Jawahar. N et al /J. Pharm. Sci. & Res. Vol. 10(3), 2018, 487-492

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Nano Drug Delivery and Targeting for the Treatment of Gastric Cancer: A Review

Jawahar. N*, Abhinav Raj Ghosh, S.R.Mahi Priyaa

Department of Pharmaceutics,JSS College of Pharmacy,Jss Academy of Higher Education and Research (Mysuru) Udhagamandalam -643001, Tamilnadu, India.

Abstract:

Gastric cancer, or stomach cancer, is a malignancy (unrestrained growth of abnormal tissue) of the lining of the stomach. Nanoparticles, part of Nano medicine can be either used as an imaging agent or therapeutic agent in different cancer therapeutics which includes gastric cancer as well. The use of nanoparticles in gastric cancer treatment could ease up the side effects of chemotherapy and increase the efficacy of treatment. There are different existing drugs which are used in gastric cancer treatment. One of the leading players to treat gastric cancer is 5-Fluorouracil, which has played a pivotal role to treat gastric cancer over the last few years. There are other anticancer agents like taxanes, platinum derivatives, and antimetabolites and so on that has also been used to treat gastric cancer. Though these agents have several cytotoxic effects on human but they are still in use. The aim of this study is to review various literatures and learn in detail about the various advances in Nano targeted drug delivery systems for the treatment of gastric cancer.

Key Words: Gastric cancer, Cytotoxic, Nanoparticles, Targeting, Drug delivery, Enhanced therapy.

INTRODUCTION:-

Nanoscale devices are 100 to 10,000 times smaller than human cells but are similar in size to large biomolecules such as enzymes and receptors. Nanoscale devices smaller than 50 nm can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they circulate through the body. Nanodevices are suitable to serve as customized, targeted drug delivery vehicles to carry large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. Nanodevices can be constructed by the moulding or etching, top-down approach, or by assembling structures atom by atom or molecule by molecule, bottom-up approach. [1,2]

We are now closer to being able to fully characterize the differences between the normal and the tumor cell. Coupled with the use of micro dissection techniques, it is also possible to interrogate the genetic make-up of individual cell types. The hope is that use of such technologies will accelerate the progress in identifying the differences between normal and tumor cells, which in turn will lead to development of new therapies that will specifically target the cancer. The ultimate goal of these strategies is to eliminate the tumor with limited effect on normal tissue. [3]

Nanotechnology and Targeted Drug Delivery

The greatest immediate impact of nanotechnologies in cancer therapy is in drug delivery. The therapeutic index of nearly all drugs currently being used can be improved if they are more efficiently delivered to their biological targets through appropriate application of nanotechnologies. [4] [5] Some drugs that have previously failed clinical trials might also be re-examined using Nano technological approaches. A number of obstacles may be overcome with various novel applications of Nano drug delivery. For example, many drugs are not very soluble, making it difficult to administer therapeutic doses. [6] [7] These compounds can be "solubilized" by formulating them into crystalline Nano suspensions that are stabilized by surfactants, [7] or by combining them with organic or lipid nanoparticles that keep them in circulation for longer periods. [8] [9] [10] If an efficacious compound has a short half-life in the circulation, its stability can be increased tremendously by encasing it within nanosized liposomes as a drug carrier. In the case of central nervous system cancers, many drugs have difficulty in crossing the blood– brain barrier to attack the tumor. Drug-loaded nanoparticles are able to penetrate this barrier, and have been shown to greatly increase therapeutic concentrations of anticancer drugs in brain tumor. [11] [12]

