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REVIEW ARTICLE

Targeted Cancer Therapy: Present Status of Small Molecules and Nanoparticles in Use

Monali Chauhan[1],Samiksha Gupta[2], Mohammad Asif Siddiqui[3], Rushikesh Shankar Chavan[4], Garima Abbi[5]

[1] High Altitude Plant Physiology Research Centre, Department of agriculture and allied sciences, Plant Physiology, Uttrakhand
[2]Department of chemical engineering, Birla Institute of Technology (BIT), Mesra, Ranchi
[3]Department of Biotechnology, Raja Balwant Singh Degree College, Agra,
[4]Department of Biology, Indian institute of Science Education and Research, Pune
[5]Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Gujarat
Email for Correspondence: monali.chauhan81@gmail.com

ABSTRACT

Chemotherapy and Radiation-therapy are the two most predominantly used therapeutic techniques for the treatment of metastatic cancer patients. However, both these techniques have certain limitations like lack of selectivity, degradation of chemotherapeutic drugs, causes toxicity to healthy cells, decreases intratumoral drug concentrations and most importantly, multidrug resistance. In order to address these limitations, several efforts have been made to discover techniques of targeted cancer therapy. Administration of chemotherapeutic drugs encapsulated in synthetic and natural polymers are one of the way outs. Introducing nanotechnology in the healthcare sector has been very promising. Drug delivery through various kinds of nanoparticles has been very effective in increasing the overall survival of cancer patients. The selection of the right polymer material in case of constructing a nanoparticle encapsulated drug becomes very vital as renal clearance is a major factor after a patient is treated with the conjugate. In case of metallic nanoparticle, AuNPs and Fe_3O_4 MNPs have gained much popularity unlike cadmium nanoparticles which has toxic manifestations. The uses of natural polymers are also preferred over synthetic ones owing to their better bioavailability and biocompatibility. Drug delivery through antibody-conjugated nanoparticles is considered one of the successful targeted therapeutic techniques, as it selectively targets the tumorigenic cells and prevents multidrug resistance with high efficacy. However, the ever-changing pathophysiology and molecular composition of tumor microenvironment is a reason researcher and pharmacologists are worried. They are putting sincere efforts in discovering even better drug delivery vehicles so that better patient compliance is achieved.

Keywords: *Chemotherapy, Radiation-therapy, Targeted therapy, Nanoparticles, Polymer-based prodrug*

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INTRODUCTION

Based on a number of studies made by the international agency for research on cancer (IARC) of the World Health Organization, GLOBOCAN 2020, Surveillance, Epidemiology and End Results (SEER) by National Cancer Institute, USA mortality files by National Centre for Health Statistics, and National Cancer Centre (NCC) of China in 2020, it is revealed that Cancer has become one of the leading causes of mortality in China surpassing the figures of USA [11, 31, 44] It is the second leading cause of death worldwide [30, 43].

Cancer is a lethal heterogeneous disease with a myriad of factors controlling its manifestation like epidemiology, gender, age, etc. [30, 40]. As far as cancer therapy is concerned, surgery, chemotherapy and radiation therapy are the primary approaches for treatment. However, Chemotherapy has its own points of limitations. Its inability to selectively work on tumor cells and affecting the normal cells leads to insufficient concentrations of drugs reaching the tumor cells and results in drug-resistant tumor cells and systemic toxicity [30]. Poor solubility of anticancer drugs is another constraint faced in treatment of

cancer. Use of polymer-based prodrugs can significantly enhance the intratumoral concentration of chemotherapeutic drugs and their bioavailability [7)].

Early prognosis and efficient therapeutic approaches like immunotherapy, biological therapy or targeted therapy can reduce the recurrence or metastasis [20] [43]. Tumor microenvironment (TME) is often ignored as a primary site for consideration for cancer therapy leading to failed cancer treatment. The Cancer-associated fibroblasts (CAFs) form a major part of the TME and are involved in vital functions like cell differentiation, proliferation, stemness, extracellular matrix remodeling, and cell migration and programmed cell death. The intracellular and extracellular factors associated with signaling pathways that are closely related to cancer progression within CAFs can be major target sites for therapy [46, 17].

