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When Chemo Fails! Nanotechnology Is Introduced:

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Abstract: ***In this article we picturised at the failure of chemotherapy in cancer treatment and how nanotechnology can be used as an alternative to chemotherapy. Main cause of Chemotherapy failure is the development of Resistance against Multiple drugs (i.e. MDR) that are used to treat cancer cells. Another supportive point in the failure of chemotherapy is absence of targeted actions, drug toxicity, harmful to healthy cells, etc. (7) To overcome these there is the introduction of nanotechnology. Nanotechnology can be defined as the Branch of science that deals in the study of manufacturing and use of small size particles (10^{-9} m) for adjustment of molecules and substances at the nanoscale level (10) Nanoparticles used for the delivery of drugs are called Nanomedicines (6). Nanomedicines are the evolution of Chemo Medicine, in that form where it just keeps the drug safe inside the outer sheath which releases these chemicals on targeted cells.***

Keywords: chemo - chemotherapy, MDR - multi drug resistance, ABC transporter

1. Introduction

Nanotechnology is a progressive field of science of molecule formulation that opens the wide range of research due to its beneficial results like disease management, treatment etc. ., nanotechnology is the use of small formulated particles to treat and manage pathological conditions. The first person who introduced or used nanotechnology was the Japanese scientist Norio Taniguchi in 1974. Nowadays nanotechnology has become the warst field of research but still there is some improvement that needs to be done like; regulation of lipid solubility of nanoparticles in blood, etc. . After these all we can conclude that nanoparticles or use of nanomedicines will be the great choice of treatment.

Chemotherapy: Term chemotherapy also coined as “chemo”. Simply, it's a use of drugs (which are chemical in nature) to block, degrade the cell growth or cause cell death in the aspect of cancer. (9) In chemotherapy we need a high amount of drugs for required pharmacological action that results in drug accumulation and leads to drug toxicity in the body; also we don't have any defined target in this kind of treatment in the case of cancer. To overcome these problems and to achieve therapeutic goals we have to move one step ahead. This results in the introduction of Nanotechnology.

How Chemotherapy Fails: failure of chemotherapy is the result of several mechanisms; multidrug resistance, stimulation of Drug efflux, change in the cell metabolism.

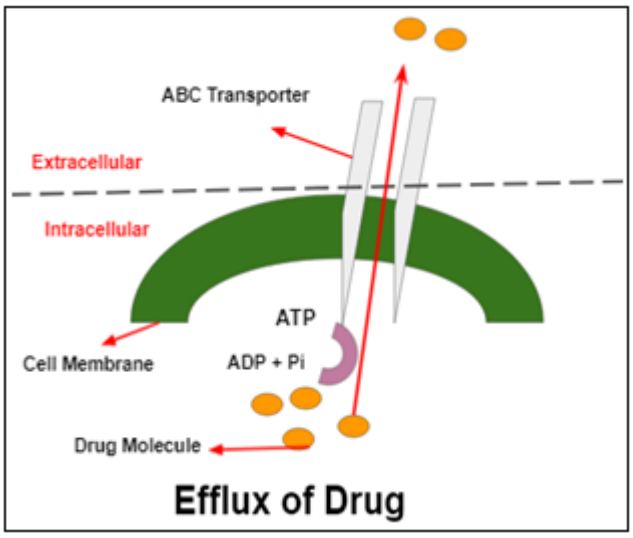
1) Development of Multidrug resistance: There are several mechanisms through which a cell can develop resistance against multiple drugs. These due to the mutations in the cells against exposure of drug or may be due to increase in the efflux of drug molecule (8)

a) **Modulation of target sites:** cells modulate their target sites to prevent themselves from the exposure of drugs. Point mutation in genes, Enzymatic alteration in binding sites which discontinue the binding of drugs, Bypass of original targets these are the supportive points in generation of multi drug resistance (8)

b) **Modification in permeability of plasma membrane:** changing the permeability of plasma membrane decreased drug uptake into the cells and less or no therapeutic effect of drug and high toxicity has been observed, (8)

c) **Release of modulated enzymes against drugs**: The pathways that are the part of drug metabolism affected due to altered metabolic signaling in cells and lead to ineffectiveness of drug. these may be due to production of; destructive enzymes that results in breakdown of drug molecules from the potential cleavaging actions of lethal enzymes produced by cells, modification of drug molecules defined by addition or subtraction of different chemical groups and rings, instability of bonds, or other structural changes. Both ultimately drive dysfunctioning of drug molecules. (8)

2) Stimulation of Drug efflux: Cancer cell acquire Multi drug resistance and express various ATP binding cascate (ABC) transporter protein. These are the family of intermembrane transporter protein which activated after binding of substrate to substrate binding site, leads to hydrolysis of ATP that drives conformational changes and eflux the substrate outside of cell. (FIGURE) [6]



3) Alteration in cell metabolism: Modification in the intracellular metabolic pathway which is in response to drug functionalization or metabolism. Generally, metabolism reactions inside the cell are classified into three portions. Portion I reactions include oxidation, reduction, and hydrolysis of substrate through the action of enzymes that belong to the cytochrome P450 family. Portion II of metabolism also known as consumption and conversion,

