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ADVANCEMENTS IN CANCER THERAPY: A COMPREHENSIVE REVIEW OF EMERGING TECHNOLOGIES (2023)

Munazzah Tehreem
M. Pharmacy
RBVRR Women's College of Pharmacy

Introduction:

Cancer, that comprises a multitude of ailments and diseases has the capacity to rapidly spread and invade other parts of the body by rapid cell multiplication. Its known to arise from malignant tumours which spread and move across various body parts. Cancer is known to be second highest cause of deaths worldwide due to the idiopathic nature of disease and the delayed diagnosis. Several studies and research institutes have been dedicated for the working in oncology department to find novel and effective ways in early detection or diagnosis, treatment, medicines and adjuvant therapies.

Various strategies of Cancer Therapy

Certain strategies and methods have been devised in the treatment of cancer since cancer requires a combination of various types of therapies.

- **Targeted therapy and Immunotherapy** – nanoparticles are functionalized with ligands that bind specifically to the cellular sites and produce its action. These include the use of folic acid and biotin which have been linked to nanocarriers in targeting endometrial and ovarian cancer.

Aptamers are oligonucleotides that have a small structure and are single stranded RNA or DNA of synthetic origin which when moulded into specific shapes makes them capable of having specific target delivery of drugs.

- **IMMUNOTHERAPY**- adoptive cell transfer (ACT) that consists of removing or isolating T-cells from the patient's blood stream which has the highest activity against cancer and modifying them ex vivo and then re incorporating them back into the patient's blood. This is a process by which immunotherapy can be achieved.
- **ANTIOXIDANTS**- Naturally occurring antioxidant agents are currently being researched and in under study to establish them as potential therapeutic and preventive agents. Some of these are vitamins, polyphenols, alkaloids, curcumin, flavonoids, berberine and other substances that are under scrutiny and have shown promising apoptotic and anti-proliferative properties.
- **NANOMEDICINE**- These are highly minute systems in which medicinal agents are incorporated to deliver them at the targeted site with minimal side effects and adverse reactions. Encapsulating drugs into these agents increases their exposure time in the body and has a quick onset of action. This topic has been further elucidated in detailed in the next sections.
- **GENE THERAPY**- A synthetic introduction of the defected gene or identical one by converting into a medicinal agent is the process of gene therapy. Cancer gene therapy involves the specific silencing of oncogenes, expression of chemotherapy sensitive genes, proapoptotic genes and specific antitumor immune responses.

Through sufficient research and findings, some of the novel methods found and that are under continuous scrutiny to make them the best for cancer patients are discussed below

1. DENDRIMERS

These are highly branched and synthetic of radial symmetry having self -organizing capacity, high biocompatibility, and low polydispersity. The first of its kind, PAMAM-Polyamidations also called as starburst dendrimers were discovered dating back to the 1980s. the structural characterization can be made by three distinct features; the center layer/core, repetitive monomeric units called as dendrons and the functional terminal groups.

Owing to their high biocompatibility that aids in the prevention of bioaccumulation and further toxicity and the polyvalence state that gives the capacity to support versatile surface functionalization and multiple functionalities with host receptors, it forms an essential basis for being great promoters in the use of cancer therapy. Few of the types of dendrimers utilized in the field of science are Glycodendrimers, Peptide dendrimer and PAMAM dendrimers.

Formulation

The process of incorporating a drug into the form of a dendrimer is done by either complexation or encapsulation. The drug substance can be filled in the inner core or can be joined with the functional groups on the terminal.

1. **Encapsulation**– this is the process where the drug molecules are loaded into the cavity of the

dendrimer making it work as a dendritic box. This allows the dendrimers to take the drug of choice by constructing skeletons that can be stabilised through non- covalency.

2. **Complexation–** this method is done by conjugation where the drug particles are attached to the dendrimers functional group on the surface on the terminal. It improves the half-life of drug and the systemic effects are also reduced.

In cancer treatment, dendrimers have found profound basis in giving promising results. While these are still under study and novel changes and way to improve are still under research, they have shown results worthy of research and better treatment. For sustain release of drug and to avoid the damaging by the host's immune system, nanoparticles have been combined with polyethylene glycol at different strengths. Following are few therapies that have been under study.

1. **CISPLATIN** – PANAM dendrimers have been used for the encapsulation of the anticancer drug Cisplatin which is the first metal-based drug sampled from Platinum. Compared to its normal administration the dendrimer form showed slower drug release. Lower toxicity levels and collection in solid tumours was also observed.
2. **Methotrexate and Adriamycin** – generation 3 or generation 4 cascade polymers conjugated with peg chains resulted in great encapsulation which was the combination

   of 26 molecules of Methotrexate/dendrimer and 6.5 molecules of Adriamycin with 2000 chains of peg. Another marked change was at low ionic strength, there was slow release of drug but in an isotonic state, it was released rapidly.
3. **5-fluorouracil** – g4- PAMAM conjugated with carboxymethyl peg5000 yielded a low hemolytic toxicity in comparison to peg free dendrimers and showed slow release.