The best way to increase the efficacy and reduce the toxicity of a cancer drug is to direct the drug to its target and maintain its concentration at the site for a sufficient time for therapeutic action to take effect. [13] For example, lipid cationic nanoparticles coupled to an integrin-targeting ligand were shown to deliver genes selectively to angiogenic blood vessels in tumor-bearing mice. As the therapeutic part of the nanocomplex, a mutant RAF gene was coupled to the particle for transfection and expression in the tumor cells; expression of this mutant gene was shown to block angiogenesis in this model. The directed nanoparticle caused apoptosis in the tumors and a sustained regression of established primary and metastatic tumors. [14] The efficiency of drug delivery to various parts of the body is directly affected by particle size. Nanostructure-mediated drug delivery, a key technology for the realization of nanomedicine, has the potential to enhance drug bioavailability, improve the timed release of drug molecules, and enable precision drug targeting. [15] [16] Nanoscale drug delivery systems can be implemented within pulmonary therapies, [17] as gene delivery vectors [18] and in stabilization of drug molecules that would otherwise degrade too rapidly. [19] [20] Additional benefits of using targeted Nano scale drug carriers are reduced drug toxicity and more efficient drug distribution. [21]

Advantages of Nano-Particles for the Treatment of Gastric Cancer: [22]

1. Entry into tissues at the molecular level
2. Increased drug localisation and cellular uptake
3. Cancer diagnosis and treatment applications
4. Feasibility to programme nanoparticles for recognising cancerous cells
5. Selective and accurate drug delivery, and avoiding interaction with healthy cells
6. Direct and selective targeting of the drug to cancerous cells (both active and passive targeting)
7. Larger surface area with modifiable optical, electronic, magnetic and biologic properties vis-à vis macroparticles
8. Assisting therapeutic agents to pass through biologic barriers, mediate molecular interactions and identify molecular changes

Inhibition Of The P38 Mapk Pathway For Gastric Cells

Tan W *et al*. on December 2014, worked on the Inhibition of the p38 MAPK pathway sensitizes human gastric cells to doxorubicin treatment *in vitro* and *in vivo*. Doxorubicin-based chemotherapeutic regimes have been the mainstay of systemic treatment for disseminated gastric cancer for numerous years. However, the efficacy of doxorubicin is severely limited due to chemoresistance. Chemoresistance is a tightly regulated process, under the control of numerous signal transduction pathways. Amongst these, the mitogen-activated protein kinase (MAPK) pathway has received much attention. This study assessed whether the p38 MAPK pathway is involved in doxorubicin resistance in gastric cancer cells. Doxorubicin alone or combined with the p38 MAPK pathway inhibitor SB203580 was used to treat gastric cancer cells (SGC7901 and BGC823 lines). The effect of doxorubicin on the growth and apoptosis of gastric cancer cells in the presence or absence of SB203580 was investigated by western blot analysis, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, Hoechst staining, Annexin V-FITC/propidium iodide staining followed by flow cytometry analysis, and the terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay. Next, the effects of doxorubicin and SB203580, on the sensitivity of BGC-823 cells were assessed in a tumor xenograft model. The results showed that the p38 MAPK inhibitor significantly increases gastric cancer cell sensitivity to doxorubicin. Doxorubicin in combination with SB203580 significantly reduced cell viability ($P<0.01$) and increased cell death ($P<0.01$), which may be associated with the inactivation of the p38 MAPK signaling pathway, followed by the induced expression of the pro-apoptotic protein Bax and a concomitant decrease in Bcl-2 expression. These findings suggest that p38 MAPK is involved in gastric cancer cell survival, and that the inhibition of p38 MAPK signaling can reduce the tolerance of gastric cancer cells to doxorubicin treatment. [23]

NOVEL TREATMENTS FOR THE TREATMENT OF GASTRIC CANCER BY NANO PARTICLES

Nanoparticles are the new hope the treatment of gastric cancer due to their advantages of target specificity and the cellular internalization. A ton of the work is been done till now to prove the statement.

