Chapter

Integrating Nanotherapeutic Platforms to Image Guided Approaches for Management of Cancer

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Abstract

Cancer is a leading cause of mortality worldwide, accounting for 8.8 million deaths in 2015. The landscape of cancer therapeutics is rapidly advancing with development of new and sophisticated approaches to diagnostic testing. Treatment plan for early diagnosed patients include radiation therapy, tumor ablation, surgery, immunotherapy and chemotherapy. However the treatment can only be initiated when the cancer has been diagnosed thoroughly. Theranostics is a term that combines diagnostics with therapeutics. It embraces multiple techniques to arrive at comprehensive diagnosis, molecular images and an individualized treatment regimen. Recently, there is an effort to tangle the emerging approach with nanotechnologies, in an attempt to develop theranostic nanoplatforms and methodologies. Theranostic approach to management of cancer offers numerous advantages. They are designed to monitor cancer treatment in real time. A wide variety of theranostic nanoplatforms that are based on diverse nanostructures like magnetic nanoparticles, carbon nanotubes, gold nanomaterials, polymeric nanoparticles and silica nanoparticles showed great potential as cancer theranostics. Nano therapeutic platforms have been successful in integrating image guidance with targeted approach to treat cancer.

Keywords: nanomedicine, theranostics, targeted delivery, cancer, functionalized nanomedicine

1. Introduction

Cancer has a major impact on society across the world. Estimated number of new cases of cancer, current cases of cancer, deaths, survival rate, mortality and in depth information, symptoms of cancer, its early detection, prevention and treatment all are provided by American Cancer Society. Nearly 13% of cancer diagnosed in 2017 was in the young at age of 20. The new review statistics shows 28 types of rare cancer which talks about mortality rate, survival, diagnosis and also provides an idea about symptoms and risk factors related to different types of cancer [1].

Therapeutic approaches such as development of nanoemulsions, liposomes, microspheres and nanoparticles have facilitated in fighting cancer. Among these,

the simplest platforms are the nanoemulsion having size range of 100 to 500 nm which are kinetically stabilized having high content of oil and low amount of surfactant [2]. Solubility of poorly soluble drugs [3, 4] and its bioavailability can be increased by converting the drug into forms like capsule and gels [5] or can be used in their original form. The method used for the fabrication of nanoemulsion are high energy methods (microfluidization and sonication) and low energy emulsification method [6–8].

Theranostics is a term originally coined to define an approach that combine's diagnostics with therapeutics [9]. It embraces multiple techniques to arrive at comprehensive diagnosis, molecular images and an individualized treatment regimen [10, 11]. Recently, there is an effort to tangle the emerging approach with nanotechnologies, in an attempt to develop theranostic nanoplatforms and methodologies [12]. Given that cancer is a highly heterogeneous and adaptable disease, diverse types of treatment options need to be chosen depending on patient's characteristics and disease progression.

2. Theranostics

Drugs or methods that are used for accompanying diagnosis and cure [13] are referred to as Theranostics. One of the achievements of nanotechnology is the fabrication of theranostic nanomedicine for the preparation of these types of drugs. The term defines "a nanotherapeutic system which can deliver targeted therapy and diagnose". This aspect provides help when fabricating nano based image contrasting agent and also in image guided therapeutics [14].

Rapid drug development, advanced disease management, reduced associated risk and cost are assumed to be the result of mutual techniques. Such type of investigation which involves quick diagnosis and treatment are very helpful in disease which are a major cause of morbidity and/or mortality and cancer is one of the disease and coincidently the initial research in theranostic is dedicated to oncology. Sound knowledge, core understanding of detection and therapy mechanism are required for the formation of theranostic agents. In order to fabricate theranostic agents one should have understanding of diagnostic strategies, molecular mechanism adverse effect and toxicity of material and techniques for nanoparticles preparation for therapy and diagnostic purpose.

