

Nanoparticles to Deal with Gastric Cancer

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Abstract

Nanomedicine has become a comprehensive field of medical science since the invention of nanoparticles namely nanotechnology. Uses of nanocarrier ease the way to deliver drugs more easily to deal with deadly diseases like cancer. Gastric cancer, another common form of cancer worldwide has little treatment option which makes it dangerous to deal with. Use of nanoparticles could boost up the process of developing new drugs in order to deal with this life threatening disease.

Keywords: Nanomedicine; Gastric cancer; Nanoparticle; Nanotechnology

Introduction

Gastric cancer, a multifactorial disease is one of the leading causes of death worldwide. Among all other cancers it ranks in number four because of its occurrence. Several factors are involved behind this deadly disease. The factors could be environmental, bacterial or it could be host related. Some of the ethnic groups are more prone to this disease in comparison with others [1]. Factors that could be responsible for gastric cancer occurrence are shown in Figure 1. Though the number of gastric cancer incidents are getting low in the Western countries, which has been observed from the past few years, but still it remains pretty high in Asian region i.e. Korea, Japan [1,2]. Despite this situation numbers of gastric cancer diagnosis and treatment methods are very limited. Surgery is considered to be the most accepted way to cure this cancer till date. So, without any hesitation more advanced options are necessary to deal with that [2,3].

overall treatment methods of cancer. Current treatment methods could destroy or hamper normal tissues. For that reason, idea of nanomedicine has been introduced [5].

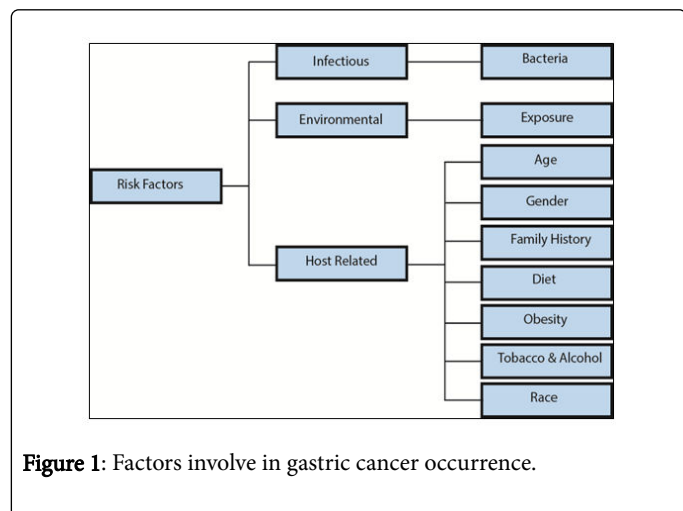


Figure 1: Factors involve in gastric cancer occurrence.

Cancer is an ancient disease which was discovered in 1500 BC. Till now diverse methods has already been incorporated to deal with it and there are other methods which are yet to come [4]. Figure 2 shows the

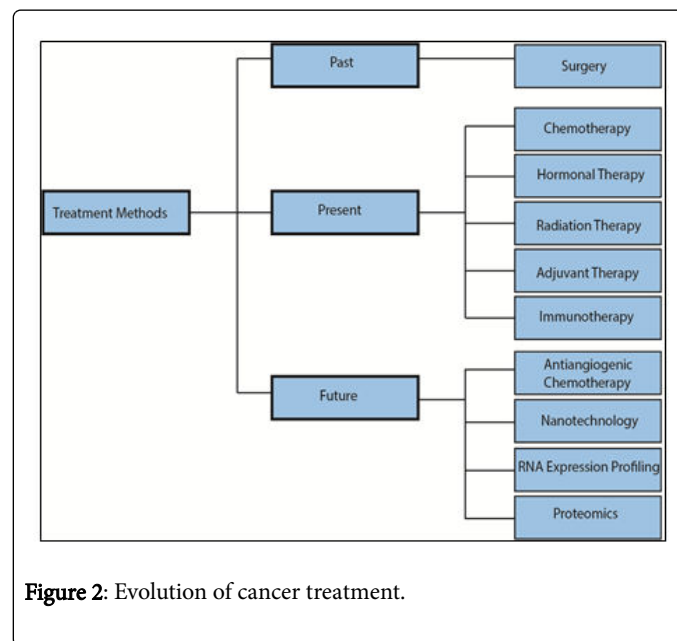


Figure 2: Evolution of cancer treatment.