Another approach can be treating patients with Kinase inhibitors. Protein kinase enzymes catalyze the transfer of phosphate groups from ATPs to certain target proteins activating a cascade of signaling pathway. There can be various ways of Kinase targeting cancer therapies, like targeting a single kinase of a pathway or targeting multiple kinases at the same time or targeting kinases with other therapeutics (27). Ibrutinib is one such kinase inhibitor that targets Bruton's tyrosine kinase and commonly used in the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia [27,47]. V-raf murine sarcoma viral oncogene homolog B1 (BRAF) forms a vital part of the MAPKinase pathway and aids in cell division and growth. Vemurafenib, dabrafenib and ecorafenib are effective kinase inhibitors that target BRAF. Geftinib and erlotinib form another group of important tyrosine kinase inhibitors. They form epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and they bind competitively and reversibly to the ATP binding site of EGFR [27,38].

Yet another emerging approach for cancer therapy is nano-technology. The issue of multiple drug resistance by tumor cells because of small molecule chemotherapeutics can be well resolved by nanoparticles. Unlike the non-targeted chemotherapeutics, well-designed nanoparticles aid in the righteous drug delivery within the tumor reducing the chances of drug efflux and in turn help in increasing the intracellular drug concentration [36]. Nano materials can be metallic nanoparticles which are active catalysts and these can be easily transformed by changing functional groups. A number of molecules called nano generators for radiotherapy are also in use. Walking DNA strands or DNA-based DNA nano motors are also coming up to pave the way for molecular robotics [10, 36].

In this review we shall discuss in great detail how nanoparticles aid in combating the anticancer drug resistance. Also how nanoparticles and other small molecules help evade the drug efflux pump and increase the concentration of anticancer drug within the tumor cells.

AN OVERVIEW OF TARGETED THERAPY IN CANCER

In recent times, a number of techniques have come up as targeted therapies for cancer. Identifying an oncogene or a tumor-suppressor gene is very crucial for developing therapeutic strategies. According to the reports by Zhu et al., the oncogenic gain of function (GOF) mutation of the tumor-suppressor gene *TP53* is observed in half of the cancer cases. Missense mutation of one the *TP53* alleles cooperatively induces mutation of the other allele resulting in loss of heterozygosity and progression in cancer. Mutp53 is known to regulate a number of chemo- and radio- resistant genes. *Multi drug resistance 1* (*MDR1*) is one such gene whose protein product is an energy-requiring efflux pump responsible for mediating resistance of cancer cells to several anti-cancer drugs. Wild type (WT) p53 on the other hand, down-regulates the *MDR1* gene expression [15, 50].

As far as immunotherapy is concerned, mutp53 and the p53-derived mutant peptide- class I MHC molecules exhibit themselves as vital targets [15,32, [50]. Another example is HER2, belonging to the EGFR family of receptor tyrosine kinases, has been vital for targeted therapies of HER2-positive breast cancers in women and also HER2-positive gastric cancer (29). Monoclonal antibodies like Trastuzumab and Pertuzumab are known inhibitors of HER2 dimerization and subsequently block PI3K-AKT signaling pathway and induce Antibody-dependent cell cytotoxicity (ADCC), aiding in increasing the overall survival of women with both early-stage and metastatic breast cancers (19). However, it has been observed that the efficacies of Trastuzumab on HER2-positive breast cancer and HER2-positive gastric cancer vary substantially, owing to their differential HER2 protein distribution (revealed by the staining) even if the immuno histochemistry (IHC) grade of the tumors are similar (18) (29).

Small molecules like APR-246, methylene quinuclidinone (MQ), COTI-2, HSP90 inhibitor Ganetespib, Histone deacetylase inhibitor Suberoylanilide hydroamic acid (SAHA), CDK1 inhibitor MK-1775- all function to revert the *Mutp53* to *WTp53 (* 22*)* (50). Batir et al. applied the technique of CRISPR/Cas9 genome edition and replaced *TP53* 414delC frameshift mutation with a *WT TP53* in prostate cancer cells (1). Besides, several small peptides like CDB3, peptide-46, pCAPs, ReACp53 have been identified which can restore the functions of p53 to tumor cells (1). Synthetic lethality can be very well-achieved through