Nanoparticles combined with low-dose irradiation

L. Zhang H. *et al*. on September 2017 researched on 50p camouflaging IRGD-EGFR anchored human cytotoxic t-lymphocyte membranes to the surface of nanoparticles combined with low-dose irradiation: new approach to enhance drug-delivery targeting in gastric cancer. Biomimetic delivery platform based on human cytotoxic T-lymphocyte membranes where the T-lymphocyte membranes were camouflaged to the surface of poly-lactic-co-glycolic acid nanoparticles, with local low-dose irradiation (LDI) as a chemoattractant. These carriers were further anchored with the recombinant protein anti-EGFR-iRGD, improving tumor accumulation, facilitating tumor uptake.The T-lymphocyte membrane coating was verified by dynamic light scattering, transmission electron microscopy and confocal laser scanning microscopy. The particle phagocytosis study was performed using a human phagocytic cell line. In vivo NIR fluorescence imaging was performed to monitor the route of nanoparticles. EGFR expression of tumor cells was tested before and after LDI. This new platform reduced phagocytosis of macrophages by 23.99% ($p = 0.002$). iRGD-EGFR anchored T-lymphocyte membrane-encapsulated nanoparticles accumulated in tumor site more than unfunctionalized groups, while LDI significantly enhanced the targeting ability. LDI could up-regulate EGFR expression on tumor cells, which was important in the process of localization of iRGD-EGFR anchored T-lymphocyte membrane-encapsulated nanoparticles in tumors. This new platform included both the long circulation time and tumor sites accumulation ability while LDI could significantly enhance the tumor accumulation ability. [24]

Biomaterials for multistage drug & cell delivery

In this process, molecularly-designed, cell-instructive biomaterials as 3D artificial matrices for the delivery of drugs, biomolecules, genes and cells with implications in tissue regeneration and cancer diagnosis and treatment was designed. Involved directing and mechanistically following cell behaviour in engineered 3D microenvironments toward the development of cell-instructive injectable biomaterials for tissue regeneration. Hydrogels were functionalized with cell-interactive peptides in order to reproduce some essential features of the extracellular matrix, namely cell adhesion, proteolytic degradation and guided cell differentiation. They are being investigated as models to study cell behaviour in 3D conditions in regenerative therapies (bone, vascular and skin) and degenerative conditions (cancer). Integrative approaches, combining molecularly-designed 3D matrices with advanced high-throughput screening (HTS) tools to design artificial 3D cell culture platforms to answer questions of fundamental biological and of clinical importance, as well as advanced *in vitro* cell models of human mucosa (gastric and intestinal) as tools to study the transport of biopharmaceuticals and nanoparticles were developed. Biofunctionalized nanoparticulate systems are also being investigated with application in the pharmaceutical and biomedical fields, to provide the controlled and targeted delivery of bioactive molecules in therapies for infectious diseases (e.g. HIV) and cancer, as well as diagnosis (e.g. cancer).[25]

Milk protein nano-capsule technology for the treatment of gastric cancer

A new nanotech-based treatment method being developed by an Israeli university team may help overcome a deadly enemy in cancer therapy – the development of drug resistance. Worse, multi-drug resistance. "Many patients who apparently respond to first-line chemotherapy frequently face tumor progression or recurrence, necessitating additional chemotherapeutic cycles," explains the Technion University team in their paper, "β-casein nanovehicles for oral delivery of chemotherapeutic drug combinations overcome Gastrointestinal cancers are a huge killer, says the Technion team of Maya Bar-Zeev, Prof. Yehuda Assaraf and Prof. Yoav Livney. As they report in the journal Oncotarget, the new treatment modality is based on delivering a chemo resistance reversal agent, which eliminates the tumour's resistance to chemotherapeutic drugs, with anti-cancer drugs – all encased in nano-sized casein micelles. [26] Casein is the main milk protein, and micelles are naturally self-organized spheres. In nature, casein micelles are found in breast milk, delivering calcium, phosphorus and protein from the mother to the baby. The form of casein that Bar-Zeev used in her doctoral work, under Livney and Assaraf, as the drug delivery platform has the ability to encapsulate substances that are not water-soluble (such as many drugs), and is efficiently digested in the stomach. The casein-based Nano capsules could then be added into a drinkable water-based preparation, which could be in the form of a tasty milk beverage. [26] The micelles have been shown capable of carrying the chemotherapy cocktail to the stomach, and release them there. The team therefore surmises that the concept will be particularly effective in treating gastric diseases of different kinds, and specifically gastric and stomach cancers in particular. The team also postulates that efficiently delivering the chemotherapy drugs together with the anti-resistance compounds in these micelles will not only improve the treatment of stomach cancer, but help prevent the development of multi-drug resistance in cancer cells,

or to overcome it if already developed. It bears noting that the notion is at a very early stage. [26]