Research in theranostics has rapidly improved in the past decade resulting into preparation of different contrast media and active ingredient with different method of preparation. Preparation of dual purpose nanoparticle system is the main aim of theranostics. Therefore it is important to put attention on all factors that influences the process, right from the preparation of nanoemulsion/nanoparticle till the removal of metabolites of the active molecules and other materials used. The factors can be the compatibility between chemicals, the condition in which the formulation is prepared, modification in formulations because of selected route of administration, the toxicity, metabolites of active ingredient, its biocompatibility and biodegradability and evaluation of pharmacodynamic and pharmacokinetic parameter and eventually the disadvantage and benefits of the process.

The basis of diagnosis in theranostics depends upon using different contrast agent during imaging. MRI is the most studied and used technique among all different imaging mechanism and a lot has been spent on research related to magnetic particles used as contrasting agent. Metals like gold, silver, iron oxide have been studied with the object of finding suitable particle for imaging with least toxicological effect. Diseased tissue and healthy tissue are differentiated in MRI by the use of these particles.

Contrast agent	Drug used	Applications	Size	Zeta potential	References
Manganese oxide	siRNA	MRI plus RNA delivery	—	—	[15]
Gold	DOX Diagnosis	tumor targeting and PTT	45.97 nm and 6.3 nm	−3.54 mV	[16–18]
Iron oxide	siRNA, DOX, docetaxel	Targeting, MRI and therapy	30 nm	−5 mV	[19–21]
Silica	Pyropheophorbide (HPPH), DOX	Drug carrier, X-ray/CT imaging, Photodynamic therapy	30 nm and 126 nm	−39 mV	[22, 23]
CNTs	DNA plasmid, DOX, PTX	Diagnosis, DNA and drug delivery	20 nm and 120.6 nm	—	[24, 25]
QDs	DOX, MTX	Imaging, therapy and sensing	—	—	[26]

Abbreviations: siRNA: short interfering ribonucleic acid, CNTs: carbon nanotubes, QDs: quantum dots, DOX: Doxorubicin, HPPH: 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-alpha, MTX: Methotrexate, PTX: Paclitaxel, MRI: Magnetic resonance imaging, CT: Computed topography.

Table 1.
Different theranostic agents used for biomedical applications.

As stated one of the brutal disease is cancer and hence theranostic research has put an eye on this area. Day by day the research is going on in positive direction and much useful research has already been carried out. In order to understand the concept of diagnosis of cancer and therapy related to it the use of nanoparticle agents is in progression [27, 28]. One such example of theranostic agent is manganese oxide nanoparticle carrying drugs and contrast agents [29] and silica nanoparticle with magnetic and fluorescent tags [30]. In the past few years, combination of metal nanoparticle or shells [31–33] with magnetic components has yielded different theranostic agents for biomedical applications which are widely used. Some examples of theranostic agents are given in **Table 1**.

3. Nano theranostics

Theranostic nanosystems comprise of platforms/nanocarriers that are used as imaging as well as therapeutic agents via a single entity. Nanotheranostic devices can be made by many types of inorganic and organic nanomaterials. Preclinical implementations make use of nanotheranostic system because they might provide a way or method of understanding many crucial aspects of drug delivery and how these systems can assist in knowing the power of personalized medicines.

4. Therapeutic agents

At present radiotherapy, surgery and chemotherapy are possible treatments for cancer patients. The purpose of the theranostic is to use these therapeutic strategies and reduce the risk associated with chemotherapy and radiotherapy and in addition to it avoid complications related to surgery and trauma. In addition, with the help

of nanotechnology, theranostics may support the diversification of therapeutic approaches like PTT, PDT and immunotherapy. Here we report some of these therapeutic strategies often used in theranostics, like radiotherapy, chemotherapy, PDT, PTT and immunotherapy.