utilizing the technique of CRISPR/Cas9. The fact that CRISPR/Cas9 generates Double stranded breaks (DSBs) and introduces specific RNA sequences within cells is a very efficient technique (12).
In case of Non-small cell lung cancer (NSCLC), targeting the Anaplastic lymphoma kinase (ALK), EGFR, c-ros oncogene1 (ROS1), BRAF has been quite successful (28). In contrast to NSCLC, developing therapeutic strategies against small cell lung cancer (SCLC) is challenging owing to their loss of function mutation in tumor suppressor genes like *RB1* and *TP53* or yet targetable genes of MYC family. Targeting poly ADP-ribose polymerase (PARP), checkpoint kinase 1(CHK1), Ataxia telangiectasia, and RAD3 related protein (ATR), Ataxia telangiectasia mutated (ATM) and WEE1 have been very effective in developing therapeutics against SCLC (6) (34) (21) (39). Targeting two of the most important epigenetic modifying proteins, enhancer of zeste homology 2 (EZH2) and lysine-specific demethylase 1A (LSD1) has been promising in combating SCLC. EZH2 inhibitor has exhibited enhanced chemotherapeutic efficiency and minimalized drug resistance in SCLC patients, *in vivo*. LSD1inhibitors block the interaction between LSD1 and SNAG domain protein, insulinoma-associated protein 1(INSM1) or Growth factor independence 1B and thereby, exert chemotherapeutic effect against SCLC (39).
One of the demerits of chemotherapeutic agents is their DNA damaging effects. For instance, Cisplatin is a drug widely used in the treatment of cancer generates DNA lesions which leads to cytotoxicity and finally cell death (42).

SMALL MOLECULES IN TARGETED CANCER THERAPY

Synthetic chemotherapeutic drug with specific target

The unprecedented development of resistance towards chemotherapeutic agents, their associated adversity and toxicity, need for combination drugs and rise in healthcare expenses is causing a havoc. The need for identifying specific chemotherapeutic drugs for specific patient types is growing simultaneously. In cases of advanced cutaneous malignant melanoma (CMM) it is observed that targeting the mitogen-activated protein kinase (MAP Kinase) and BRAF is an effective way of treating the cancer. Pyridinyl imidazole compounds such as SB202190, SB203580 and SB590085 are used in the treatment of CMM whose mode of action is to inhibit the BRAF V600E kinase, activate the lysosomes of the cancerous cells and block the proliferative pathway (37).
The generation of extracellular matrices, cytokines, inflammation-supporting molecules by the non-cancerous cells seem to be a major cause of resistance towards treatment by chemotherapy. Treatment with anti-fibrotic drugs, like Nintenadib and Sorafenib have proved to be successful in treating CMM. Another combination of drugs used as targeted therapy of CMM is that of Dabrafenib/Trametinib (DAB/TRA) (37).
In case of NSCLC patients with T790 mutations, EGFR inhibitor Osimertinib has been an excellent drug. However, studies have shown some patients are resistant to even Osimertinib after prolonged treatment. Researchers have found that Gefitinib can be used in case of Osimertinib resistance and in fact, these two drugs can be used in combination to treat drug-resistant NSCLC patients (28). An important hallmark of cancer is angiogenesis and simultaneous treatment of NSCLC patients with EGFR-inhibitor and anti-angiogenesis antibody, like Ramucirumab becomes crucial as it identifies the vascular endothelial growth factor and regulates tumor angiogenesis preventing cancer progression (28).

Drug delivery vehicle mediated delivery system

The conventional drug delivery systems (DDSs) like oral administrations and injections had their own advantages of easy administrations. However, oral administration of certain drugs can cause their disruption even before they can enter the bloodstream, owing to the low pH levels of the digestive system. Another disadvantage is the lack of selectivity. Orally administered drugs have a poor biodistribution and they cannot be used to target specific tissue/cells/organs (5).
In order to solve the problems of conventional drug delivery system, new controlled drug delivery systems have emerged. Nanoparticles and polymer-based prodrugs are advanced drug delivery systems that not only solve the issue of target site selectivity but also enhances the circulation of drug in the system, their retention, permeation, increases their concentrations in the target cells, maintains their structure and also aids in inhibition of multidrug resistance (5).