Passive and active targeting Nano particulate drug transported to the tumor cells

Syed Abdul Kuddus, 17 March 2017 had worked on "Nanotechnology to treat with gastric cancer" Nanotechnology helps to target the tumor identically either in an active or passive way. Nanoparticles loaded with anticancer drugs then attack the specifically targeted cancer cell and get rid of them without altering or hampering the surrounded non-cancerous tissues. In case of passive targeting Nano particulate drug transported to the tumor cells using either passive diffusion or the convection process. Then the drug works with the help of enhanced permeability retention, also known as the EPR effect. This effect is applicable towards most of the tumor. On the other hand, surface attached ligand on the nanocarrier helps to bind with the over expressed receptor of the tumor cells which is rather different than the healthy cells. This ligand specific anticancer therapy is also known as ligand targeted therapeutics. [27] Nanoparticles are used in gastric cancer treatment either revealing a new way or modifying the existing way of cancer treatment. Different types of nanoparticles either single or in a combination could be used in gastric cancer. Wide range of studies has already been done by different researchers to prove the effective quality of nanoparticles to treat gastric cancer. In a study, Wu et al. experimented with the polymer-based nanoparticle to treat gastric cancer. PEG-modified polyethyleneimine copolymer was used in that study to deliver siRNA in order to suppress the activity of CDD4 cells, a molecule that involves in the progression of gastric cancer. Gene therapy, for example, siRNA is an efficient tool to treat cancer but it is unstable. This newly modified copolymer helps to hold down the activity of siRNA and ensure the safety of this procedure. In another gene therapy approach which turns out as beneficiary, calcium phosphate nanoparticles were combined with suicide genes e.g. bCD (Bacterial cytosine deaminase). This in vivo test was done to find out the efficacy of that nanoparticle against gastric cancer cells. Immunoagents are also essential candidate for cancer therapy. For example, use of poly (I:C) is widely acceptable and known as anti-cancer drugs but their action on gastric cancer cells are not well known, though few studies were done before. But Qu et al. and others tested this on gastric cancer cell both in vitro and in vivo. Their findings proved that it could persuade the apoptosis on human adenocarcinoma cells in vitro and could hold back tumor growth in vivo. Chitosan nanoparticles are extensively studied nanoparticle because of their safety, bioavailability, and biocompatibility in anticancer treatment. In order to find out the effect of these nanoparticles on the proliferation of gastric cancer cell line MGC803, Qi et al. and his co-workers used high positively charged chitosan nanoparticles. They figured that it is cytotoxic towards the cell line and could induce cell death. Naturally obtained molecules like ursolic acid is a good candidate for cancer treatment but the hydrophobic nature of this material holds back its true potential. Zhang et al. prepared ursolic acid loaded nanoparticles, where mPEG-PCL (methoxy poly (ethylene glycol)-polycaprolactone) co-polymer work as a carrier system and tested it on gastric cancer cells. They found increased apoptosis of gastric cancer cells. Another well-known anticancer agent cerium oxide nanoparticles also known as CNP has been tested by different scientists for years. Xiao et al. used CNP obtained from cerium nitrate using the thermal decomposition method. He and his colleagues then tested it on gastric cell lines.[28] The outcome suggests that CNP has an inhibitory effect on gastric cancer migration both in vivo and invitro which is dose independent. However, the inhibitory effect of CNP on gastric cancer proliferation is dose dependent and there is a high concentration of CNP is needed for that. Yao et al. used a combination of single walled carbon nanotubes (SWNT) used as targeting drug delivery system, salinimycin (SAL) used as an anti-cancer agent and hyaluronic acid (HA) used as targeting ligand in order to treat the gastric cancer stem cell and found productive result that helps to minimize the movement and intrusion of gastric cancer stem cell as well as eradication of it. In another study combinations of neem and silver nanoparticles were used gastric cancer cells invitro. In the experimented procedure neem works not only as an anticancer agent but also as an antibacterial agent too. On the other hand, silver nanoparticles were used to target the gastric cancer cells that increase the potential of the experiment. The experiment is rather safe and easy, as well the it helps to surpass the drawbacks of all other available cancer treatment. Above approaches by the scientists shown that nanoparticles show promises to unlock a new way to treat gastric cancer.[29] But it needs to be mentioned that there are some other approaches where the nanoparticles could aid in the existing gastric cancer treatment options. Magnetic nanoparticles are excellent candidates to treat gastric cancer. They could increase the competency of existing cancer therapy. In order to support this theory Yoshida and his colleagues used magnetic nanoparticles with chemo-thermal agent Docetaxel to improve the thermal process in subcutaneously grafted gastric cancer cells in mice to boost the efficacy. [30] F-b Cui *et al*. demonstrated an experiment using docetaxel-loaded gelatinase stimuli PEG-Pep-PCL nanoparticles in gastric cancer cell lines to solve the problem and found out that it increased the radio sensitivity of Docetaxel and made it specific as well as reduce the side effects. Camptothecin and its analogues e.g. Irinotecan and topotecan are extensive anticancer agents which are effective against multiple types of cancer but can't be used clinically because of their toxic nature, though Irinotecan and topotecan have minimal toxicity in compare with their parent drug. Ghaur et al. experimented using a combination of camptothecin and cyclodextrin-based polymer against gastric cancer cell line BGC823 xenografts and found out that it is safe, effective and more bioavailable than the previous way. Like many other anticancer drugs Sorafenib has failed to show its true potential in early days when it comes to bioavailability. As they are less soluble in water they couldn't be given orally. However, in a study Zhang et al. showed that Nano diamond, a member of carbon nanoparticle family loaded with polymer could increase the oral bioavailability of sorafenib and increase its efficacy in suppression of metastasis of gastric cancer. Graphene, is another useful member of the carbon family. Nanoparticles based on graphene oxide also holds promising property to treat cancer. Li et al. used grapheme oxide nanoparticles facilitated with a femtosecond laser to make microbubble formation of water that helps to treat gastric cancer effectively in vitro. To treat different cancer Paclitaxel is the most commonly and widely used chemotherapeutic agent but it enhances different undesirable side effects in the treatment procedure as it needs to deliver intravenously. Though different approach was made by scientists to give paclitaxel orally by using organic and synthetic delivery system, but still it fails to achieve the full potential as the probability of side effects still remains. Shapira et al. used beta-casein nanoparticles as drug delivery system to deliver paclitaxel orally and found out promising results against gastric cancer, as it holds the anticancer activity and have less side effects and cytotoxicity. [31]

