEUTIC POTENTIAL

Active targeting is a sophisticated cancer nanomedicine tactic that increases selectivity of the drug delivery system. In contrast to passive targeting, which has to rely on the enhanced permeability and retention (EPR) effect, active targeting uses tailoring the nanoparticles surface with special ligands that specifically bind to overexpressed tumor cell receptors or tumor-related endothelial cells(18). Nanoparticles use specialized chemical links to conjugate ligands (e.g. peptides, antibodies, vitamins, carbohydrates or nucleic acids) to nanoparticle. After administration of these altered nanoparticles, they find and attach to the target receptors on the surface of the tumor cell and trigger the endocytosis which is mediated by the receptor(19). The process leads to the ability to internalize the nanoparticle into the cancer cell whereby the therapeutic payload is released either in the cytoplasm or into the nucleus leading to better treatment improvement and



reduction of side effects to the normal tissue. A number of receptors have been targeted actively(20). As an example, transferrin receptor, which is overexpressed in most cancers, and folate receptor with the general overexpression in cancers, is prominent within the examples of targeted nanoparticle conjugation with transferrin or folic acid. Like the above, the 3v integrin (alpha-v-beta-three) also very prevalent in tumor angiogenesis and some cancer cells is usually targeted against with cyclic RGD (Arg-Gly-Asp) peptides that have a high affinity to bind this integrin(21). RGD-peptide-modified chitosan nanoparticles have been found to be more tumor specific and therapeutically effective against ovarian cancer models. Targeted therapy is also revolutionized by monoclonal antibodies (mAbs). The antibodies are specific and they attach themselves to surface proteins in the cancer cells(22). Rituximab is specific to the target CD20 in non-Hodgkin lymphoma, trastuzumab targets the HER2/new oncogene in breast cancer and bevacizumab targets VEGF in colorectal cancer among others. In addition to free antibodies, conjugates including antibody-drug conjugates (ADCs) are employed, e.g. Mylotarg (a conjugate of the CD33 antibody with the chemotherapy insenferim) in treating leukemia. Radio immune conjugates which incorporate antibodies with a radioactive isotope such as Bexxar and Zevalin are also permitted to treat cancer(23). Another novel type of targeting ligand with potential uses is the nucleic acid aptamers. Aptamers can be short, single stranded length of DNA or RNA material that is chosen through the SELEX (Systematic Evolution of Ligands by Exponential Enrichment) method. Aptamers have high affinity and specificity of binding a molecular target because of their unique three-dimensional structures(24). These have many attributes to their benefit which are low immunogenicity, simple to manufacture, inexpensive to produce and can be modified.

Pegaptanib PEGylated aptamer which has been approved by FDA inhibits angiogenesis by targeting VEGF binding to its receptor. Finally, active targeting improves the efficacy of nanocarrier delivery by concentrating them in a single cancer tumor cell or in tumor vasculature(25). Such a strategy minimizes toxicity of the system, augments accumulation of the drug on the site of tumor, and enhances therapeutic index of the whole process. Active targeting remains one of the growing and potent mechanisms of precision treatment of cancers given the numerous formulations approved and also in clinical trials(26).

3. LIPOSOMES AS NANOCARRIERS IN CANCER DRUG DELIVERY

One of the most clinically successful and studied nanocarriers in cancer therapy is the liposomes. Liposomes are spherical vesicles that structurally form themselves, having one or more phospholipid bilayers. These phospholipids have both hydrophilic (water attracting) heads and hydrophobic (water repelling) tails which are structured to form a bilayer through which an aqueous core is compartmentalized(27). The special shape enables the transport of both hydrophilic and hydrophobic drugs (respectively in the water and lipid compartments) and thus they become a versatile drug delivery system. It can be stated that the creation of liposomes as carriers of drugs started in the 1960s and has resulted in a number of formulations approved by the FDA to use under clinical conditions(28). The best-selling one is PEGylated liposomal doxorubicin (Doxil). PEG in this formulation is coupled to the surface of the liposome which assists it to avoid the immune system CEL and survive longer in the circulation(29). This increases the half-life of the drug and leads to an increase in its concentration at the tumor site through the Enhanced



Permeability and Retention (EPR) effect that leads to better therapeutic effects. Kaposi, ovarian cancer and multiple myeloma are all treated with Doxil(30).