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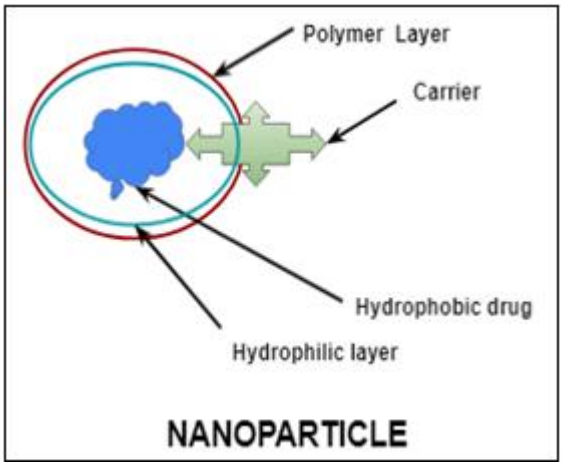
here primary function is shown by glutathione S - transferase (GST) family. They conjugate glutathione (GSH) to a wide range of hydrophobic and electrophilic molecules, making them less toxic, and predisposing them to further modification and being expelled from the cell These conjugate actively transported out of the cell by different transmembrane efflux pumps known as phase III reactions [6]

Nanotechnology: The Branch of science that deals in the study of manufacturing and use of small size particles (10^{-9} m) for adjustment of molecules and substances at the nanoscale level. (10) A new term coined to that nanoparticles which is used as medicines is "Nanomedicine". nanotechnology composed of two words " nano - dwarf/small" and "technology - use of formulation or techniques for human welfare" so we can coined that nanotechnology is the use of nanoparticles formulations for human welfare and those particles which carry drugs are nanomedicines (6), nanomedicines envelope the hydrophobic molecule of drug and release it inside the cancer cell because they act on carrier binding site on the cancer cell i. e. . They become target specific by the help of a targeting system. These nanomedicines are given by intravenous (IV) injection directly into the blood. So there is a chance of elimination of particles from the excretory system, chances of blocking the microtubules and also a chance of attack by the immune system. to overcome these all we set some properties of nanomedicines or nanoparticles.

Properties of Nanomedicines: there are several properties that promote action or deplete the problems caused by nanoparticles in the blood: (6)

1) Nanoparticles must be compatible with the immune system. .
2) Nanomedicine residues must be completely degradable.
3) Nanomedicines must have a carrier transporter on them.
4) Nanomolecules target the specific site.
5) Nanomolecules will be easily acceptable by cancer cells.
6) Nanomolecules don't cause hypersensitivity

Structure of Nanomedicines: Nanoparticles hydrophilic outerly and have a sheath of polymer that results in hiding nanomolecules. these Nanomolecules must be greater than 10 nm to increase their blood time by avoiding faster elimination through kidney and smaller then 200 nm to avoid the obstruction of microcapillary. and this hydrophilic membrane of nanomedicine contain a special carrier transporter that attach to carrier binding site these carrier transporter may be antibody, protein or other favorable molecule in center of particle there is hydrophobic drug that will release when outer layer will be degraded by the action of enzymes inside the cell. Minding these all things nanoparticles will formulate (6)



Mechanism of Action of Nanomedicines: nanoformulations inject inside the vein through injection. These nanomolecules or nanomedicines distribute in the blood their polymer layer helps them to prevent the immune system generally moving in blood vessels at the site of action of chemotaxins released by the toxic or cancerous cell. There is a gap between the cells of the epithelium layer from where these nanomolecules will leak and they bind with carrier binding sites present in cancerous cells. After recognition they get inside the cells, vesicles cover these nanomolecules and transport them to the lysozyme and merges it for further chemical reactions and leads to the degradation of the hydrophilic layer of nanoparticles and release of drugs inside the cancerous cell. According to the nature of pharmacological action, a drug hidden inside the nanoparticle will perform its action and finally lead to the death of cancerous cells without causing toxicity to other cells. (1)