5. Chemotherapy for management of cancer

Anticancer drugs have proven beneficial in improving survival rate of cancer patients [34]. There are huge numbers of clinical anti-cancer drugs which are broadly applied to theranostics. On the basis of structure and resource of chemotherapy drugs, cancer therapeutic agents can be classified into six types: alkylating agent, antitumor antibiotic, phytogenic anticarcinogen, antimetabolites, hormone and miscellaneous anti-cancer drugs. Thermo DOX for liver cancer, Doxil for ovarian cancer therapy and Myocet for metastatic breast cancer are few cancer nanomedicines that have been approved by the FDA. Theranostic systems also make use of prodrugs like platinum (IV) prodrug to reduce the toxicity of drug and by increasing the active hits to the cells of tumors site. Due to their broad availability these prodrugs are very popular option. The UV light is transformed from NIR light by UCNP which activates the prodrugs to highly toxic platinum (II) complexes that enters the cell by endocytosis after grafted onto up converting nanoparticles (UCNP) [35]. In order to attain best therapeutic efficacy of drug delivery systems a high payload is essential. In theranostics, in order to maintain the original size and solubility in aqueous media a carrier with large pore volume and surface area are given preferences so that more therapeutic agent can be carried [36]. For example, Sorafenib with a loading ration of 28.2% can be loaded on porous silica nanoparticles and may release the therapeutic agent in sustained fashion [37]. GO, Ws2 and MoS2 are some of the popular 2-D nanomaterials that have a very high drug payload as they can bear chemotherapeutics on both sides of sheet. Some of the example of high drug payload include 118% for 7-ethyl-10-hydroxycamptothecin (SN38) and approx 239% for DOX were observed on MoS2 [38], DOX (approximately 400%) on GO [39] was also significant. Cancer cells show multidrug resistance (MDR) often when they are treated by single drug which can be overcome by employing efficient strategies of theranostics. By combining P-glycoprotein (P-gp) reversing agent with anticancer drug the hurdle of MDR can be resolved [40]. The function of P-gp reversing agent is to avoid the pumping of chemotherapeutic drugs out of cancer cells due to over expression of P-gp. One way to overcome MDR is by covering the positive change that is present on anticancer drugs. DOX alone cannot produce significant cancer effect but when it is adsorbed on the surface of polymeric nanoparticle more chance are there that cancer cell may readily uptake it and accumulate within cancer cell and produce more cytotoxicity to cancer cell. Nanocarriers loaded with combination of anticancer drugs provide synergistic effect thereby improving overall management of cancer [41, 42].

6. Photothermal therapy for management of cancer

Microwave, light irradiation or magnetic field can potentiate the effect of thermal therapy which in turn employs hyperthermia to kill cancer cells. Among all the above mentioned therapies photothermal therapy has the maximum capacity to destroy cancer cell while causing least damage to nearby healthy cells. Localized hyperthermia under light irradiation at tumor site is generated by using NIR absorbing agent in photothermal therapy [43]. In MR region an ideal PTT agent

should show strong absorbance and must exhibit less fluorescence quantum yield thereby promoting efficient conversion of absorbed light energy into heat via non-radiative transition rather than fluorescence emission.

Inorganic nanoparticles and organic dyes are extensively employed as PTT agents. Examples of organic dyes include Prussian blue, IR780, ICG, IR820, Cypate, IR825. These organic dyes have an added advantage of ease of loading on nanoplatforms and ideal NIR absorbance [44]. In order to improve the photostability and targeting ability of organic dyes they are being encapsulated into nanocarriers [45]. Carbocyanine dyes namely cypate and ICG were loaded into the polymeric micelle with loading rate of 50% and 20% for cypate and ICG respectively. Upon comparing loaded theranostic polymeric micelle with carbocyanine dye alone showed marked cellular uptake and longer retention time at the site of tumor. Remarkable PTT results were observed along with increased photothermal effect and photostability of organic dyes when nanomaterials like graphene derivatives absorbing strongly in the NIR regions were employed [46]. In NIR and PTT imaging techniques both cypate and ICG can be used as theranostic agents.