Because of their unique physico-chemical properties nanomedicine are ace candidate for cancer diagnosis and treatment. Incorporation of nanotechnology in medical application is known as nanomedicine. It involves detection, diagnosis as well as treatment of different disease with the help of nanosized materials [6]. Nanoparticles, part of nanomedicine 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 [7]. 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, 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 [8]. Table 1 show some list of drugs which are already been use and/or could be used in gastric cancer treatment.

Type	Name	Route	Reference
Fluoropyrimidines	Capecitabine	Oral	[9]
	Doxifluridine	Oral	[2]
	UFT	Oral	[2]
	S-1	Oral	[9]
Non-fluoropyrimidine antimetabolites	Pemetrexed	I.V.	[2]
Direct thymidylate synthase inhibitors	Raltitrexed	I.V.	[2,10]
Platinum derivatives	Oxaliplatin	I.V.	[11]
	Carboplatin	I.V.	[11]
Topoisomerase inhibitors	Topotecan	I.V.	[12]
	Irinotecan	I.V.	[12]
Taxanes	Paclitaxel	I.V.	[13]
	Docetaxel	I.V.	[13]
Anthracyclines	Epirubicin	Oral	[14, 15]
Matrix metalloproteinase inhibitors	Marimastat	Oral	[2]
Tyrosine Kinase Inhibitor	Lapatinib	Oral	[16]
	Foretinib	Oral	[16]
	Sunitinib	Oral	[16]
Monoclonal Antibodies	Ramucirumab	I.V.	[16]
	Pertuzumab	I.V.	[16]
	Trastuzumab	I.V.	[16]

Table 1: Anticancer drugs for gastric cancer treatment.

The above listed drugs may work as an individual anticancer drug or as a combination [9,13]. Despite their anticancer properties these drugs still show different sort of side effects and there delivery method is somehow difficult. That's where the use of nanoparticles become handy as it could reduce the side effects and improves the efficacy of the treatment [7].

Nanoparticles in Gastric Cancer Treatment

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 [17]. 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. These

ligand specific anticancer therapy is also known as ligand targeted therapeutics [18]. Figure 3 shows a schematic representation of the process.

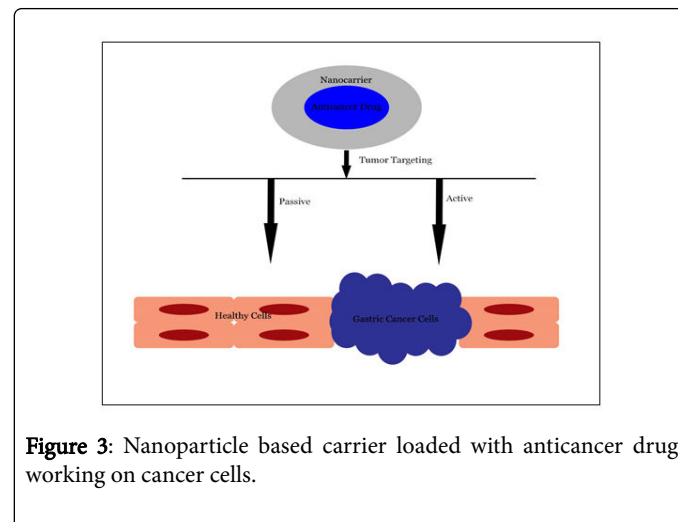


Figure 3: Nanoparticle based carrier loaded with anticancer drug working on cancer cells.

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. Table 2 shows some example of the nanoparticles.

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 [19]. 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 [20]. Immunoagents are also essential candidate for cancer therapy. For example use of poly (1: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* [21]. 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 [22]. 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 [23]. 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. The outcome suggests that CNP has an inhibitory effect on gastric cancer migration both *in vivo* and *in vitro* 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 [24]. 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 [25]. In another study combinations of neem and silver nanoparticles were used gastric cancer cells *in vitro*. 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 [26].