Polymer based prodrugs

Poor drug solubility in aqueous phase and reduced bioavailability are major setbacks of treating with chemodrugs. The successful administration of chemotherapeutic drugs requires high concentration and smaller particle size. Smaller particle size of drugs come with larger surface area increasing the chances of interaction with solvent. Owing to serving this issue, certain techniques like micronization, nanosuspension, sonocrystallization, supercritical fluid processes and wet milling have been acquired (7). A comparatively newer technique of drug delivery is conjugating the anti-tumor drugs with high

molecular weight polymers which function with enhanced permeation and retention (EPR) effect. With this technique, targeting and delivering drugs to specific tumor cells becomes possible reducing the possibilities of drug toxicity and other side effects. Among synthetic polymers, polyethylene glycol (PEG), N-(2-hydroxypropyl)-Methacrylamide (HPMA) copolymer, Poly-(styrene-co-maleic acid/anhydride) (SMA), polyglutamic acid polymer, poly-(Lactic-co-glycolic acid) (PLGA) are frequently in use for anticancer drug delivery. Conjugation with PEG and HPMA both enhances the solubility, bioavailability greatly and prevents immunogenic responses. Administration of poorly soluble yet important anticancer drugs like Paclitaxel conjugated with PEG-b-poly-(l-lysine) and GFLG Cathepsin linked H1-S6A, F8 peptide (c-Myc inhibitory peptide) conjugated with HPMA (R8NLS-HPMAcoPolymer-GFLGH1-S6A, F8A) have proved to be very effective targeted anticancer therapies (23,48). SMA prodrug conjugates administration is another method acquired for the treatment of solid tumors owing to their enhanced solubility and bioavailability. Natural polymers like chitosan, dextran, pullulan, heparin, alginate, albumin, gelatin are frequently used for delivering otherwise insoluble drugs, like methotrexate (MTX-CS-NPs), mitomycin C (MMC), Doxorubicin, folic acid-doxorubicin- coupled derivative (FA-PEG)-Pull-(Cyst-Dox) specifically to tumor cells (8) (7). Yet another prodrug construct called semiconducting polymer nanoprodrug (SPN) is highly efficient towards exhibiting chemotherapeutic effects against hypoxic TME which is a great challenge faced in Photodynamic therapy (PDT) (4). PEG and SMA are used for the construction of these SPNs and it is evidenced that light irradiation during photodynamic therapy has increased the cytotoxicity upto six fold when SMA-ZnPP conjugates are administered (9).

NANOPARTICLE IN TARGETED CANCER THERAPY

Nanoparticle as drug delivery vehicle

The emergence of nanotechnology in healthcare sector, called nanomedicine is a recent phenomenon. There are basically three drug targeting mechanisms, viz., passive drug targeting, active drug targeting and triggered drug targeting. The mechanism of passive drug targeting exploits the pathophysiological and anatomical features of a tumor. The effect of enhanced permeability and retention (EPR) is an example of such method of drug targeting. Active targeting, on the other hand, directly relies on the binding of receptors on tumor cells to specific ligands on the nanoparticles. For instance, with overexpressed receptors on the surface of tumor/cancerous cells forming conjugates with ligands like folate, transferrin or galactosamine that are localized on the nanoparticles, the mechanism of active drug targeting can be achieved (8) (45). Triggered drug targeting requires an external stimulus to release the encapsulated drug at the specific site by the nanoparticle. The external stimulus can be light, hyperthermia, presence of an electric or a magnetic field or ultrasound (8). Different types of nanovehicles have been developed for the purpose of targeted anticancer therapy, viz., polymeric NP, co-polymer-based micellar NP, micro- or nanoemulsion based nanovehicle, quantum dot-conjugated co-polymeric NP, liposome, bacterially-derived targeted minicell, metallic or magnetic NPs based on cross-linked polymers, and mesoparous silica NPs (41) (36).