Application of gold nanoparticles for the treatment of gastrointestinal cancer theranostics

Mohan Singh *et.al* 25 May 2015 had worked on "Application of gold nanoparticles for the treatment of gastrointestinal cancer theranostics" Gold nanoparticles (GNPs) are readily synthesised structures that absorb light strongly to generate thermal energy which induces photothermal destruction of malignant tissue. This

review examines the efficacy, potential challenges and toxicity from in vitro and in vivo applications of GNPs in oesophageal, gastric and colon cancers. Two hundred and eighty-four papers were reviewed with sixteen studies meeting the inclusion criteria. The application of GNPs in eleven in vivo rodent studies with GI adenocarcinoma demonstrated excellent therapeutic outcomes but poor corroboration in terms of the cancer cells used, photothermal irradiation regimes, fluorophores and types of nanoparticles. There is compelling evidence of the translational potential of GNPs to be complimentary to surgery and feasible in the photothermal therapy of GI cancer but reproducibility and standardisation require development prior to GI cancer clinical trials. [125] Theranostics refers to agents that are simultaneously therapeutic and diagnostic. Theranostics using NPs implies a robust system which can diagnose, deliver targeted therapy and monitor response. When excited with laser energy with a wavelength that is tuned to the gold nanoparticle's (GNP) specific surface plasmon resonance (SPR), valence electrons on the surface of GNPs exhibit very strong oscillatory energy, which induces high temperatures that are useful for causing localised tissue death. When these NPs are heated within cancer tissue, this is then termed photothermal therapy (PTT). This photothermal reaction can be applied to kill cells within tumours, specifically in places that are difficult to reach surgically or require a palliative debulking procedure.[32] The SPR of GNPs can be tuned to absorb light in the near infrared (NIR) region to harness the potential of applying this photothermal effect to cancer tissue in vivo. The first use of GNPs in photothermal ablation was described by Hirsch et al in SKBr3 human breast epithelial carcinoma cells in 2003.[33]