Above approaches by the scientists shown that nanoparticles shows promises to unlock a new way to treat gastric cancer. 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 [27]. Clinically Docetaxel is one of the most efficient chemotherapeutic agents used in radiotherapy for different cancer treatment. But, their applicability is less effective because of its non-specific distribution that raises several side effects.

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 radiosensitivity of Docetaxel and made it specific as well as reduce the side effects [28]. Camptothecin and its analogs 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 [29]. 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 nanodiamond, 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 [30]. 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* [31]. To treat different cancer Paclitaxel is the most commonly and widely used chemotherapeutic agent but it enhance 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 [32].

Name of Nanoparticle	Use	Stage of Development	References
Dendrimer	Carrier	<i>In vivo/in vitro</i>	[5]
Immuno PEG Liposomes	Carrier	Clinical trial (Phase-1)	[5]
Immunoliposomes	Carrier	<i>In vivo</i>	[5]
Quantum Dot (QD)	Imaging agent	<i>In situ</i>	[33]
Gold	Theranostic	<i>In vivo/In vitro</i>	[34]
PLGA	Carrier	<i>In vivo/ In vitro</i>	[35]
Super paramagnetic iron oxide	Imaging agent	<i>In vivo</i>	[36]
Au- Ag alloy coated with MWCNT	Sensitizing agent	<i>In vivo</i>	[37]
Silica	Imaging agent	<i>In vivo/In vitro</i>	[38]
Combination of silica, gold nanorod, carbon nanotubes	Imaging agent	<i>In vivo</i>	[39]
Combination of CdTe and QD	Imaging agent	<i>In vitro</i>	[40]
Fluorescent Magnetic Nanoparticle	Targeted imaging	<i>In vivo</i>	[41]

Table 2: List of some nanoparticles used in gastric cancer.

Some of the nanoparticles are already marketed or are in clinical trial stage like liposome, polymeric conjugates, and polymer micelles

[42]. Others are still in laboratory experimenting stage and will be soon available as the nanomedicine based science is developing rapidly.

Toxicity of Nanoparticles

While dealing with nanoparticles toxicity of these need to be taken under consideration. For example, nanoparticles made from copper could damage gastric tissues because of increase hydrogen and bicarbonate ion. This study was proved by Chen et al. [43]. High intake of supermagnetic nanoparticles can lead to accumulation of iron in a specific organ to which it is delivered. This produce toxic effects and leads to DNA damage as well [44]. It has been proved that nanoparticles when used in a high dose could provide toxic results. Several in vivo studies proved that low dose of nanoparticles provides nontoxic results [45]. Nanoparticles which could be used in the treatment of gastric cancer still shows side effects which have been found out by different experimentation. Like the platinum based nanoparticles show strong response against gastric cancer cells but could still accumulate in the liver or spleen and show cytotoxic effect. To counter this problem steps have already been taken. Incorporation of polymer which is safe as well as easily biodegradable could assist to reduce the side effects of the nanoparticles based anticancer formulation i.e. use of hyaluronan in platinum nanoparticulate based anticancer drug [46].

Conclusion

Introduction of new diseases hasn't been stopped and who knows what we need to face in the future. But no matter what it is, right from the very beginning cancer is one of the deadly and most fearsome diseases human kind has ever seen. Still people of all kind live in panic when they hear something regarding cancer and numbers of the infected people are increasing daily. Like all other cancers gastric cancer is a threat to us all. It is mandatory to find new ways to deal with it, as the existing ways are not enough. There were approaches to vaccinate people against cancer that may help to lessen the number of gastric cancer occurrence [47]. But still, that is not easy and enough. Nanomedicine, namely use of nanoparticles could pave the way of treating gastric cancer more easily than before as it could blend with the existing treatment methodology or could create new treatment options which is effective and safe as well. However, many more researches are needed to be done in laboratory scale in order to unlock the full potentiality of nanoparticles to treat gastric cancer and transfer it safely to clinical trial that eventually leads it to industrial based production.

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