2. GOLD NANOSYSTEM

The continuous integrative study of nanoparticles with metal to generate treatments in the field of cancer lead to a series of experimentations which gave rise to the findings of promising results when gold was used in combination with nanoparticles. Gold has several characteristics that makes them easy to use and incorporate with nanoparticles such as high stability, low chemical reactiveness, and an established biocompatibility. It also has high content of electron and is quite easy to prepare.

Such properties of gold combined with the exquisite properties of nanoparticles have proven to be a great advantage in the treatment methods of cancer. Based on this the different forms that have been used are Gold Nanoparticles or AUNP, Gold Nanoclusters or AUNC and Gold Nanorods or AUNR.

PROPERTIES

GOLD NANOPARTICLES

1. Strong absorption phenomena leading to Localized Surface Plasmon Resonance (LSPR)

2. Strong photothermal conversion ability
3. SERS property – photons present in molecules are augmented by inelastic light scattering which attains high energy levels of both rotational and vibrational leading to the phenomena of Surface-enhanced Raman Scattering.

GOLD NANOCLUSTERS

1. Discrete absorption peaks of visible area to close-infrared area.
2. Strong fluorescence based on charge, dimension, and surface ligand.

GOLD NANORODS

1. High absorption rate
2. Decreased toxicity levels
3. Rapid clearance from the body

ADVANTAGES

- Process of synthesis is simple and easy.
- Remarkable physicochemical characteristics make it idealistic to be utilized in multiple therapies.

DISADVANTAGES

While the use of gold in onco therapeutics has yielded promising results, there have also been a few disadvantages which have hindered the progress.

- Toxicity – cancer being a chronic illness requires treatments for long durations of time and the use of gold nanotechnology for long periods of time has proven to cause toxicity. Au nanostructures are difficult to degrade which leads to accumulation and can further cause unexpected adverse effects. This becomes a chain of damage as prolonged accumulation can again damage the body organs such as liver, spleen, kidney and lungs.
- Target site – due to the common delayed diagnosis of cancer, problems arise in target specifity since at later stages of cancer diagnosis, it spreads and at faster rates.
- Biological environment – the human body is an intricate and complex structure and this biological state can be challenging to work since the interactivity of gold nanostructures with biological components still requires further study research.

3. SHIKONIN NANOMEDICINE

Shikonin is a plant derived medicine that has been used in Traditional Chinese Medicine which has been harvested from the dried roots of the medicinal plant Zi Cao – Lithospermum erythrorhizon, arnebia euchroma and arnebia guttata. It is an active naphthoquinone with anti- inflammatory, anti-oxidative and anti-cancer activities. It has also been synthesised by chemical means and biosynthesis.

MECHANISM OF ACTION

Shikonin shows its effects in the treatment of oncology by causing cell death by ways of apoptosis, necroptosis, and autophagy. It also shows its effects by causing blockages in the cell proliferation through means of cell cycle arrest, cell growth and metastasis that can induce immunogenic cell death.

The given compound also suppresses tumor microenvironment by inhibiting glycolysis and repolarizing tumor-associated macrophages (TAMs).

A study of literature has revealed that the mechanisms by which shikonin exerts its anti-cancer effects are ER stress, ERK pathway GSH depletion, p53, ROS generation, PARP cleavage, catalase, and Bcl-2 down-regulation.

Cell cycle arrest is also caused by SHK through p21 and p27 up-regulation, CDK down regulation and cyclin. Hence a few ways are involved in SHK-induced anti-oncologic effects that gives rise to a broad media of activities.

The SHK nanomedicine is employed in different types of cancer through various mechanisms. Breast

cancer – inhibits cells proliferation, induces apoptosis and necrosis.

Cervical carcinoma – cell proliferation inhibition Glioma –

induction of necrosis and apoptosis.

Lung cancer – inhibit cell proliferation, metastasis, and invasion.

Shikonin in nanotechnology has been devised into several different forms owing to their improved pharmacokinetic properties. These have been formulated into polymeric micelles, nanoparticles, nanogels and liposomes.

ADVANTAGES

a) Deep and prolonged circulation in the body
b) Ability of targeting tumours.