Photothermal conversion efficiency will decrease in presence of high fluorescence quantum yield and fluorescence imaging is disturbed in case of low quantum yield hence there is not much surety in theranostic application of organic dyes. Apart from the organic dyes, a wide range of inorganic nanoparticles have been fabricated for theranostic applications. Inorganic nanoparticles exhibit strong photothermal conversion efficiency and NIR absorption for PTT. It encompasses customized gold nanostructure like nanoshell, nanocages, nanorods and nanotubes. On comparing the gold nanorods alone against gold nanorods coated with Pt nanodots, the latter showed significant better photothermal effect than the former [47]. And the better results were due to the presence of Pt shell in the endosomes which not only prevented the original sharp LSPR band of gold nanorods from shifting and dampening but also prevented the aggregation of gold nanorods. Carbon nanotubes [48], carbon dots [49], GO are some of the other nanomaterials that can used for PTT. GO for in-vivo PTT was used for the first time by Liu group. Further they reduced the GO to rGO which had 7 times more NIR absorption than GO hence increasing the PTT effect [50]. PTT for now might only be used for treating skin cancer and not for internal cancer because of limiting light penetration depth but its noteworthy therapeutics capacities with minimum possible side effect cannot be ignored. Further study is required to get deeper insight about how phototoxicity is caused by PTT.

Apart from PTT, hyperthermia induced magnetically is also one of the non-invasive procedures to treat cancer [51]. Dielectric constant and microwave frequency between malignant tissue and normal tissue in breast can be employed for the detection and treatment of breast cancer. Dielectric contrast is used for scattering of an illuminating microwave signal and the incident microwave produces hyperthermia thereby treating malignant tissues [52].

7. Photodynamic therapy for management of cancer

Photosensitizers (PSs) used in PDT plays a vital role in the treatment of cancer and possess enormous potential. Cytotoxic reactive oxygen species or free radicals are generated when the molecular oxygen surrounding the diseased cell reacts with the absorbed light that is being transferred by PSs under laser irradiation which finally causes cell apoptosis and damage to cancerous cells [53]. No side effects are observed from photosensitizes and generate ROS only when laser light is irradiated upon them.

PDT requires low light density to cause damage to cancer cell unlike the PTT which requires high density laser light to generate hyperthermia that can cause damage to cancer cells [54]. PDT encompasses noteworthy advantages like very less invasiveness, on repeating the therapy is show no cumulative toxicity, very less damage to immune and hemopoietic system thereby improving the overall health and contributing to quality life for the patient. An ideal PS must have following properties like triplet state formation of high quantum yield and a good amount of triplet lifetime so that interaction with ground state oxygen is possible thereby generating sufficient ROS. However many PSs does not have good tumor selectivity, good amount of photosensitivity and absorption maxima above 700 nm [55]. A distinctive NIR absorption at 700 nm was observed by the help of extra axial mob linkers in monosubstituted phthalocyanine [56] that produced 20 nm red shift of characteristic Q band. PEG functionalized iron oxide nanocluster surface when loaded with Ce6 the absorption peak of chlorine e6 (Ce6) showed red shift from 650 nm to 704 nm [57]. The energy transferred from UCNPs to PSs are able to excite the combination of PSs and UCNP's, therefore inhibiting the growth of tumor by generation of cytotoxic singlet oxygen [58].

8. Radiation therapy for management of cancer

Radiation therapy has become an integral part to treat many sarcomas. The mechanism of action of radiation therapy is that the radiation damages strings of DNA in the nucleus of cells which stops the cell multiplication. Apart from aforementioned functions of radiation therapy, it also produces reactive oxygen therapy (ROS) which indirectly damages the tumor cell and also damages the DNA of mitochondria and other organelle of cell. In case of surgical resection, the survival could be prolonged by employing radiation therapy. However due to frequent and repeated high dose of X-ray irradiation that causes systemic side effects and resistance to radiation had been noticed in cancerous cells.