Advantages

Evading the reticuloendothelial system (RES), enhancing drug permeability and retention and targeting cancerous cells specifically are the primary objectives attained through utilizing nanoparticles (NPs) as drug delivery vehicle. The appropriate drug delivery system requires taking certain factors like pH, molecular weight, particle size, surface charge and ionic strength into consideration (14). It utilizes nanoparticles as a vehicle for drug delivery to specific tumor cells thus reducing unnecessary accumulation of chemotherapeutic drugs in healthy cells and consequent multidrug resistance. The particle size are typically of the order 10 and 100 nm aiming at better intracellular uptake, high loading capacity, and targeting specific cancerous cells. One of the objectives achieved through drug delivery by nanoparticles is prolonging the circulation of anticancer drugs in the bloodstream thus, enhancing the intratumoral drug concentrations. Nanovehicles deliver the sensitive and insoluble drugs to their target site in a controlled manner and also prevent their degradation (8).

The mechanisms by which cancer cells develop multiple drug resistance are overexpressed drug efflux transporters, defective apoptotic pathways, defective DNA damage repair (DDR) pathways, and hypoxic TME. Evading immune clearance by the nanoparticles is an intelligent way out to sustain and exhibit their therapeutic effects. For example, PEG coated nanoparticles being hydrophilic in nature reduce the possibilities of immune clearance by opsonisation and thus their systemic circulation is prolonged. Administration of anticancer drugs like Paclitaxel and Doxorubicin encapsulated within liposomes in cases of breast and prostate cancers have been very effective as they showed reduced cardiotoxicity, higher efficacy and better bioavailability (45) (49).

Gold nanoparticle as DD vehicle

Gold nanoparticles (AuNPs) are widely used and are thought to be a promising drug delivery vehicle owing to their inert and non-toxic nature. Surface-functionalized AuNPs have been found to enhance intratumoral drug accumulation to the target sites, and reduce multidrug resistance significantly. These highly efficient inorganic NPs offer multimodal anticancer therapies like photothermal therapy (PTT), immunotherapy and gene therapy (45).

Chemodrug resistant K562 human erythroleukemia cells when treated with AuNP encapsulated Daunorubicin (DNR) co-polymerized with polybutyl-cyanoacrylate (water-in-oil emulsified), significantly enhanced the DNR accumulation in the cancer cells (as depicted in figure 1) (36).

Iron oxide nanoparticle as DD vehicle

Fe_3O_4 NPs also called Magnetic NPs (MNPs) have proved to be highly efficient as drug delivery vehicle used in chemotherapy and gene therapy. The targeted drug delivery mechanism by MNPs and AuNP is schematically depicted in Figure 1. MNPs are often co-polymerized with organic polymers and fatty acids, to increase their stability and bioavailability. Thermal ablation of tumors called Magnetic hyperthermia is an alternative means of cancer therapy achieved through use of Fe_3O_4 NPs (35,45). Doxorubicin (Dox) and tetrandine (Tet) encapsulated Fe_3O_4 MNPs have been reported to reverse the multidrug resistance in leukemic cells, K562 (as depicted in figure 1). It is observed that the incorporation of Tet aided in down-regulation of *MDR1* gene and P-gp protein levels. It is also evidenced that Tet not only decreased the *MDR1* mRNA expression but also inhibited P-gp efflux activity and enhanced the accumulation of Dox to 5 folds, in the cancerous cells (36).

A brominated-derivative of Tet, Bromotetrandrine (BrTet) is found to have shown synergistic effect with Fe_3O_4 MNPs against DNR treated K562/AO2 cells. Simultaneous application of BrTet and Fe_3O_4 MNPs aided in inhibition of Bcl2 and increased the expression of Bax and caspase3 protein resulting in apoptosis of the K562/AO2 leukemic cells (2). According to a study, combination of BrTet, Fe_3O_4 MNPs and DNR has a tremendous tumor-suppressing activity in mouse model (3). A comprehensive list of nanoparticles in use as drug delivery vehicle is listed in Table 1.