They are other authorized formulations of liposomes, which are as follows:

1. Myocet (non PEGylated liposomal doxorubicin)
2. daunoXome (liposomal daunorubicin)
3. Abelcet (liposomal amphotericin B in fungals in cancer patients)
4. DepoCyt (liposomal cytarabine used in the prevention of leptomeningeal metastasis)
5. Lipoplatin (liposomal cisplatin)(31)

Antisense oligonucleotides, short fragments of DNA or RNA, which bind to a specific mRNA sequence and prevent the manufacture of a disease-specific protein is also potentially carried by liposomes. As an example, encapsulated Bcl-2 antisense-oligonucleotides have been demonstrated to inhibit synthesis of the Bcl-2 protein in cancer cells, which is important in cancer cell survival, whilst causing the death of tumor cells in models of follicular lymphoma(32). Remarkably, these liposomal oligonucleotides were well-tolerated as animal studies revealed its widespread distribution and low toxicity with 6-week procedures. The other example is Lerafaon that is a liposomal delivery of antisense oligonucleotide that targets the c-raf gene which is involved in cell growth and radiation resistance. This formulation showed a positive indication in Phase I of clinical trials on solid tumor, implying that it could be used as a sensitizing agent to chemotherapy and radiation(33). It has gone further to utilize the small interfering RNA (siRNA) and microRNAs (miRNAs) short RNA molecules which can silence genes. These RNAs are capable of down regulating the expression of the oncogenes or reinstate tumor suppressor

functions. Yet, they are unstable in nature and are not effectively taken up by cells, thus, efficient delivery vehicles are essential regarding their use in the treatment of disease(34). As an example, liposomes based on DOPC were effective in transporting siRNA that targets EphA2 proportions, which are typically overexpressed in ovarian cancer resulting in very favourable preclinical results. A second version, SNALP (Stable Nucleic Acid Lipid Particle) loaded with siRNAs targeting VEGF and KSP1 was highly active in anti-tumor response and was entered into clinical trials (ALN-VSP02)(35). This bi-targeting method also has a good tolerance and its objective was to diminish proliferation of liver cancerous growths. Likewise, TKM 080301, a lipid nanoparticle which carried siRNA targeting PLK1, has gone through Phase I trial across various types of cancer treatments (i.e. colorectal, pancreatic, breast and ovarian cancers that have metastasized in the liver). Therapies based on miRNA were also examined recently(36). An example concerns the development of lipid nanoparticles loaded with a tumor suppressor miRNA, miR-133b, which leads to a greater chemo sensitivity of lung cancer. These nanoparticles were accumulated in the lungs and caused an upsurge of 52x miR-133b, thus, showing an efficient inhibition of the tumor(37). The other miRNA, miR-29b also applied with the lipid-based carriers showed a response to tumor down 60 Percent in lung cancer models(38). Success in cancer using lipid nanoparticles to deliver therapeutic miRNAs has also been demonstrated in breast cancer, melanoma, pancreatic cancer, prostate cancer, lymphoma, and hepatocellular carcinoma. These findings reaffirm the wide-ranging possibility and potential of liposome-based delivery systems in gene treatment of cancer(39).

4. POLYMERIC NANOPARTICLE FOR TARGETED CANCER DRUG DELIVERY



Polymeric nanoparticles are a significant type of cancer treatment nanocarrier that provides benefits of high biocompatibility, biodegradability, and multifaceted structure engineering. These nanoparticles are constructed in a way that they can be made using special shapes, sizes, surface characteristics and internal structures and so they are useful in the specific applications of drug delivery(40). The polymers to be applied in these systems may come from natural products such as chitosan (chitin), human serum albumin, or can be synthetically produced such as poly (lactic-co-glycolic acid) (plga). Other frequently found polymers are arginine, hyaluronic acid, and alginate used in preclinical trials and demonstrates promising outcomes(41). The chitosan nanoparticles have become of special interest in the delivery of the genes especially those related to small interfering RNA (sirna). Chitosan is positively charged and thus can be used to bind sirna with negatively charged RNA by electrostatic association to form stable complexes which can circulate safely in the blood(42). To give an example, Kim et al. employed chitosan nanoparticles loaded with sirna targeted at the src and fgr code in ovarian cancer models, which demonstrated the reduction of tumor growth by more than 85 percent. The other key characteristics of polymeric nanoparticles is that they can deliver two or more therapeutic agents, hence patil and panyam developed an effective plga-based nanoparticle, consists of polyethyleneimine to deliver the genes effectively(43). The subsequently, they overcame drug resistance in their application by targeting p-glycoprotein (p-g p) using the same nanoparticle, the researchers co-loaded sirna which targets p-g p and paclitaxel, a chemo-therapeutic into the nanoparticle and in order. This system was very effective in treatment in comparison with paclitaxel alone, which demonstrated the possibility of polymeric systems to overcome multi drug resistance(44). In clinical