Metal nanoparticles in strong association with strong capacities of photoelectric absorbance are used as radiation dose enhancing agents. For example research shows that radio sensitization is being mediated by Gold NP due to greater energy deposition and absorption in surrounding tissue from photoelectrons. Radiotherapy with prolonged circulation time in blood has been demonstrated by Auger electrons and characteristic X-rays [59] and polyethylene glycosylation modified gold nanoparticle (N GNPs). Radiotherapy can relieve the symptoms and prolong the lives of terminal cancer patients. However radiotherapy is not an easy task and may cause loss of organ functions also as it may also induce many complications. Moreover, it cannot completely remove cancer cells. In coming future we may see highly accurate and precise exposure of tumor site to high radiation by the application of radiation wave knife for much better clinical results.

9. Immunotherapy for management of cancer

After radiotherapy, surgery or chemotherapy it has been observed that a small number of cancer cells may still remain alive and in addition to it the overall treatment quality is also decreased due to drug resistance. Immunotherapy has great potential to treat cancer as it acts on the immune system rather than on the tumor itself. Immunotherapy is considered as a unique and promising strategy for cancer therapy [60] and the main advantages include its specific promotion on immune cells only aiming on target cells or target tissues. So far, the related investigations

have been gradually transformed from laboratory research to clinical practice. For clinical treatment the use of immunotherapeutic drugs such as immune checkpoint inhibitors and T cells have been approved by FDA and have great potential for cancer treatment. Improved immunotherapeutic nanomaterials loaded with antigens, immune adjuvants and nucleic acids have been demonstrated to be helpful. The nanoplatforms may affect and alter immune cell actions and response non-specifically. They may easily damage the cancer cells and achieve tumor targeting with pathogens factors. For e.g. repetitive and homogenous antigens conjugated with gold nanoparticles are able to trigger immune response in an in-vitro setting even without the use of adjuvant. Recently a combination of IR phthalocyanine dye IR700 with monoclonal antibodies had been fabricated and this novel technique is known as Photoimmunotherapy [61]. Least side effect and significantly fast cell necrosis rate is observed when antibodies bind to target tumor cells during the PIT and is activated by NIR light irradiation. Hence for monitoring and treating cancer in a highly selective manner PIT is a good theranostic approach.

10. Multimodal therapy for management of cancer

Conventional cancer therapies often do not succeed to eradicate tumor completely. In order to recover anticancer efficacy, the arrangement of two or more therapeutic modalities such as chemo photodynamic, photothermal photodynamic, chemo photo thermal synergistic formulations have been explored. Thermomotherapeutic characteristics in association with theranostic methods result in development of anticancer drug that possess synergistic therapeutic effect [62]. Chemotherapy could be improved by the use of photothermal effect which aids the intracellular translocation of anti-cancer drugs [63]. Risk of overtreatment could be minimized along with the reduction in dose of therapeutic agent with less laser exposure time. All these can be attained by combination of PDT/PTT. Synergistic effect of PTT/PDT have been seen when GO was loaded with methylene blue [64]. In this system, lesser dose of nano GO was applied, as compared to the particular PTT treatment of nano GO. In addition, the PTT and PDT combinational treatment could be spoil both superficial and deep regions of the tumor, and thus overcome the drawbacks of single treatments [65]. To further progress cancer therapy efficacy, numerous types of theranostic platforms were developed to combine chemotherapy, PTT and PDT simultaneously [66]. Treating cancer with combinational therapy has become an essential trend in cancer therapeutics. Compared to single modality therapy, the combined therapy can reduce the dosage of the drugs and thus decrease the side effects in treatment. More prominently, the combined therapy has the potential to decrease multidrug resistance of tumor cells, thus improving the therapeutic efficacy. The combined therapy may bring a novel opportunity to the next invention of cancer treatment [67].