Metallic Nanoparticles and their mode of drug delivery to the human erythroleukemic cells, K562/ AO2

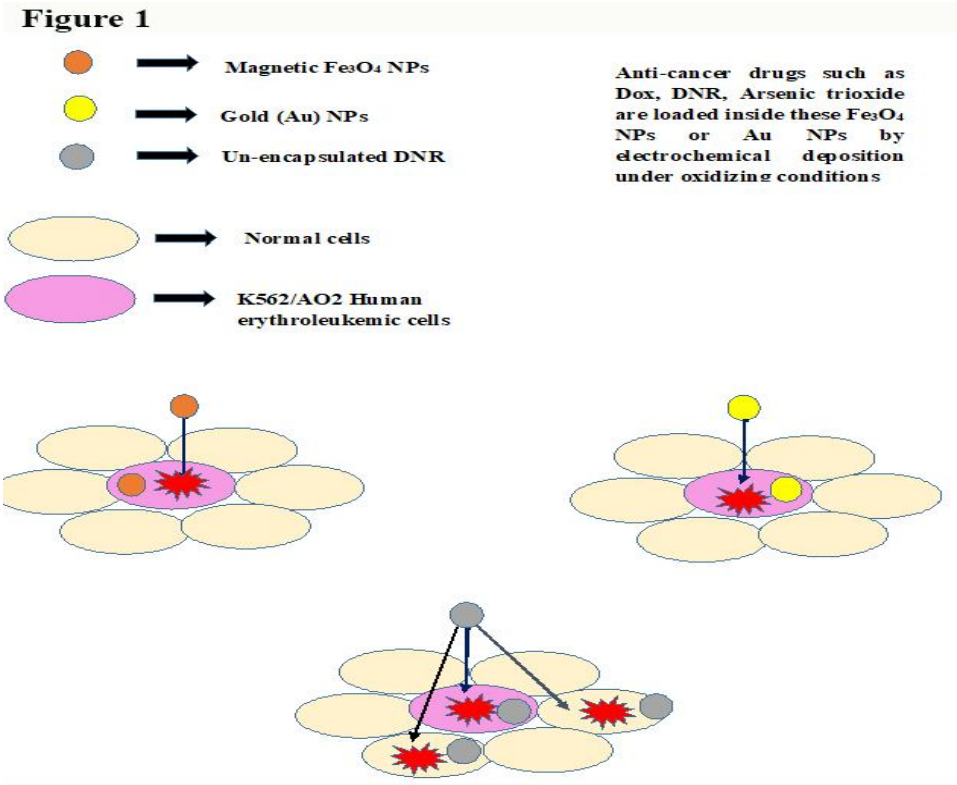

Figure 1: The Fe_3O_4 NPs encapsulated and Gold NPs encapsulated DNR molecules specifically target the tumorigenic K562/AO2 cells whereas the un-encapsulated DNR molecule target both normal and tumorigenic cells

Metallic Nanoparticles	Chemotherapeutic Drug	Target Site/ Effective Against	Citation
Au-NPs/PEG	5-Fluorouracil	M139 and M213 cells	[46]
Au-NPs/Chitosan	5-Fuorouracil	HepG2	[47]
Au-NPs/Polyamic acid	5-Fluorouracil	HeLa cells	[48]
Quercetin and Dextran sulphate encapsulated Au-NPs	Folic acid	NIH 3T3 FB and MCF-7 breast cancer cell line	[49]
Au-NPs surface functionalized with Folic acid	Folic acid	Cervical cancer cells	[50]
Au-Photoactive polymer NPs	Folic acid	C6 glioma brain cancer cells	[51]
Au-NPs Pectin	Doxorubicin	Breast cancer cells	[52]
Colloidal Au-NPs	Doxorubicin	HepG2	[53]
Cisplatin and Dox-conjugated bromelain-encapsulated Au-NPs	Doxorubicin	MG-63 and Saos-2	[54]
Au-Paclitaxel nanoconjugate	Paclitaxel	H460 and H460PTX	[55]
Liposomes and Au-NPs hybrid bomb structure	Paclitaxel	HepG2	[56]
Biocompatible Au-NPs/ Chitosan oligosaccharide	Paclitaxel	MDA-MB-231 TNBC cells	[57]
Chitosan-co-PEG/poly(glycerol sebacate)-co-PEG-coated Fe_3O_4 MNPs	5-Fluorouracil	HT29 cell lline	[58]
Polyglycerol coated Fe_3O_4 MNPs	Folic acid	Human cervical carcinoma cell line	[59]
Chitosan functionalized Fe_3O_4 MNPs	Doxorubicin	Ovarian cancer cell line SK-OV-3 and breast cancer cell line MCF-7	[60]
PEG carboxyl–poly(ε-caprolactone)-modified Fe_3O_4 MNPs	Paclitaxel	Mouse H22 hepatocarcinoma cells, human embryonic kidney cells (HEK293T), HepG2	[61]