practice, polymer Nano particles broke through with the approval by the U.S, FDA of abraxane, an albumin bound version of paclitaxel, against metastatic breast and lung cancers. Abraxane exploits the natural affinity of albumin to bind to the gp60 receptor (albondin) on endothelial cells and resulting in a caveolin-1-mediated endocyt In addition, albumin is conjugated with sparc (secretory protein acidic and rich in cysteine) which is overexpressed in several tumors; this further enhances accumulation of drugs at the tumor site(45). One of the breakthroughs was in the year 2010 when Davis et al. reported the first use of a cyclodextrin polymer based nanoparticle to deliver sirna systemically in human cancer patients. This system targeted an important gene called the rrm2 and was involved in DNA synthesis. to generate additional specificity, the nanoparticle(46). Due to the constant progress in the clinical, preclinical spheres, these systems demonstrate enormous potential in overcoming the shortcomings of the standard ways of cancer treatment. Systemic cancer treatment with siRNA/miRNA depends on the successful delivery through polymeric nanoparticle which can enhance uptake and targeting of drugs to the cells(47). Recent clinical and preclinical studies have shown that polymeric nanoparticle delivery is promising in overcoming issues of resistance and efficacy of drug treatment of cancer in lung and pancreatic tissue with sirna and miRNA, respectively(48).

5. POLYMERIC MICELLES

Nano drug delivery systems Polymeric micelles Polymeric micelles are Nano size drug delivery systems (10100 nm) consisting of amphiphilic block copolymers self-assembled in aqueous media. They are also made up differently with a water-repelling center and a water-attracting shell or corona(49). This architecture renders them



particularly appropriate to entrap/incorporate a poorly water-soluble (hydrophobic) drug into the core and increase solubility, stability, and bioavailability of drugs. These micelles can prevent the degradation of the drug in the biological environment/medium, they enable passive targeting (due to the Enhanced Permeability and Retention EPR effect), and active targeting (by the addition of special ligands that bind to certain cells (receptors on cancerous cells))(50). As an example, Genexol-PM is a polymeric micelle formulation of paclitaxel that is under investigation in breast, lung and pancreatic cancer. Others are Pluronic and NK911 micelles of doxorubicin and NC-6004 delivering carboplatin. In experimental models, doxorubicin-loaded PLGA-b-PEG micelles demonstrated enhanced uptake by the tumor and a great tumor regression(2). Besides, specific (targeting) micelles with ligands such as folates or antibodies (e.g., mAb C225 against EGFR) are further used to deliver the drug to a certain type of cancer. These encouraging findings indicate that polymeric micelles are potent instruments of targeted cancer treatment in future(51).

6. DENDRIMERS AS NANOCARRIERS IN CANCER THERAPY

Dendrimers are a distinct family of hyper branched Nano- sized and highly branched macromolecules that are having a well-defined and tree-like architecture. They are composed of a central core, repetitive branching units as well as numerous terminal functional groups on the surface(52). Among the advantages that this unique structure gives dendrimers as drug delivery vehicles, the most noticeable ones are its use in cancer treatment. The major advantage of the dendrimers is their capability of the application of repeatedly held therapeutic agents. The drugs may be either physically contained in the internal cavities of the