11. Imaging-guided therapy for management of cancer

The theranostic nanoparticles have an ever increasing consideration for image guided therapy in current years because these nanoparticles can follow the pharmacokinetic process, guide the treatment and monitor therapeutic process and outcome. They could be employed to imagine and quantify the performance of drug delivery systems for numerous special purposes such as biodistribution and pharmacokinetics of nanocarriers, metabolic response and drug release process of the nanocarriers. Koukourakis group and Harrington group engaged Technetium

Imaging method	Imaging agent	Therapeutic agent	Function
Optical Imaging	Cy5.5	Paclitaxel	Real time tracking of NP location
	FITC-coumarin pair	Doxorubicin	Drug release monitoring
	Dicyanomethylene-4H-pyran	Camptothecin	Drug release monitoring
	Cy7, 111In	Cyclophosphamide, etoposide	Real time imaging of apoptosis
	Cy5.5-BHQ pair	Doxorubicin	Real time imaging of apoptosis
	Ce6	Ce6	Real time tracking of NP location & PDT
	Ce6-BHQ pair	Ce6	Drug release monitoring & PDT
	UCNP (β-NaYF4:Yb3+,Er3+)	Cisplatin prodrug	Imaging of NP location
	UCNP (NaYF4:Er)	TPGSd	Dual imaging (optical, CT) & reducing multidrug resistance
	UCNP (NaYF4:Yb/Er)	Ce6, doxorubicin	Imaging of particle location & chemotherapy/PDT
MR imaging	Gd	Doxorubicin	Real time monitoring of drug delivery
	SPION	SPION	Detection & hyperthermia treatment of tumor
	SPION	Doxorubicin	Tumor detection & chemotherapy
	SPION/FITC	siRNA	MR imaging & gene therapy
CT imaging	GNP	Doxorubicin	CT imaging of cancer & chemotherapy
	GNR	GNR	Dual imaging (X-ray/CT) & PTT/radio sensitization
PET Imaging	64Cu	Doxorubicin	Quantitative biodistribution analysis & Chemotherapy
	64Cu	siRNA	Quantitative determination of biodistribution & efficacy of siRNA NPs
US imaging	Perfluoropentane	Docetaxel	Triggered drug release & chemotherapy
	CaCO3	Doxorubicin	Tumor imaging & triggered drug release
	Perfluorooctyl bromide	Camptothecin	Chemotherapy & ablation therapy
	Perfluorohexane	CPT11m	Tumor imaging & chemotherapy/ablation Therapy

Table 2.
Theranostic technologies for cancer treatment [68].

and Indium labeled PEGylated liposomes respectively to monitor drug targeting to the sarcomas and breast cancer sites [69]. In the clinical practice, surgical resection is a regular and inevitable procedure for cancer therapy. Theranostics gives a possibility in intraoperative imaging to guide the operation process. During the surgery,

physicians could congregate the diagnostic information for precise imaging as well as visualized therapy. In theranostic platform, DOTA-Gd act as a MRI contrast agent for preoperative finding and surgical planning; the Raman molecules visualized the excellent margin of tumor, allowing precise resection for the duration of operation process. The multimodal NP could recognize tumor edge for precise resection of tumor. This approach could be planned for simple intraoperative navigation and real-time imaging [70]. Theranostic technologies commonly utilized for cancer treatment are given in **Table 2**.

12. Conclusion

Theranostic approach to management of cancer offers numerous advantages. They are designed to monitor cancer treatment in real time. A wide variety of theranostic nanoplatforms that are based on diverse nanostructures like magnetic nanoparticles, carbon nanotubes, gold nanomaterials, polymeric nanoparticles, or silica nanoparticles showed great potential as cancer theranostics. Nano therapeutic platforms have been successful in integrating image guidance with targeted approach to treat cancer.

Conflict of interest

Authors declare no conflict of interest related to this manuscript.

Abbreviations

PTT	Photothermal therapy
PDT	Photodynamic therapy
DOX	Doxorubicin
NIR	Near infrared
MRI	Magnetic resonance imaging
PET	Positron emission tomography
CT	Computed topography
UNCPs	Up converting nanoparticles
GO	Grapheme oxide
MDR	Multidrug resistance
MoS_2	Molybdenum disulfide
ICG	Indocyanine green
WS_2	Tungsten disulfide
Ce6	Chlorine e6

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