Table1: Examples of common Metallic and polymer based nanoparticle, their encapsulated chemotherapeutic drugs and the target sites

Antibody conjugated Nanoparticle as DD vehicle

Rituximab is the first, FDA approved antibody used as a means of therapeutics developed in the year 1977. The technique of encapsulating chemotherapeutic drugs into NPs and surface functionalization with monoclonal antibodies (MAb) is attracting attention in recent times. This helps maintaining drug efficacy at specific target sites, increases the drug loading capacity and also protects the drugs from degradation. Appropriately designed antibody conjugated NPs should overcome the pathophysiological and anatomic barriers in reaching the target cells, and bind to the cells through specific antibody-antigen interactions and internalized to perform its intended function (24) (25). The main advantages of drug delivery through antibody conjugated NP vehicle are controlled and slow drug delivery, maintenance of chemical integrity and structure of the drug, decreased risk of forming secondary metabolites, and diminished toxicity [13, 15].

One of the widely used antibody conjugated NPs is Trastuzumab-NP conjugate that interacts with HER2 surface receptor in breast cancer patients. The antibodies can be conjugated to NPs following several methods of covalent bonding like, carbodiimide chemistry, maleimide chemistry, click chemistry, or non-

covalent methods like adsorption, binding by adapter molecules. Biotin-conjugated PEG-PCL NPs loaded with Dox and Quercetin are often used in the treatment of Dox-resistant breast cancer cases (15,24). Antibody conjugated NPs are mainly employed for the differentiation of malignant tumor cells and normal cells. We have already discussed about AuNPs and their advantages. Raoof *et al*. have constructed an antibody bioconjugated AuNP using the glycosylated Fc region of an antibody specific to EGFR and have found it to be effective against targeting liver cancer cells (36). The hepatic cancerous cells have internalized the antibody-conjugated AuNPs by receptor mediated endocytosis and the NPs got accumulated within the endolysosomes. The non-aggregated AuNPs on exposure to an external non-invasive Radiofrequency (RF) field, dissipated the absorbed heat energy and this in turn, killed the targeted tumor cells by thermal damage (36).

FUTURE PROSPECTS AND CONCLUSION

Currently two challenges need to be addressed. First, recognizing the best polymeric structure so that the EPR effect could be achieved, structural integrity of the drug is maintained and high therapeutic efficacy is attained. Second, the selection of antibody and its mode of conjugation to the NP that will direct it to the desirable site (26) (15).The emergence of new drug delivery system and targeted therapies are the need of the hour. As we have mentioned above, several nanovehicles have been developed and researchers are working towards developing even safer and efficient drug delivery vehicles to treat cancer. However, all these experiments have been successful in small animal models and translation of these therapeutic strategies into preclinical and clinical trials is a big challenge. Even the advantages and disadvantages of using these drug delivery vehicles are yet to be elucidated (35).

Improving the therapeutic index of a drug is vital. Despite having so many chemotherapeutic agents, several strategies to deliver them at the desirable target site, and having a number of antibody-conjugated polymer-linked NPs, every other day we are facing new challenges and limitations. The incurred cost in developing MAb and conjugating it with NPs is yet another challenge. The selection of the material of NP should be made carefully owing to the safety of the patient (24).

In case of classic radiation therapy, mostly x-rays are used which can get dissipated on the way to reach the target site and damage normal cells. Instead, using proton beams or beams of heavier ions like, carbon and neon can be more effective. Heavier ions or proton therapy targets small and large tumors specifically and destroys them selectively and most importantly requires less number of doses (35).

Among all the targeted drug therapeutic strategies, antibody-conjugated NPs has gained special attention owing to their advantages. However, heterogeneous molecular composition of the TME is a major challenge faced by pharmacologists and researchers. A concept of “personalized medicine” is coming up which means a specific patient is to be treated with a specific drug for a specific time. Therefore, discovery of a potent anticancer drug requires next generation genome sequencing, studying the molecular pathology and systems biology (30).

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