The information presented here is encouraging in demonstrating that GNPs do have the potential to be excellent tumour targeting agents due to their ability to extravasate from leaky endothelial walls surrounding a GI cancer, and remain in-situ sufficiently long to absorb NIR light and generate heat that is capable of destroying cancer cells.[34] Active targeting to tumours can also be accomplished by conjugation with moieties that are over-expressed on cancer cells, namely antibodies, folic acid and peptides.Further chemical refinement of NPs is being developed, such that the cytotoxicity of these particles is becoming much less pronounced.[35]

Nanosol (LDH@Au) loaded Doxorubicin for gastric cancer

Hu Zhao, Xueqin Zhang had worked on **"**Enhanced apoptosis and inhibition of gastric cancer cell invasion following treatment with LDH@Au loaded Doxorubicin" The suppression of cancer cell growth and invasion has become a challenging clinical issue. In this study, they used nanotechnology to create a new drug delivery system to enhance the efficacy of existing drugs. They developed layered double hydroxide by combing Au nanosol (LDH@Au) and characterized the compound to prove its function as a drug delivery agent. The anti-cancer drug Doxorubicin was loaded into the new drug carrier to assess its quality. They used a combination of apoptosis assays, cell cycle assays, tissue distribution studies, cell endocytosis, transwell invasion assays, and immunoblotting to evaluate the characteristics of LDH@Au as a drug delivery system.[36] The LDHs were plate-like hexagons approximately 60–120 nm in size. The Au nanosol was sol–gel with granulated Au nanoparticles smaller than 5 nm. The images also showed that Au nanoparticles were distributed on the edge of the hexagonal LDH, which are approximately 120 nm. The level of Au in LDH@Au was 10− 5 mol/l. The presence of the diluted nanoparticles on the surface was measured by zeta potential [37] LDH@Au had a negative zeta potential of − 12.3 mV ± 1.2 mV. The size of LDH@Au was determined using Distribution by Intensity Study (DLS). The DLS results for LDH@Au showed an average diameter of 118 nm.[38] The apoptosis of treated SGC-7901 cells was measured by MTT assay and flow cytometry. The data showed more than 90% of cells survived after being treated with LDH@Au, and 57% cells survived in the group treated with 2.5 μg/mL. The MTT results showed a clear increase of LDH@Au-Dox induced SGC-7901 death compared to Dox only treated cells. There is an enhanced cell growth inhibition activity of LDH@Au-Dox compared to Dox only. There were 67% dead or apoptotic cells after co-incubating cells with 4 μg/mL LDH@Au-Dox. However, there were only 36% apoptotic cells in the Dox treated group.[39] In this study, they synthesized and characterized LDH@Au nanoparticles and then loaded the particles with the anti-cancer drug Dox. The LDH@Au-Dox showed enhanced anti-cancer effects and both improved tumor cell apoptosis and inhibited cancer cell invasion. These characteristics of LDH@Au-Dox may be due to anti-angiogenic action and activation of the caspase pathways. Their work provides a promising drug delivery system to solve the clinical anti-cancer problem.[40]