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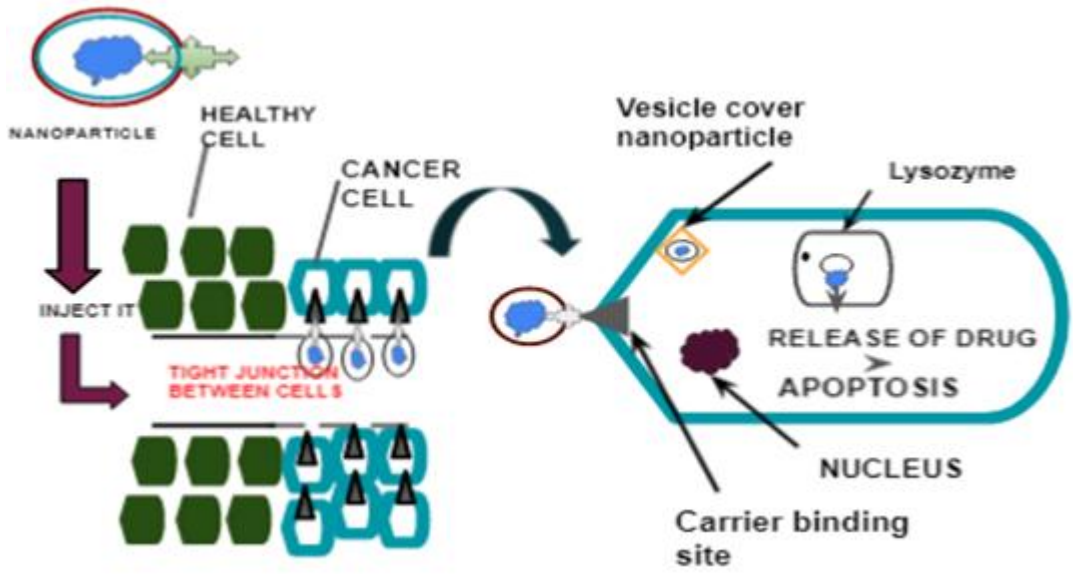

Nanoparticles and Immune system: Immune system treat these medicinal particles as forgein invaders. if they interact with macrophages results in multiple immune responses which stimulate the toxicity or loss of pharmacological action of drug. to overcome these nanoparticles recognised as self cells or loss of recognition against them. Like Polyethylene glycol (PEG) and other polymers used to hide themself from the immune system by providing hydrophilic sheath (11). There are several polymers which can be used according to drug molecule they enlist down in the table;

Formulated Drug	Polymer Type	Applications	Ref.
Coumarin - 6	• PCL [Poly (ε - caprolactone)]	• Used for bioimaging.	-1
	• PLA [poly (lactic acid)],	• For drug delivery	
	• PLGA [poly (lactide - co - glycolide)]		
Rapamycin	• PLGA [poly (lactide - co - glycolide)]	• anti - glioma activity	(2).
Hyperforin	• Acetalated dextran	• anti - inflammatory activity	-3
Fenofibrate	• PLGA [poly (lactide - co - glycolide)]	• High cholesterol	-4
Curcumin (Cur)	• PLGA [poly (lactide - co - glycolide)]	• pancreatic cancer	-5

Use of Nanotechnology: Nanotechnology has a great role in the health industry but also plays an important role in other fields like; food industry, electronic industry and much more. An overview on the use of nanotechnology in different field enlisted;

1) **Health Industry:** this portion has a wide range of uses in different aspects. As treatment or management of disease by compatible formulations, in formulations of drugs, as in internal organs screening,
2) **Food Industry:** Nanotechnology has a potent role in food packaging, food preserving, etc. (5)
3) **Electronic industry:** In this field nanotechnology is also formulated or used as nanosensor (small particles that are not even able to see but they can sense), nanomachines which are used in several perspectives like cleaning etc. . (12)
4) **Agriculture Industry:** In this field we can use nanotechnology to decrease the crop destruction by parasites or weeds and by increasing nutritional value in the plant. (2)

List of Approved Nanomedicines: There are some FDA approved drug enlisted down (4)

Product	Nanoparticle material	Drug	Indication	FDA
Abraxane	Nanoparticle - bound albumin	Paclitaxel	Breast cancer, Pancreatic cancer, Non - small - cell lung cancer	2005
DaunoXome	Liposome	Daunorubicin	Kaposi's sarcoma	1996
DepoCyt	Liposome	Cytarabine	Neoplastic meningitis	1999
Doxil	Liposome	Doxorubicin	Kaposi's sarcoma,	1995
			Ovarian cancer,	1999
			Breast cancer,	2003
			Multiple myeloma	2007 (Europe, Canada)
Genexol - PM	PEG - PLA polymeric micelle	Paclitaxel	Breast cancer, Lung cancer, Ovarian cancer	2007 (South Korea)
Lipo - Dox	Liposome	Doxorubicin	Kaposi's sarcoma, Breast cancer, Ovarian cancer	1998 (Taiwan)
Marqibo	Liposome	Vincristine	Acute lymphoid leukemia	2012
Mepact	Liposome	Mifamurtide MTP - PE	Osteosarcoma	2009 (EU)
Myocet	Liposome	Doxorubicin	Breast Cancer	2000 (EU)
NanoTherm	Iron oxide nanoparticle		Thermal ablation glioblastoma	2010 (EU)

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Oncaspar	Polymer protein conjugate	L - asparaginase	Leukemia	2006
Onivyde	Liposome	Irinotecan	Pancreatic cancer	2015

2. Future Perspectives

There are several disease in which we can use it for treatment and management like tumor, cardiovascular diseases, obstructive disorders, respiratory disorders or may be in COVID - 19 (3). To achieve the better outcome we must need to overcome its high lipid solubility due to which it can easily cross the blood brain barrier and may lead to complications. Once its lipid solubility is regulated then its value in the health industry will rise soon, there are several researches which are trying to get this. in future it might possible and this field become more warsed. (5)

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