DISADVANTAGES

1. Pharmacokinetic – integral to have a stable connection with the production at a large scale and smartly designed to have minimal complexity and to optimum efficacy.
2. Biosafety – the use of novel organic solvents in the preparation of SHK nanomedicine. Materials that have been approved thoroughly by the FDA should be utitlised in designing the SHK nanomedicine. Other materials should be biocompatible, food- derived and natural in nature.
3. Drug resistance – a major problem faced during the oncologic treatment is development of resistance to drugs which causes chemotherapy failure.
4. Site delivery – multiple biological barriers hinders the easy passage of nanomedicine. Nanomedicine formulated based on the EPR effect fail to deliver drugs to areas of tumour cells

that is away from the blood stream or blood vessels that leads to minimised clinical efficacy.

4. CURCUMIN NANOMEDICINE

Curcumin is an active polyphenol of plant origin which is derived from the rhizome of turmeric plant Curcuma longa of the Zingiberaceae family. Besides having therapeutic effects on multiple organ systems in the human body it has also shown to produce promising anti-cancer action and lowering the risk of developing severe adverse reactions produced during the course of chemotherapy.

ANTICARCINOGENIC ACTION

Curcumin has shown to cause apoptosis and has antiproliferative action against different types of cancer such as pancreatic, kidney, breast, colorectal and prostate cancer. It acts by inducing various mechanisms such as the suppression of telomerase reverse transcriptase enzyme, cell death, p53, Akt, PTEN.

Nanomedicine: various methods have been developed for the synthesis of nanocurcumin which include the standard methods such as wet milling, ionic gelation, Fessi method, microemulsion, solvent evaporation, nanoprecipitation, spray drying, coarcevation process and thin-film hydration.

It has been synthesised into the different nano forms of micelle, liposome, cyclodextrin, magnetic, nanogel, polymer, solid and polymer conjugate. This modification from the natural curcumin to nanocurcumin has yielded better stability, bioavailability, pharmacokinetics, and site targeting of the curcumin nanomedicine. It has also overcome the weak hydrophobic property of curcumin. With improved cytotoxicity curcumin nanogels have also shown better cellular absorption. In several experiments curcumin has also shown to be an inhibiting factor which has the ability of preventing cancer in its earlier stages and acts as a suppressive agent preventing the multiplication during the succession of carcinogenesis. With a plethora of functions and promising results, curcumin holds a stronghold as being produced as a promising anticancer agent.

Curcumin nanomedicine has been employed in the treatment of ovarian cancer, prostate cancer, breast cancer and colorectal cancer. Curcumin nano formulations have been tested and used as combinational chemotherapy with agents like doxorubicin, cisplatin, celecoxib, paclitaxel.

S.NO	NANOFORMULATION	AGENTS	EFFECTS	CANCER TYPE
1.	Cationic polymeric nanoparticles	Camptothecin & curcumin	Influence on the synergistic anticancer activity	Colon cancer
2.	Liposomes	Paclitaxel & curcumin	Effective cancer cell death	Breast cancer
3.	Nanoparticles of iron oxide	Curcumin & gemcitabine	Effected targeted delivery of active curc to affected pancreatic cells and enhanced uptake of gemcitabine	Pancreatic cancer
4.	Lipid nanoparticle	Curcumin & Doxorubicin	Cytotoxicity enhancement and reduces the inhibitory concentration in HepG2 cells	Liver cancer

ADVANTAGES

- Decreased systemic toxicity
- Great patient compliance
- Targets tumours in depth
- Better potency

DISADVANTAGES

- Complications regarding organic solvent residues, poor dispersion and aggregation
- Nano emulsions: improvements have to be made in the development of low toxic and effective surfactant and the problems of poor thermal stability and reduced industrial production have to be tackled.
- Instable formulations which lead to reduced efficacy
- Leakage of drugs from the nanotech such as liposomes.

5.MICRONEEDLES

Microneedles (MNs) is a unique effective parenteral route of drug administration that has been developed to deliver immune drugs. These are used by inserting into the skin that cause minimal pain and are proven to be more effective than injections. The tips pf MNs are long of around hundreds of micrometers that penetrate the epidermal layer and reach the stratum corneum which thereby reaches the resident T cells and APC’s.

MNs are of varied types such as coated, solid, hollow, hydrogel forming and dissolving.

MECHANISMS

The MNs when inserted reach the systemic circulation by the following four mechanisms:

- Poke and Release
- Poke and Flow
- Poke and Patch
- Coat and Poke

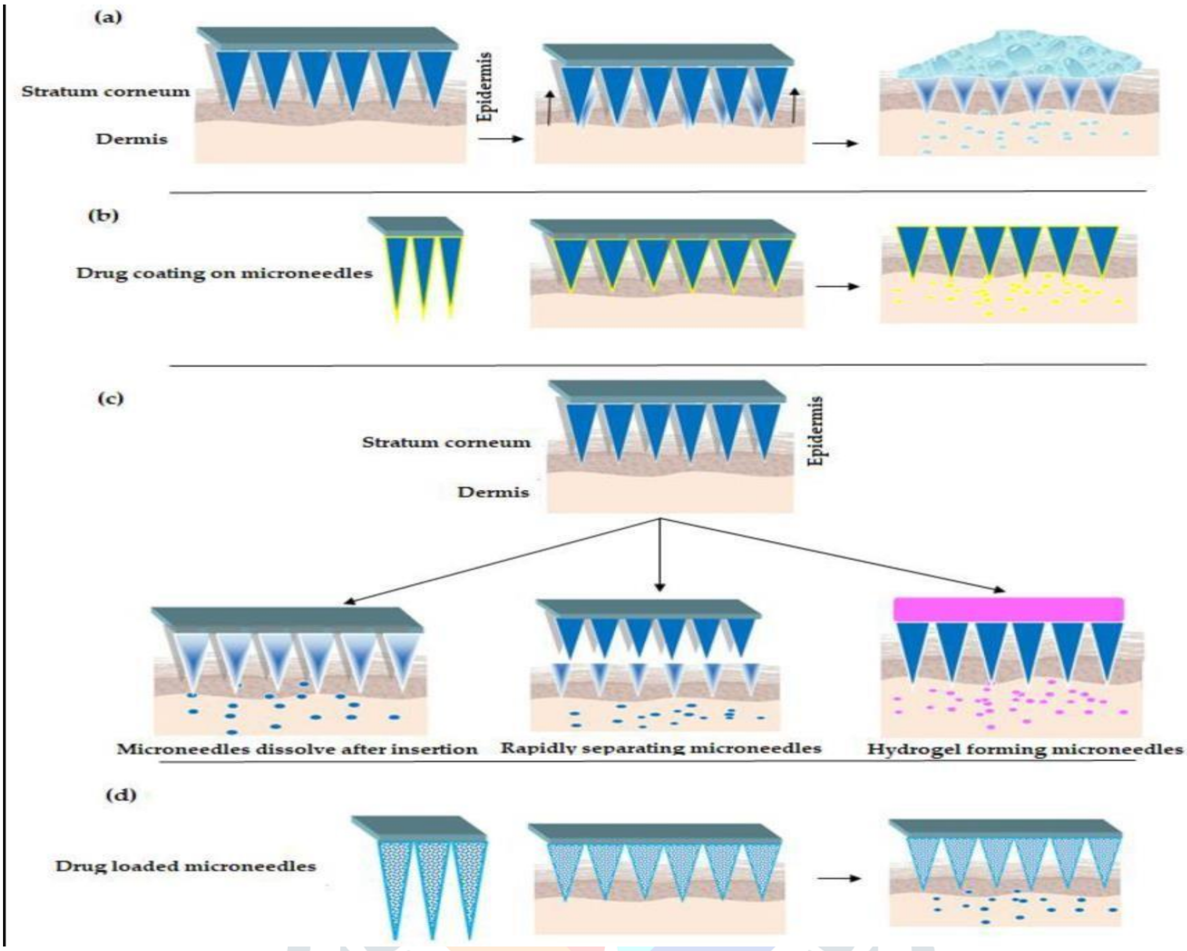

Figure: Depiction of Different Microneedle Mechanisms

(a) Poke and Patch (b) Coat and Poke (c) Poke and Release & (d) Poke and Flow

ANTICANCER ACTIVITY

A combinational drug of Tamoxifen and Gemcitabine with microneedles of Zein was employed for treating breast cancer. Another study revealed the dissolving microneedles consisting of combined delivery of Doxorubicin and Docetaxel which was prepared using polyvinyl pyrrolidone and polyvinyl alcohol in the treatment of breast cancer.

This co-delivery of drugs via microneedles showed a significant reduction and controlled growth of tumour compared to when it was administered individually. It also exerts its action by reaching the deeper tissues thereby minimising the leakage and causing reduced side effects.

ADVANTAGES

- Large substances can be delivered effectively.

- Medication can be self-injected.
- Rapid healing compared to conventional methods.
- Onset of action is quick.
- It has the ability to bypass hepatic metabolism.
- Minimal to zero pain and irritation.

DISADVANTAGES

- Breakage of the needle tips
- Degradation

CONCLUSION

From the review conducted, through the findings it can be concluded that major advancements made through nanoscience have proven to be of impact and benefit to the world of oncology. It has helped in point and intricate targeting of tumours and to deliver medicines to the exact site. Different forms and mechanisms have been developed through nanotechnology that include dendrimers, microneedles, gold, shikonin and curcuma nanomedicines that have astounding attributes. Modifications of these systems according to the need and requirements can yield even better products. With further proper and incessant research, finalised and exceptional models of these nano systems can be achieved that can provide treatment to the patients at later stages and have more potent and quality delivery system.

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