Magnetic nanoparticles for treatment of gastric cancer

Depending on the location of tumor and stage of cancer patients, hyperthermia can be achieved by a number of approaches. These include whole body hyperthermia, local hyperthermia by external or internal energy sources, or regional hyperthermia by irrigation of body cavities or perfusion of organs. Particularly, thermotherapy using magnetic nanoparticles (MNPs) is gaining increasing attention as a potential new cancer treatment.[40] The technical principles behind magnetic hyperthermia involve the coupling of an external alternating current (AC) magnetic field to magnetic particle-loaded tumors. The magnetic particles used in hyperthermia have permanent magnetic orientations or moments, while an applied alternating magnetic field can provide the energy necessary to reorient the particles magnetic moments. This magnetic energy, when dissipated, is converted to thermal energy.[41] Cancerous cells typically have diameters between 10 and 100 μm and have been shown to absorb magnetic particles. This increases the effectiveness of hyperthermia by delivering therapeutic heat directly to cancerous cells. Since nanoparticles (NPs) possess unique properties that include non-toxicity, biocompatibility and high level of accumulation in target tissues, they are ideal candidates for hyperthermia cancer treatment. On the other hand, although magnetic hyperthermia methods are promising, the risk of local overheating remains a major concern. To address this challenge, MNPs have been incorporated with thermally responsive agents (e.g. hydrogels, thermosensitive polymers, lipids) to aid in specific NP tumor retention. Alternatively, chemotherapeutic agents incorporated with NPs have also been used to augment hyperthermia effects such that less heating would be required to achieve the same therapeutic effect.[42] In their second study, which is published in the current issue of the Journal of Gastroenterology and Hepatology, the authors report their further investigation of the interaction of chemotherapy and hyperthermia by comparing the docetaxel and tumor necrosis factor (TNF)-α concentration, and cell cycle as well as cell death among different treatment groups. They reported that the ratio of dead cells and the TNF-α concentration in chemo with magnetic hyperthermia group increased more significantly and was sustained for much longer than that in the other groups.[43] Although the authors did not provide direct evidence for the causative effect of TNF-α on cell death, the significant tumor regression in the "chemo with magnetic hyperthermia" group seems to be attributed to the sustained high level of TNF-α and enhanced rate of cell death. Thus, the authors conclude that the effectiveness of the DML-inductive heating treatment is derived from a combined effect of chemotherapy and magnetic hyperthermia. [44]

LIMITATIONS OF NANO- PARTICLES FOR THE TREATMENT OF GASTRIC CANCER

Cellular toxicity

The increasing use of nano-medicine as a current technology to treat various diseases has raised concerns about their toxicity in living beings. Synthetic preparation of nano-medicines have been used tremendously in a wide range of applications (in medicine and surgery) and living beings are being exposed to them at an elevated levels [45,46].

Gastrointestinal disorders

Considerable potential health risks are documented on human health and environment due to nanoparticle. Nanoparticles are extensively used in biomedical fields showing complex and unexpected interactions with the biological systems particularly with oral route drug administration [47]. A number of diseases are caused due to widespread usage of nanoparticles.

Gut microbiome alteration

Gut microbiome alteration can cause enteric disorders in humans and animals [48] as the gut microbiota is playing a key role to maintain the GI homeostasis [49]. Altered microbiota can cause serious health risks including cancer risks also.

CONCLUSION:

Nanotechnology is playing an increasingly important role in gastric cancer diagnosis and treatment. The size regime of NPs is small compared to cells and cellular organelles permitting NPs to interact with specific features of cells and allowing for tumor cell localization through active targeting [50, 51]. The size regime of NPs is also appropriate for passive targeting to tumor tissue [50]. Thus, nano-sized materials have particular advantages for cancer treatment with distinct features relative to low molecular weight drugs. These properties are being effectively exploited for improved delivery of chemotherapeutic drugs [52] resulting in both enhanced anticancer activity and reduced systemic toxicity.

The chemical diversity of NPs allows for interactions with magnetic fields [53], NIR irradiation [54], and other external fields to provide a conduit for highly specific interactions between external fields with tumor tissue and potentially with individual malignant cells in vivo. The diverse material composition of NPs also permits perturbation of external fields providing enhanced contrast for imaging applications [55]. The unparalleled specificity of coupling between external fields and malignant cells in the context of normal tissue provided by appropriate NPs is expected to lead to more accurate and earlier diagnoses and improved treatment outcomes. One concern potentially limiting the applicability of some NPs for cancer treatment is the toxicity [56] of nanomaterials that requires further investigation. Nonetheless, improved cancer treatments using nanotechnology will continue to be developed and result in improved treatment outcomes.

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