dendrimer or be chemically attached to the functional groups in the surface of the drug(53). The versatility allows the preparation of multifunctional dendrimer-based carriers which can be used to deliver drugs with controlled release properties. One such highly developed system is founded on poly amidoamine (PAMAM) dendrimers, among the most studied varieties of dendrimers. The chemical modification of PAMAM dendrimers allows furthering their biocompatibility and maximization in the release of drugs(54). An example is surface modification, through addition of polyethylene glycol (PEG) chains a procedure termed as PEGylation, which enhances circulation time and immunogenicity. Also, the dendrimers can be further functionalized by chemically attaching acid sensitive linkers to enable their drug release in acidic conditions, i.e. the tumor microenvironment or inside the cell, in lysosomes(55). An example of the practical use of this design is the conjugation of the anticancer agent doxorubicin to acid-sensitive doxorubicin conjugated to PEGylated PAMAM dendrimers (IEC). In vitro experiments done using ovarian cancer cells (SKOV-3) demonstrated that the release of doxorubicin occurred at a higher rate in an acidic environment that is similar to that in the tumor microenvironment(56). These dendrimers showed increased uptake into the cells by the process of clathrin-mediated endocytosis, and in vivo studies in use of dendrimers in the treatment of tumor-bearing mice showed that dendrimers that were more PEGylated had more uptake into the tumor, which enhanced the delivery of the therapeutic agent to the diseased site and enhanced therapeutic success(57). In addition to drug delivery, dendrimers may be designed in targeted therapy. As another instance, polylysine dendrimers functionalized with ligands that bind to overexpressed integrins on cancers may be created. An example of such target is the activated alpha 5 beta 1 integrin that is highly expressed in



the breast cancer cells and that plays a significant part in the invasion and metastasis tumor(58). Polylysine dendrimers were conjugated to the PHSCN peptide ligand that binds to 8 and blocks the action of 85B1 integration. This specific maneuver led to a considerable decrease in the invasive qualities of the human breast cancer cells in the cell cultures and, in the experimental models of the metastatic breast cancer, it displayed the prevention of the development of the lung metastasis(59). Nevertheless, these encouraging outcomes are associated with the fact that dendrimers have problems with potential immunogenicity and long-term safety. Further studies are needed to make them safer to use in repeated clinics and optimize their design and reduce immune responses(60). To conclude, dendrimers provide a flexible and potent cancer drug delivery platform comprising, multi functionality, targeted delivery, and programmed drug release. In the context of continuing developments, dendrimer-based therapeutics has the potential of being applied in the clinical arena of oncology in future(61).

7. CHARACTERISTICS OF NANOPARTICLES

Nanoparticle properties such as physical and chemical properties as well as more specifically size and shape, Surface and Drug Release, are critical factors in their fate within the body, their half-life in the blood, their localization distribution and their cellular uptake efficiency(62).

7.1 SIZE: The basic considerations with the nanoparticle design include size. Nanoparticles that are accompanied with intravenous administration have a drawback of being caught up by the spleen as a result of mechanical filtration by the Reticuloendothelial system (RES). This is because the fenestrations (tiny openings) of the filtering units of the spleen measure roughly 200-

500 nm. Those that have dimensions above this size should be deformable in order to go through(63). The optimal size of Nanoparticle is 100-200 nm so that it may enjoy the Enhanced Permeability and Retention (EPR) effect as the process can make the majority of NPs to accumulate in tumor through leaky blood vessels rather than fast elimination by the liver or kidneys. The particles that are less than 5 nm are cleared rapidly by the kidneys and take shorter circle time. Particles that are incredibly big (>15 micrometres) on the other hand have a tendency of depositing in the liver, spleen, and the bone marrow(64).

7.2 SHAPE: Nanoparticle behavior is also importantly influenced by shape. Experiments indicate that cells take up nanoparticles with the same size in vastly different rates depending on their geometry. Following an illustration, discoidal (disk-shaped) nanoparticles were found to accumulate in tumor five times compared to nanoparticles of the same size and shape, but spherical(65). Particle shapes affect the rate of degradation and pattern of drug release, usually in a different pattern to other shapes. Additionally, deformability of particles can assist avoidance of filtration by the organ like the spleen(66). Studies that integrate size and shape demonstrate that such interplay of both parameters controls the circulation of the nanoparticle, its residence at the target tissues and its efficacy. Thus, the size as well as shape should be carefully regulated when working on effective delivery systems of nanoparticles(67).

7.3 SURFACE AND RELEASE CHARACTERISTIC OF NANOPARTICLES IN DRUG DELIVERY

The specifications of the surface of the nanoparticle have a significant effect on their circulation period, bio distribution and fat liability within a body. After administration, the



nanoparticle will bind to proteins in the blood resulting in a phenomenon known as opsonisation in which immune proteins label them to be removed by macrophages(68). This makes them less effective. This is avoided by surface modifications. Nanoparticle coating with relatively neutral molecules, such as PEG (polyethylene glycol) or albumin minimizes protein binding and extends blood circulation(69). As an example, the PEGylated liposomes doped with doxorubicin and coated with albumin have better targeting of the tumor and decreased clearance. In addition, ligands conjugation or antibodies (e.g., HER2 antibodies) on the surface of the nanoparticle makes it target specific tumor cells actively(70).

7.4 DRUG RELEASE:

The success of nanoparticles-based therapy is determined with the use of drug release behavior. The circulation time of traditional drugs and their concentrations are variable and short. Sustained and controlled releases occur by nanoparticles often by zero orders of releases keeping the drug in the therapeutic window(71). Polymers that are biodegradable such as PLGA and PLA are able to regulate the rate of their release according to their molecular weight. The new generation of systems, e.g., mesoporous silicon particles, is capable of controlled release of their payload, e.g., siRNA, over a long period(66). Also, pH and temperature stimuli-responsive systems release drugs under higher or lower pH or other factors outside of the body such as ultrasound increasing more accurate delivery. Such inventions increase the effectiveness and safety of nanoparticle systems in cancer treatment(72).

CONCLUSION

The continued cancer menace to the health of the world community justifies the development of less

toxic, and more precise, and modern medical treatment methods. The common tradition of treating cancer by the use of chemotherapy tends to produce no variances between the healthy tissues and the cancerous tissues which make the traditional chemotherapy very toxic to the system and results in poor side effects and the reduction of the quality of the life of the patient using the chemotherapy(73). The emergence of nanotechnology has provided hope of change of paradigm in the treatment of cancer and especially in the development and utilisation of Nanocarrier-based drug delivery systems. These Nanoscale systems offer an advanced approach to resolve the inherent drawback that conventional therapeutics have created, where they form an enhanced solubility, stability, and bioavailability of the drug and allow selective delivery of the drugs to tumor tissues(74). Nanocarriers work by entrapment or conjugation of chemotherapeutic agents in Nanoscale matrices that are considered to be biocompatible and stop the early breakdown of the chemotherapeutic agents in the systemic circulation. This permits longer-term circulation and it enables the selective deposition at the tumor, in large part through the enhanced permeability and retention (EPR) effect, and is a feature of passive targeting(75). Moreover, development of active targeting strategies like conjugating ligands, like antibodies, peptides, or small molecules by surface conjugation to recognize and bind overexpressed cancer cell proteins on the surface, further improves the specificity of the nanocarriers towards cancer cells. This twofold strategy active and passive increases the therapy efficiency and reduces the effect on normal tissues(76). The key attribute to the functionality of nanocarriers is their physicochemical characteristics. The bio distribution, pharmacokinetics, cellular uptake and immunogenicity of these systems are directly affected by parameters like particle size, particle shape and surface charge, and hydrophilic-



lipophilic balance(77). Nanoparticles of a size between 10-200 nm were found to perform especially well in terms of tumor penetration and retention, surface modifications, like PEGylation, have proved to greatly enhance the lifetime in the systemic circulation, and avoid the immune system. . Having such properties which could be tuned enables researchers to modify nanocarriers to suit distinct cancer needs and therapeutic agents(78). In addition to conventional nanoparticle designs, new developments have led to emergence of the second generation of nanocarriers. These involve stimuli-activated nanoparticles that can be induced to liberate medications through a response to a variety of inside/external cues including however not constrained to pH variations, enzyme-sensitivity, redox circumstances or temperature gradients common in the tumor microenvironment(79). Moreover, multifunctional hybrid nanoparticles allow introducing therapeutic, diagnostic, and imaging applications on the same platform with the possibility to open the perspective of theranostic applications, which allow real-time monitoring of therapy outcomes(80). The Council further advances precision and efficacy of cancer treatment by personalized nanomedicine methods where the unusually different genetic and molecular characteristics of the individuals are taken into account, pioneering towards individualized treatment(81). To sum up, nanocarriers imply a breakthrough in the oncological experience that will allow delivering drugs smarter, safer, and even more efficiently. In addition to their potential to improve the therapeutic index of anticancer drugs, they have the potential to transform the general cancer-treating methodology by means of specific delivery, regulated delivery and individualized customization(82). Although hurdles like the production at a large quantity, regulatory approval and the safety testing in the long term are still

present, the research and development in nanocarrier technology are very promising(83). That will involve a positive trend in ongoing interdisciplinary efforts by materials scientists, pharmacologists, oncologists, and regulatory organizations to turn laboratory advances into clinically useful cancer therapies(84). By continuing their progress, nanocarriers will serve as one of the foundational arms of the fight against cancer to increase the survival rates and the life quality of millions of people in every corner of the globe(85).

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